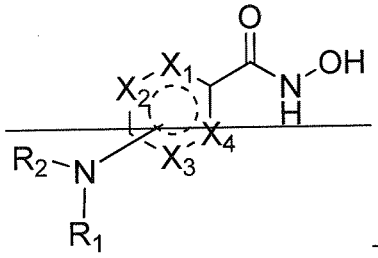
~~WHAT IS~~ CLAIM~~ED~~:

~~1. A compound of formula I:~~



~~(I);~~

~~or a pharmaceutically acceptable salt, ester or prodrug thereof,~~

~~wherein,~~

~~each of X_1, X_2, X_3, or X_4 is independently N or CR', wherein 2 of X_1, X_2, X_3, or X_4 are N;~~

~~each R' is independently H, optionally substituted alkyl, optionally substituted aryl, or halo;~~

~~R_1 is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, carbocyclic, $C(O)R_5$, or $S(O)_pR_5$; each of which may be optionally substituted; and~~

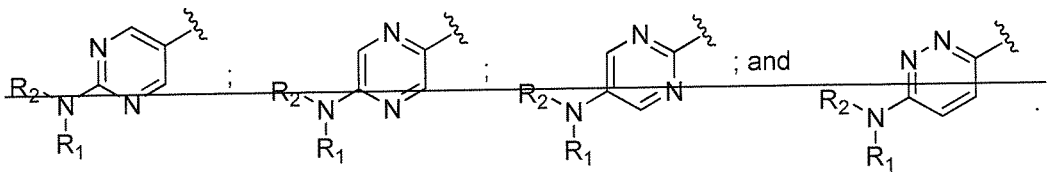
~~R_2 is H, alkyl, haloalkyl, alkenyl, arylalkyl, aryl, heteroaryl, heterocyclic, carbocyclic, $C(O)R_5$, or $S(O)_pR_5$, each of which may be optionally substituted;~~

~~each p is independently 0, 1, or 2; and~~

~~each R_5 is independently H, optionally substituted alkyl, optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl;~~

~~wherein R_1 and R_2 are both not simultaneously H.~~

~~2. The compound of claim 1, wherein the ring comprising X_1, X_2, X_3, and X_4 is selected from the following:~~



; and

.

3. The compound of claim 1, wherein R_2 is H, methyl, ethyl, propyl, i-propyl, butyl, s-butyl, t-butyl, pentyl, hexyl, heptyl, phenyl, naphthyl, anthracenyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, imidazolyl, oxazolyl, furyl, thienyl, thiophenyl, thiazolyl, triazolyl, isoxazolyl, quinolinyl, pyrrolyl, pyrazolyl, or 5,6,7,8-tetrahydroisoquinoline; each of which may be optionally substituted.

4. The compound of claim 1, wherein R_1 is H, optionally substituted alkyl, optionally substituted aryl, optonally substituted arylalkyl, optonally substituted heteroarylalkyl, or optionally substituted heteroaryl.

5. The compound of claim 4, wherein R_1 is H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, phenyl, benzyl, phenethyl, naphthyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, thiophenyl, or tetrahydrofuranyl, each of which may be optionally substituted.

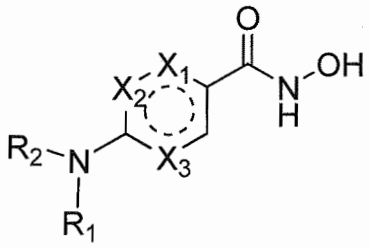
6. The compound of claim 5, wherein R_1 is substituted with 1-4 groups independently selected from optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, halo, haloalkyl, alkoxy, haloalkoxy, and nitro.

7. The compound of claim 6, wherein R_1 is substituted with 1-4 groups independently selected from methyl, phenyl, pyridyl, morpholino, indolyl, pyrazinyl, F, Cl, Br, methoxy, OCF_3, and trifluoromethyl; each of which may be further substituted.

8. The compound of claim 7, further substituted by alkyl, aryl, haloalkyl, haloalkoxy, halo, or alkoxy.

9. The compound of claim 4, wherein R_2 is H.

10. The compound of claim 1, of formula II:



(II);

or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein,

each of X_1, X_2, or X_3, is independently N or CR', wherein 2 of X_1, X_2, or X_3 are N;

R_2 is H, an optionally substituted alkyl, an optionally substituted aryl or an optionally substituted heteroaryl;

R_1 is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, or carbocyclic, each of which may be optionally substituted; and

each R' is independently H, optionally substituted alkyl, optionally substituted aryl, or halo.

11. The compound of claim 10, wherein X_2 and X_3 are N.

12. The compound of claim 10, wherein R_2 is H, methyl, ethyl, propyl, i-propyl, butyl, s-butyl, t-butyl, pentyl, hexyl, heptyl, phenyl, pyridinyl, pyrimidinyl, or pyrazinyl; each of which may be optionally substituted.

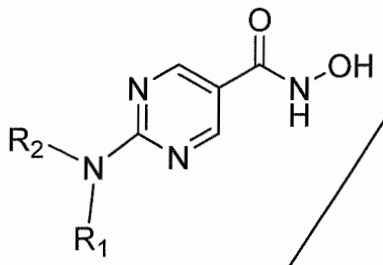
13. The compound of claim 12, wherein R_2 is substituted by 1-4 groups independently selected from optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aralkyl, alkoxyl, haloalkyl, halo, OH, NH_2, NHR", CN, N_3, and NO_2, and R" is H or alkyl.

14. The compound of claim 10, wherein R_1 is H, methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, hexyl, phenyl, naphthyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, benzyl, phenethyl, or pyridyl, each of which may be optionally substituted.

15. The compound of claim 14, wherein R_1 is substituted by 1-4 groups independently selected from optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aralkyl, alkoxyl, haloalkoxy, haloalkyl, halo, OH, NH_2, NHR", CN, N_3, and NO_2, and R" is H or alkyl.

16. The compound of claim 14, wherein R_2 is H.

17. The compound of claim 1, of formula III:



(III);

or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein,

R_2 is H, methyl, pyridyl, or phenyl, each of which may be optionally substituted;

R_1 is H, methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, benzyl, phenethyl, pyridyl, or phenyl, each of which may be optionally substituted.

18. The compound of claim 17, wherein R_2 is optionally substituted with 1-4 groups independently selected from optionally substituted aryl, optionally substituted heteroaryl, F, Cl, Br, methyl, ethyl, propyl, methoxy, and CF_3.

19. The compound of claim 17, wherein R_1 is optionally substituted with 1-4 groups independently selected from methyl, phenyl, pyridyl, morpholino, indolyl, pyrazinyl, F, Cl, Br, methoxy, OCF_3, trifluoromethyl, OH, NH_2, CN, and NO_2, each of which may be further substituted.

20. The compound of claim 19, further substituted by alkyl, aryl, haloalkyl, halo, or alkoxy.

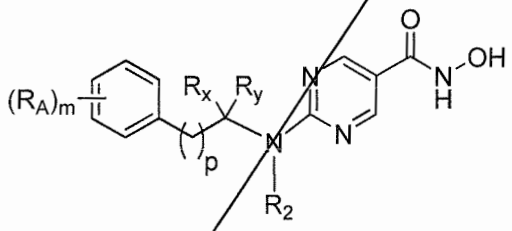
21. The compound of claim 17, wherein R_2 is H.

22. The compound of claim 17, wherein R_1 is phenyl or pyridyl, and R_2 is H or Me.

23. The compound of claim 22, wherein R_1 is further substituted with 1-4 substituents independently selected from alkyl, halo, alkoxy, haloalkyl, haloalkoxy, aryl, heteroaryl, carbocyclic, heterocyclic, and NO_2.

24. The compound of claim 23, wherein R_1 is further substituted with 1-4 substituents independently selected from methyl, F, Cl, OCH_3, CF_3, OCF_3, phenyl, pyridyl, morpholinyl, or NO_2.

25. The compound of claim 1, of formula IV:



(IV);

or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein,

R_2 is H, alkyl, haloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, carbocyclic, -$C(O)R_5$, or -$S(O)_pR_5$, each of which may be optionally substituted;

R_x is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, carbocyclic, -$C(O)R_5$, or -$S(O)_pR_5$; each of which may be optionally substituted;

R_y is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, carbocyclic, -$C(O)R_5$, or -$S(O)_pR_5$; each of which may be optionally substituted; or

R_x and R_y together with the carbon to which each is attached, forms a cycloalkyl or heterocycloalkyl, each of which is optionally substituted;

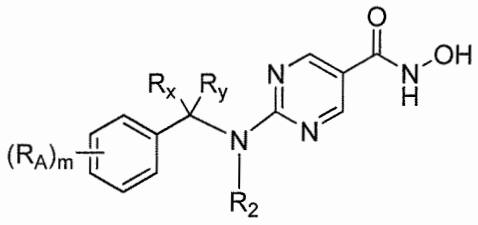
each R_A is independently alkyl, alkoxy, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, haloalkyl, haloalkoxy, halo, OH, -NO_2, -CN, or -NH_2; or two R_A

groups together with the atoms to which each is attached, can form an optionally substituted ring;

m is 0, 1, 2, 3, or 4; and

p is 0, 1, 2, or 3.

26. The compound of claim 1, of formula V:



(V);

or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein,

R_2 is H, alkyl, haloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, carbocyclic, -$C(O)R_5$, or -$S(O)_pR_5$, each of which may be optionally substituted;

R_x is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, carbocyclic, -$C(O)R_5$, or -$S(O)_pR_5$; each of which may be optionally substituted;

R_y is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, carbocyclic, -$C(O)R_5$, or -$S(O)_pR_5$; each of which may be optionally substituted; or

R_x and R_y together with the carbon to which each is attached, forms a cycloalkyl or heterocycloalkyl, each of which is optionally substituted;

each R_A is independently alkyl, alkoxy, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, haloalkyl, haloalkoxy, halo, OH, -NO_2, -CN, or -NH_2; or two R_A groups together with the atoms to which each is attached, can form an optionally substituted ring; and

m is 0, 1, 2, 3, or 4.

27. The compound of claim 26, wherein R_2 is H or Me.

28. The compound of claim 26, wherein R_x is H, alkyl, or aryl; and R_y is H or alkyl; each of which is optionally substituted.

~~29. The compound of claim 28, wherein R_x is H, methyl, ethyl, or phenyl.~~

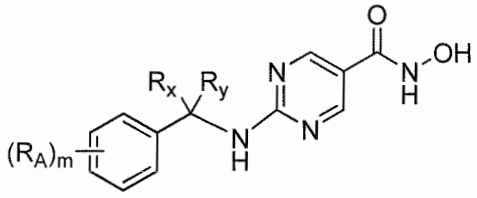
~~30. The compound of claim 28, wherein R_y is H, methyl or ethyl.~~

~~31. The compound of claim 26, wherein R_x and R_y together with the carbon to which each is attached, forms a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, each of which is optionally substituted.~~

~~32. The compound of claim 26, wherein R_x and R_y together with the carbon to which each is attached, forms tetrahydropyran, piperidine, piperazine, morpholine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, oxozolidine, or imidazolidine, each of which is optionally substituted.~~

~~33. The compound of claim 26, wherein R_A is H, alkyl, alkoxy, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, haloalkyl, haloalkoxy, halo, OH, $-NO_2$, -CN, or $-NH_2$, and m is 0 or 1.~~

~~34~~1. ~~The~~ A compound ~~of claim 26,~~ of formula VI:



(VI);

or a pharmaceutically acceptable salt~~,~~ or ester ~~or prodrug~~ thereof,

wherein,

R_x and R_y together with the carbon to which each is attached, forms a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydropyran, piperidine, piperazine, morpholine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, oxozolidine, or imidazolidine~~, each of which is optionally substituted~~;

each R_A is independently alkyl, alkoxy, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, haloalkyl, haloalkoxy, halo, OH, $-NO_2$, -CN, or $-NH_2$; ~~or two R_A groups together with the atoms to which each is attached, can form an optionally substituted ring;~~ and

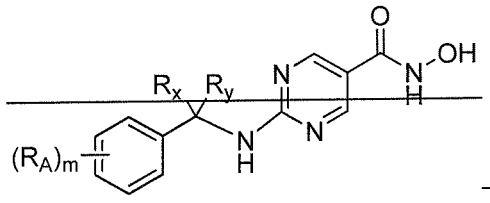
m is 0, 1, or 2.

~~35~~2. The compound of claim ~~34~~ 1, wherein R_x and R_y together with the carbon to which each is attached, forms a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or tetrahydropyran.

~~36~~. The compound of claim ~~34~~ 1, wherein m is 1 or 2, and each R_A is independently methyl, phenyl, F, Cl, methoxy, OCF_3, or CF_3~~; or two R_A groups together with the atoms to which each is attached, can form an optionally substituted cycloalkyl or heterocyclic ring~~.

~~37~~4. The compound of claim ~~36~~ 1, wherein m is 0.

~~38. The compound of claim 26, of formula VI:~~



~~(VI);~~

~~or a pharmaceutically acceptable salt, ester or prodrug thereof,~~

~~wherein,~~

~~R_x is H, alkyl, or aryl; each of which is optionally substituted;~~

~~R_y is H or alkyl; each of which is optionally substituted;~~

~~each R_A is independently alkyl, alkoxy, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, haloalkyl, haloalkoxy, halo, OH, NO_2, CN, or NH_2; and~~

~~m is 0, 1, or 2.~~

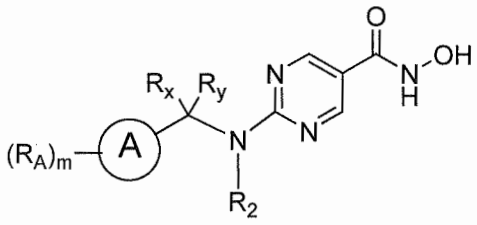
~~39. The compound of claim 38, wherein R_x is H, methyl, ethyl, or phenyl.~~

~~40. The compound of claim 38, wherein R_y is H, methyl or ethyl.~~

~~41. The compound of claim 38, wherein m is 1 or 2, and each R_A is independently methyl, phenyl, F, Cl, methoxyl, or CF_3; or two R_A groups together can form an optionally substituted cycloalkyl or heterocyclic ring.~~

~~42. The compound of claim 38, wherein m is 0.~~

43. The compound of claim 1, of formula VII-A:



(VII-A);

or a pharmaceutically acceptable salt, ester or prodrug thereof,

wherein,

ring A is a heteroaryl or heterocyclic;

R_2 is H, alkyl, haloalkyl, arylalkyl, aryl, heteroaryl, heterocyclic, carbocyclic, -$C(O)R_5$, or -$S(O)_pR_5$, each of which may be optionally substituted;

R_x is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, carbocyclic, -$C(O)R_5$, or -$S(O)_pR_5$; each of which may be optionally substituted;

R_y is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, carbocyclic, -$C(O)R_5$, or -$S(O)_pR_5$; each of which may be optionally substituted; or

R_x and R_y together with the carbon to which each is attached, forms a cycloalkyl or heterocycloalkyl, each of which is optionally substituted;

each R_A is independently alkyl, alkoxy, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, haloalkyl, haloalkoxy, halo, OH, -NO_2, -CN, or -NH_2; and

m is 0, 1, 2, 3, or 4.

44. The compound of claim 43, wherein ring A is acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl; 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl,

~~phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H* pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H* 1,2,5 thiadiazinyl, 1,2,3 thiadiazolyl, 1,2,4 thiadiazolyl, 1,2,5 thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3 triazolyl, 1,2,4 triazolyl, 1,2,5 triazolyl, 1,3,4 triazolyl, or xanthenyl.~~

~~45. The compound of claim 43, wherein R_2 is H or Me.~~

~~46. The compound of claim 43, wherein R_x is H, alkyl, aryl, or heteroaryl.~~

~~47. The compound of claim 43, wherein R_y is H, alkyl, aryl, or heteroaryl.~~

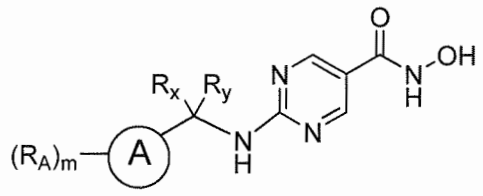
~~48. The compound of claim 43, wherein R_x is H, methyl or pyridine, and R_y is H.~~

~~49. The compound of claim 43, wherein R_x and R_y together with the carbon to which each is attached, forms a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, each of which is optionally substituted.~~

~~50. The compound of claim 49, wherein R_x and R_y together with the carbon to which each is attached, forms tetrahydropyran, piperidine, piperazine, morpholine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, oxozolidine, or imidazolidine, each of which is optionally substituted.~~

~~51. The compound of claim 43, wherein R_A is H, alkyl, alkoxy, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, haloalkyl, haloalkoxy, halo, OH, NO_2, CN, or NH_2, and m is 0 or 1.~~

52. ~~The~~ A compound ~~of claim 43,~~ of formula VIII:



(VIII);

or a pharmaceutically acceptable salt~~,~~ or ester ~~or prodrug~~ thereof,

wherein,

ring A is benzofuranyl, benzothiofuranyl, furanyl, imidazolinyl, imidazolyl, isoquinolinyl, morpholinyl, oxazolidinyl, pyrimidinyl, piperazinyl, piperidinyl, pyridinyl, pyridyl, pyrazinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiophenyl, or triazinyl;

R_x and R_y together with the carbon to which each is attached, forms a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydropyran, piperidine, piperazine, morpholine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, oxozolidine, or imidazolidine~~, each of which is optionally substituted~~;

each R_A is independently alkyl, alkoxy, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, arylalkyl, heteroarylalkyl, haloalkyl, haloalkoxy, halo, OH, $-NO_2$, -CN, or $-NH_2$; and

m is 0, 1, or 2.

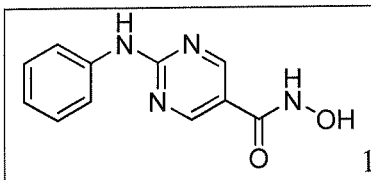
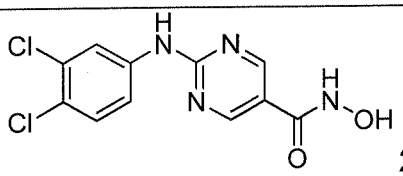
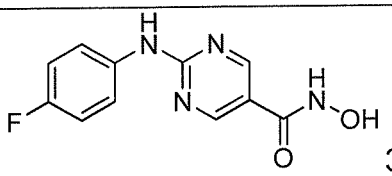
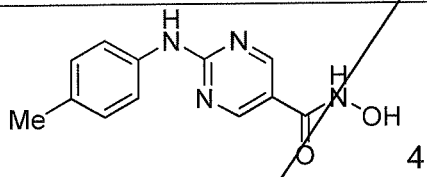
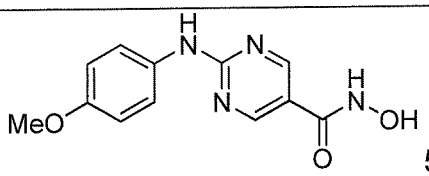
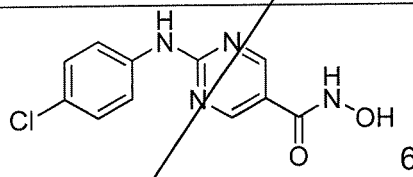
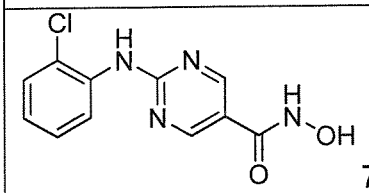
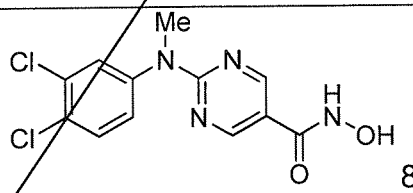
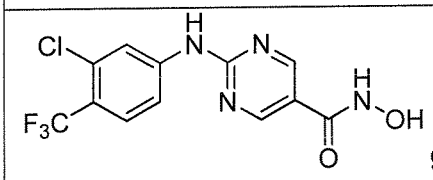
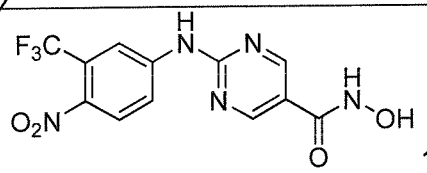
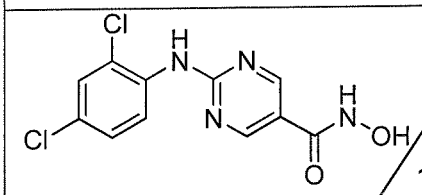
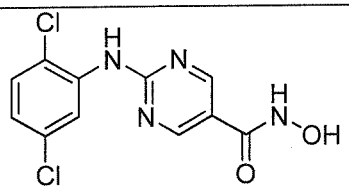
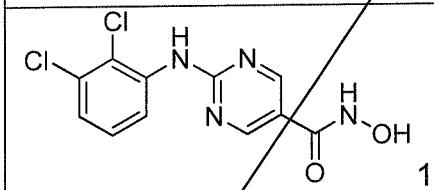
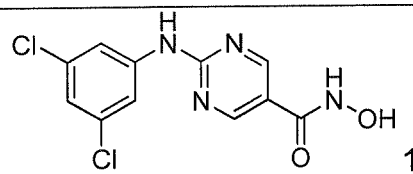
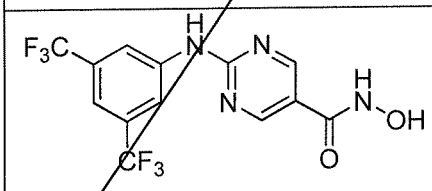
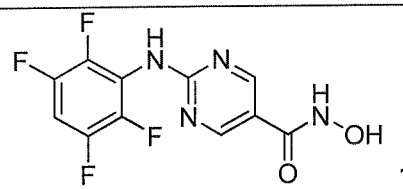
~~53~~6. The compound of claim ~~52~~, wherein ring A is benzofuranyl, benzothiofuranyl, furanyl, pyridyl, pyrazinyl, pyrimidinyl, or thiophenyl.

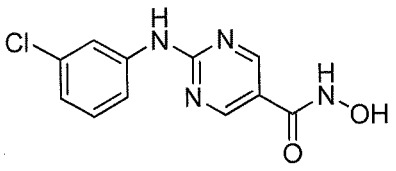
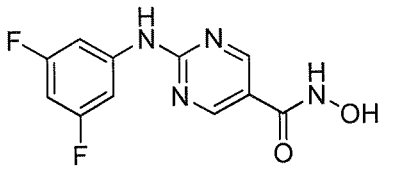
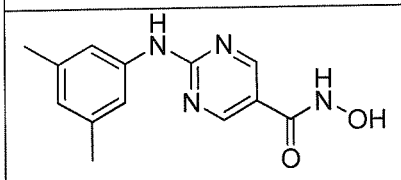
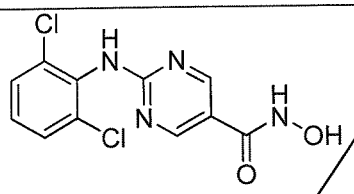
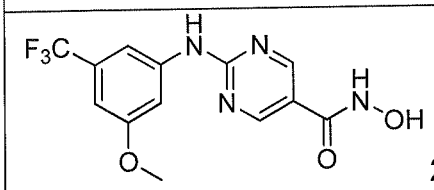
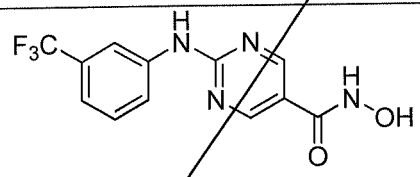
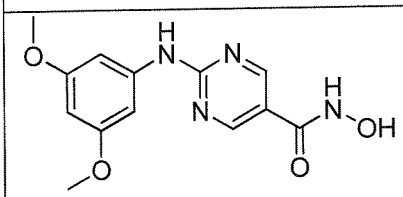
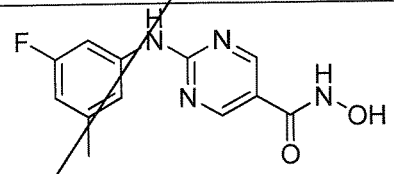
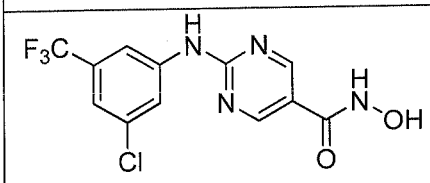
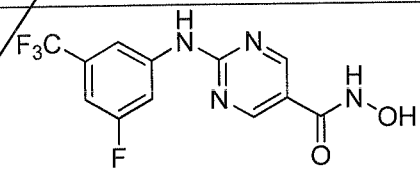
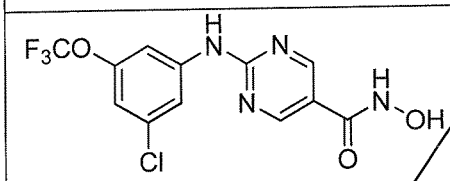
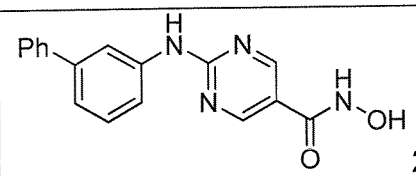
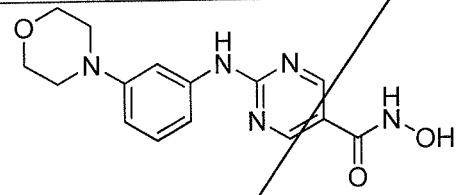
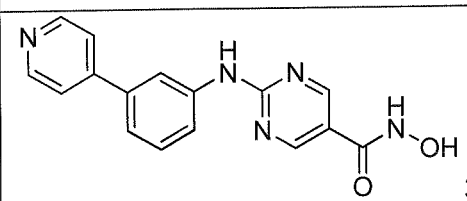
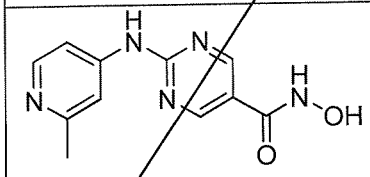
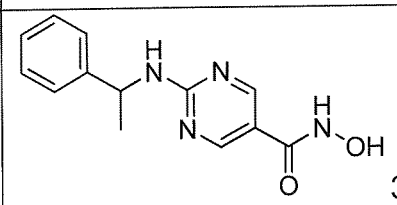
~~54~~7. The compound of claim ~~52~~, wherein R_x and R_y together with the carbon to which each is attached, forms a cyclopropyl, cyclopentyl, cyclohexyl, or tetrahydropyran.

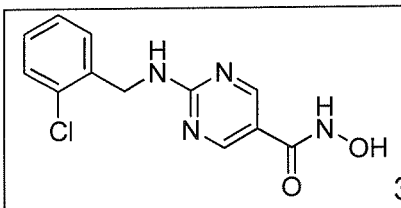
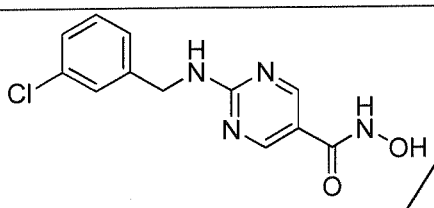
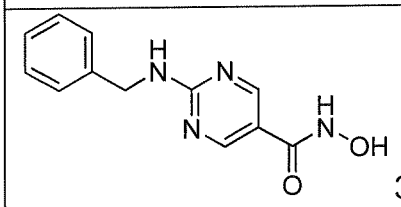
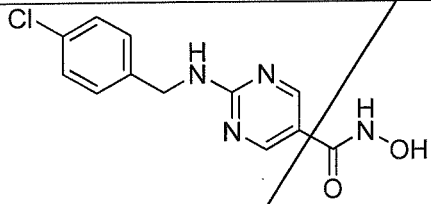
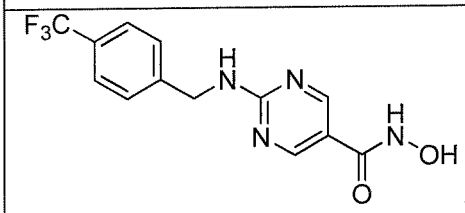
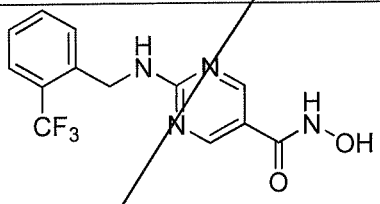
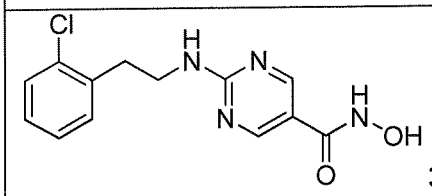
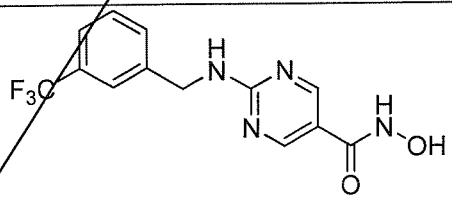
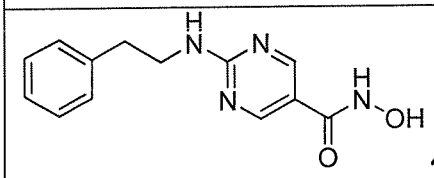
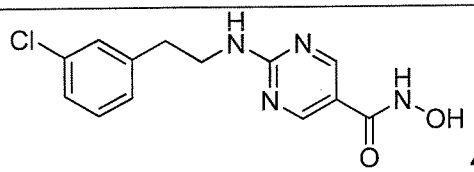
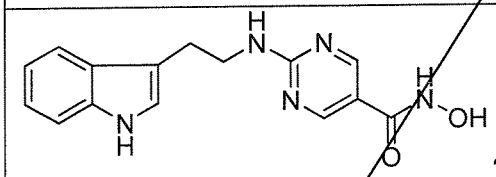
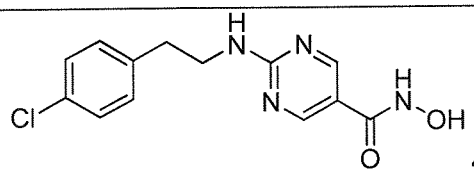
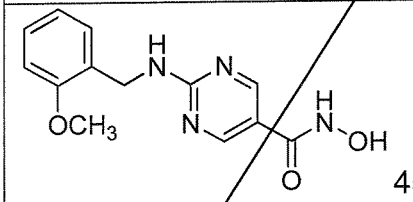
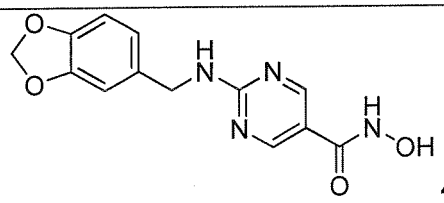
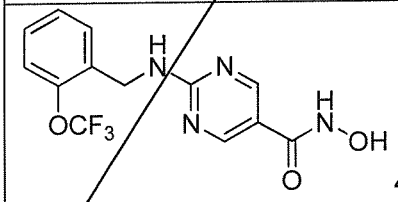
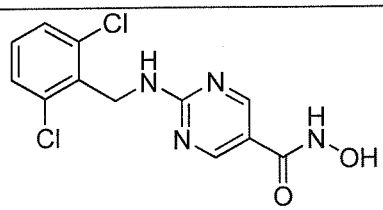
~~55~~8. The compound of claim ~~52~~, wherein m is 1, and R_A is F, Cl, methoxyl, or CF_3.

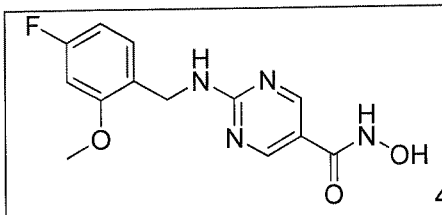
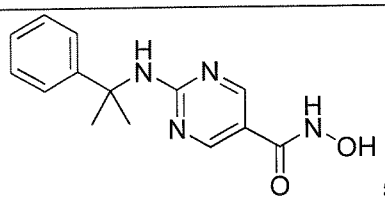
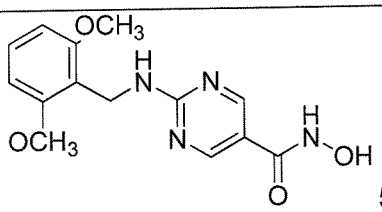
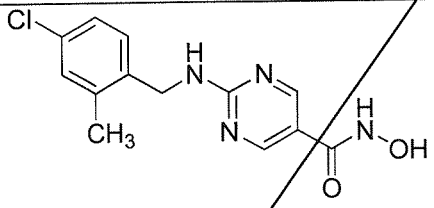
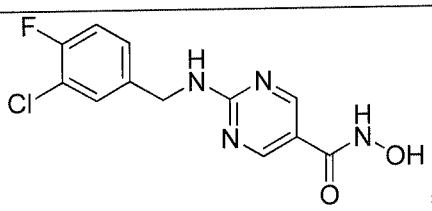
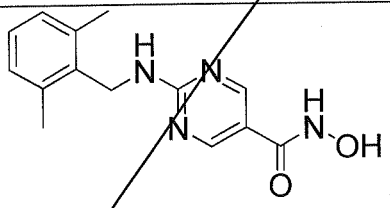
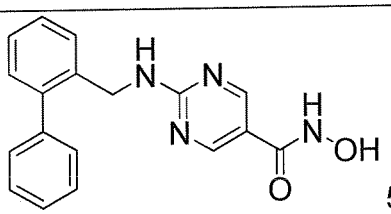
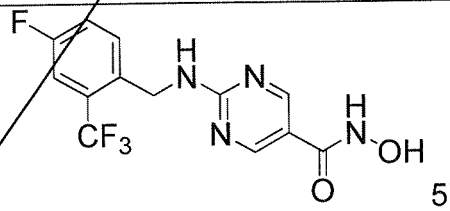
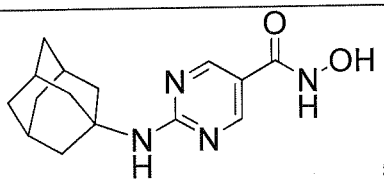
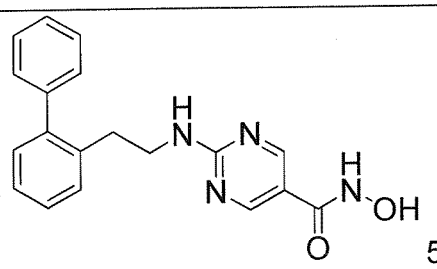
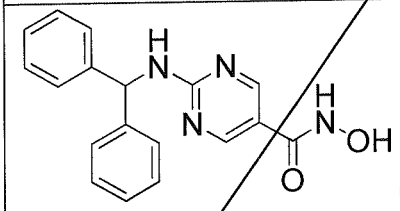
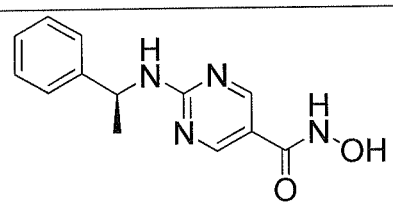
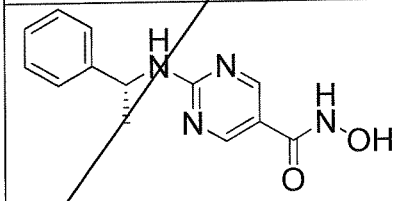
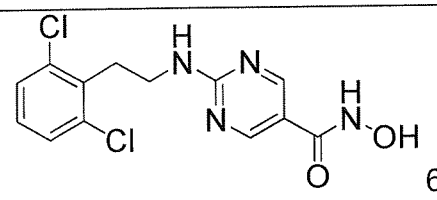
~~56~~9. The compound of claim ~~52~~, wherein m is 0.

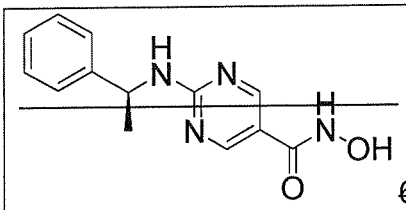
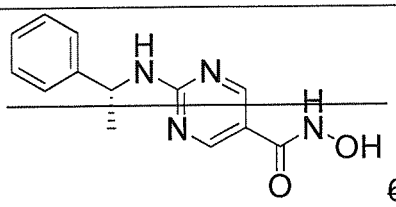
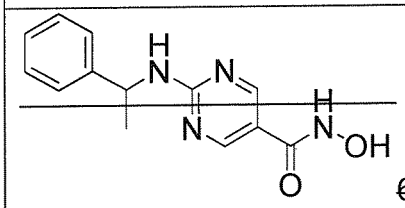
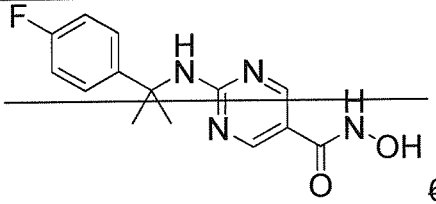
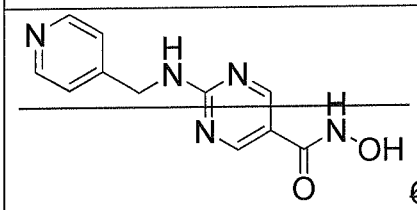
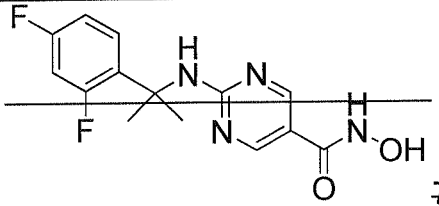
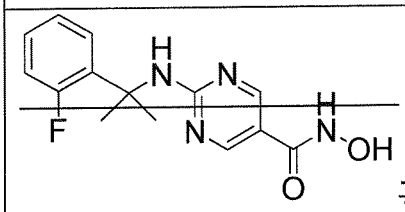
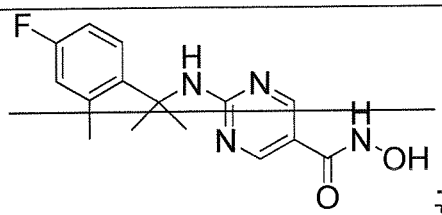
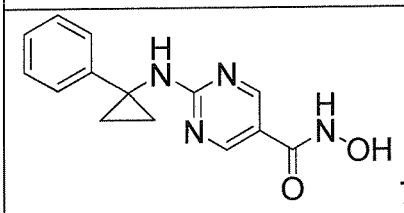
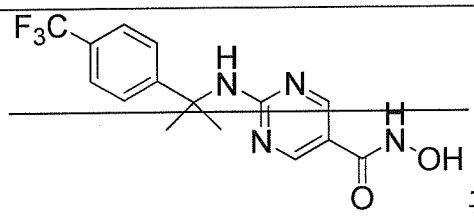
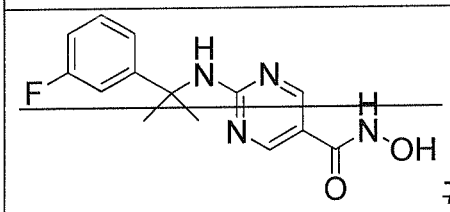
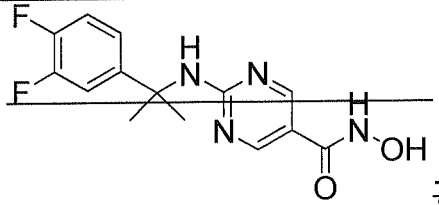
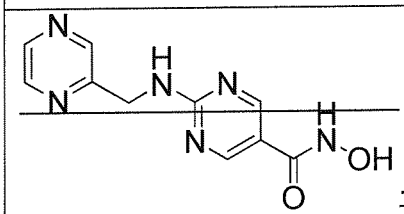
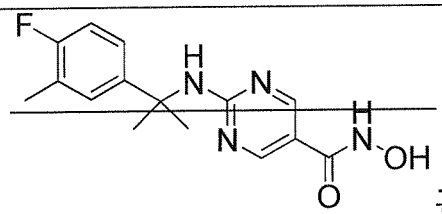
~~57~~10. The compound of claim 1, selected from the following:

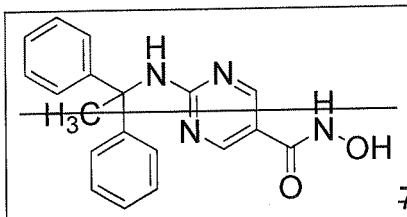
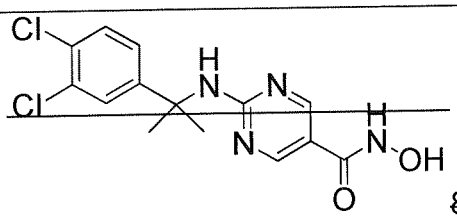
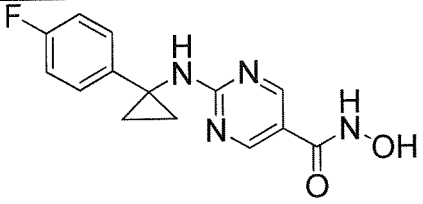
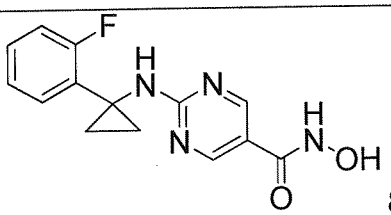
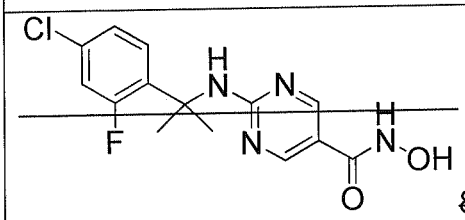
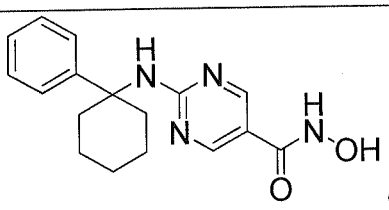
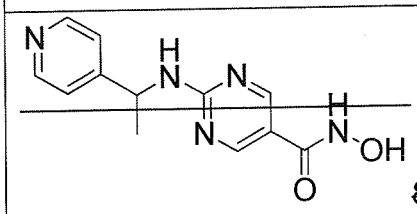
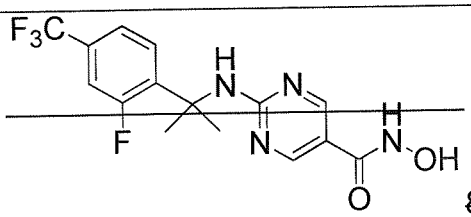
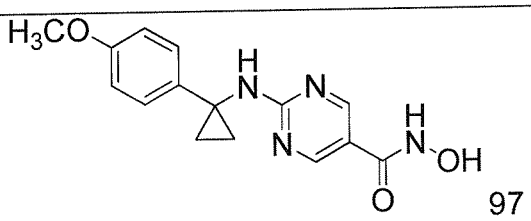
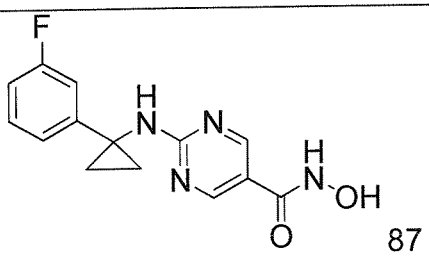
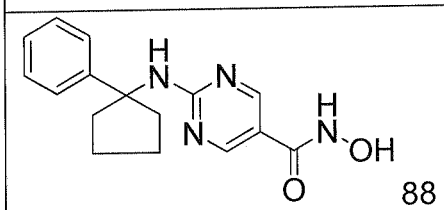
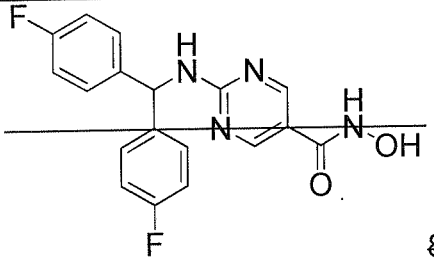
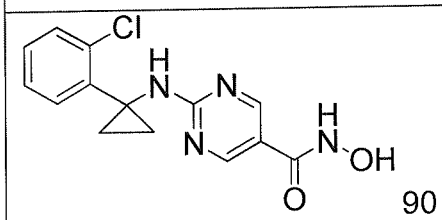
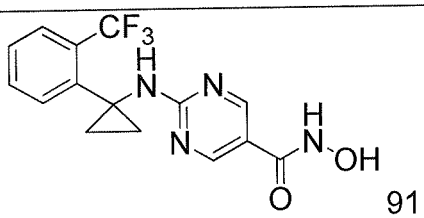
 1	 2
 3	 4
 5	 6
 7	 8
 9	 10
 11	 12
 13	 14
 15	 16

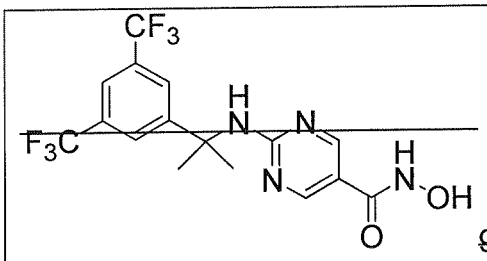
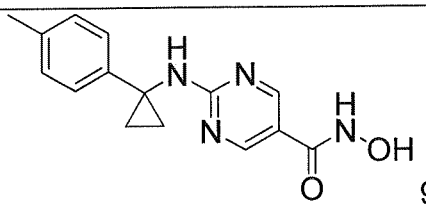
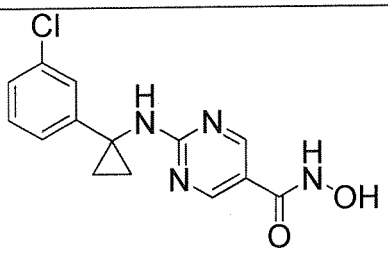
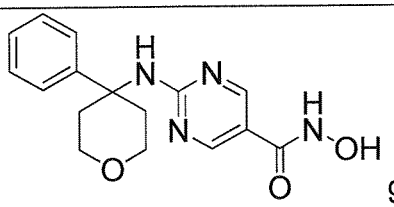
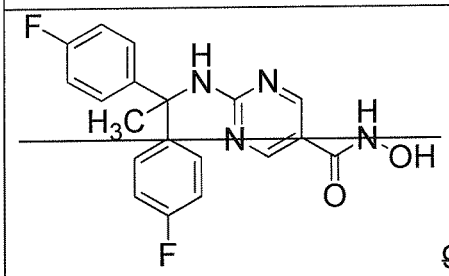
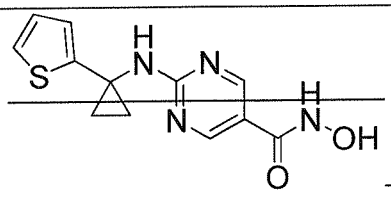
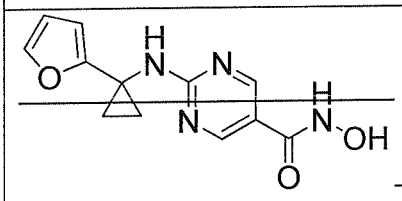
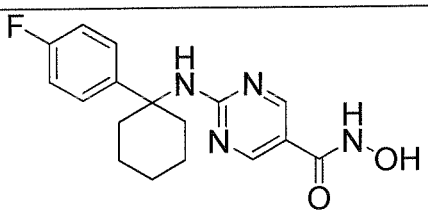
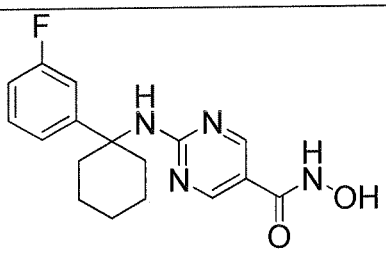
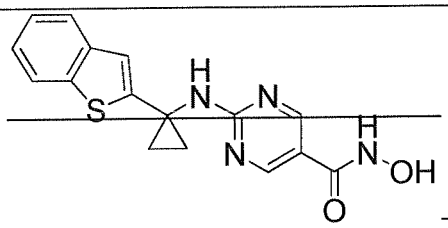
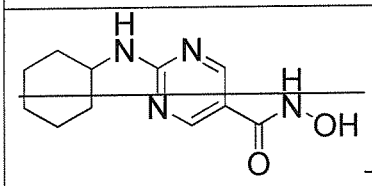
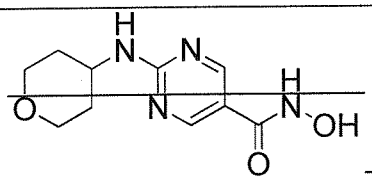
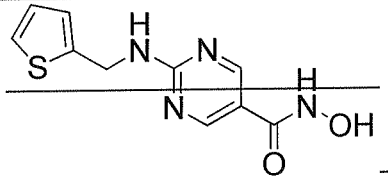
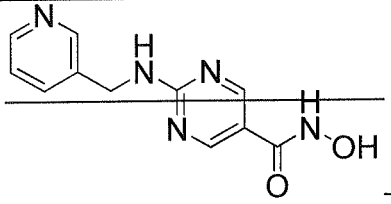
 17	 18
 19	 20
 21	 22
 23	 24
 25	 26
 27	 28
 29	 30
 31	 32

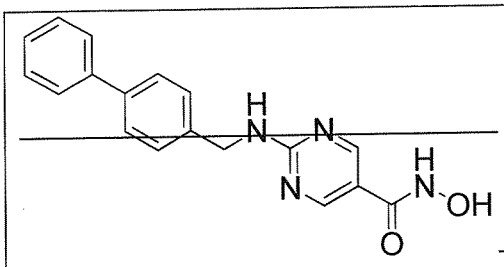
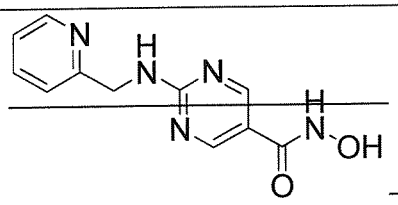
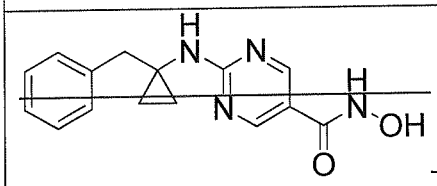
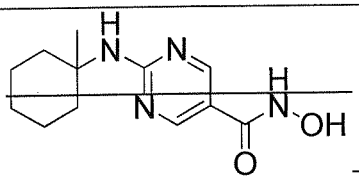
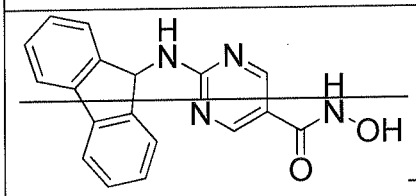
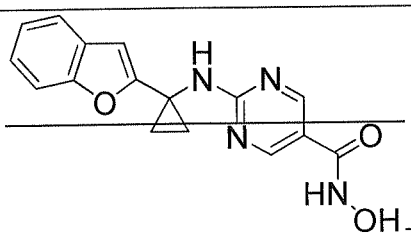
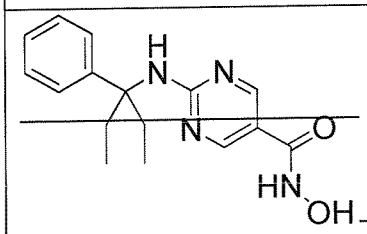
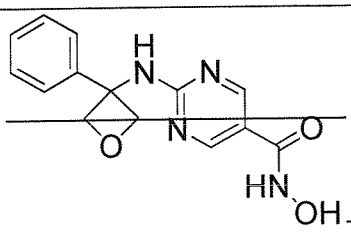
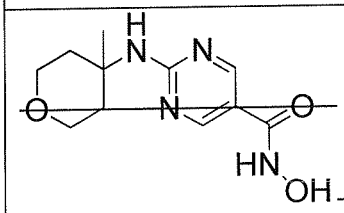
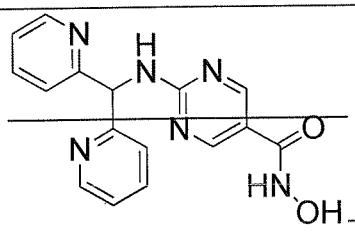
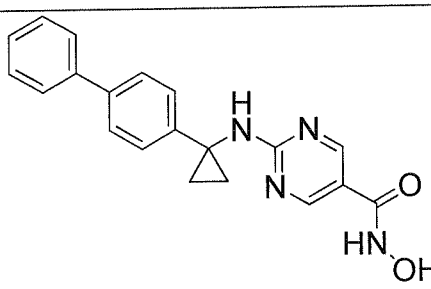
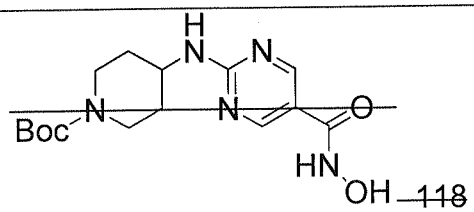
 33	 34
 35	 36
 37	 38
 39	 40
 41	 42
 43	 44
 45	 46
 47	 48

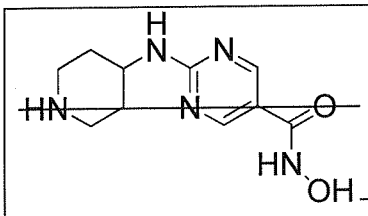
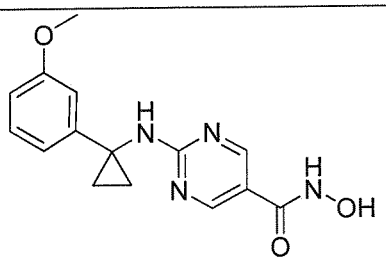
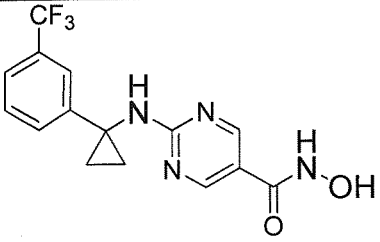
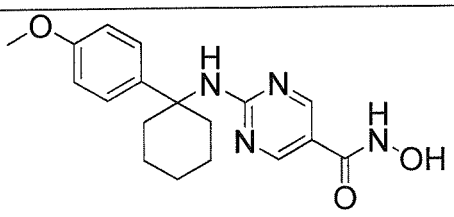
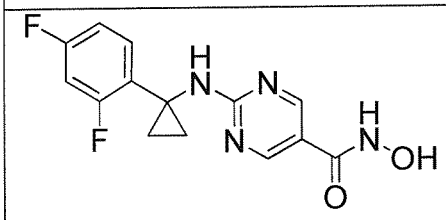
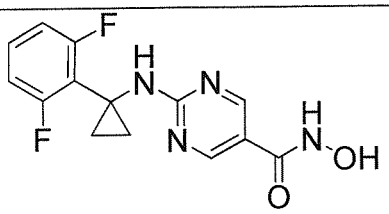
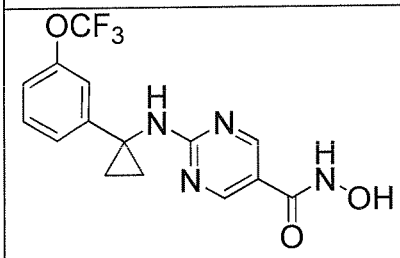
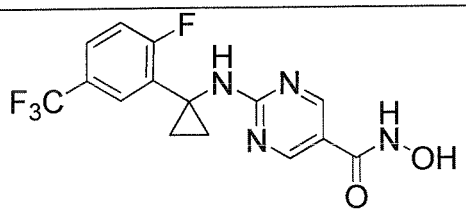
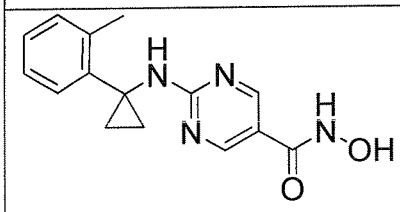
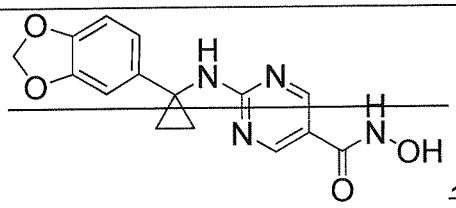
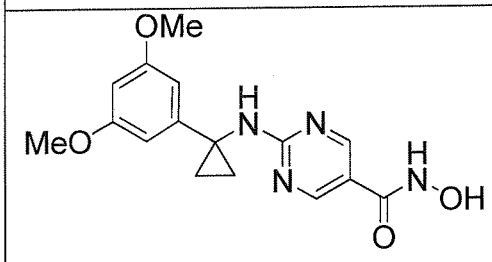
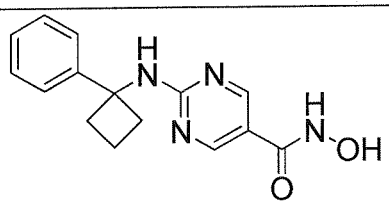
 49	 50
 51	 52
 53	 54
 55	 57
 58	 59
 60	 61
 62	 63

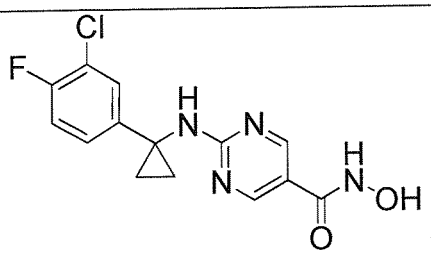
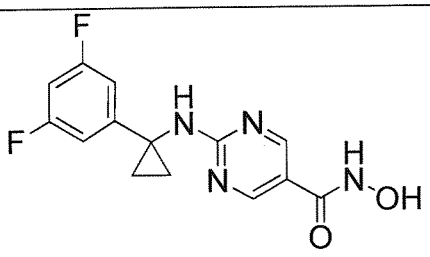
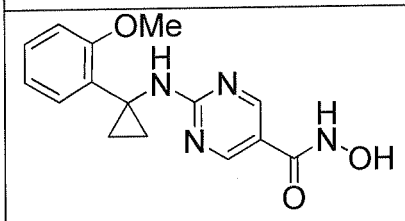
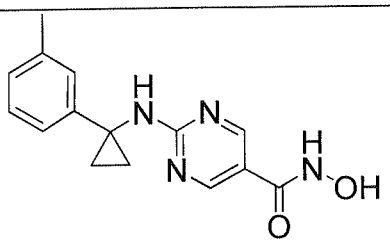
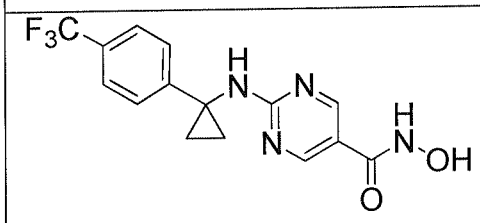
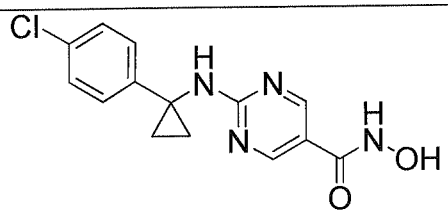
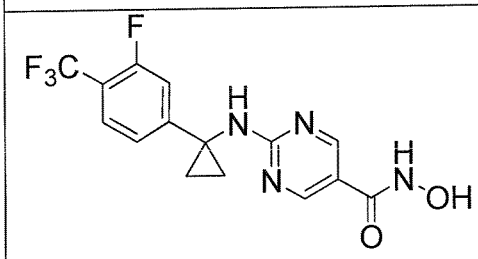
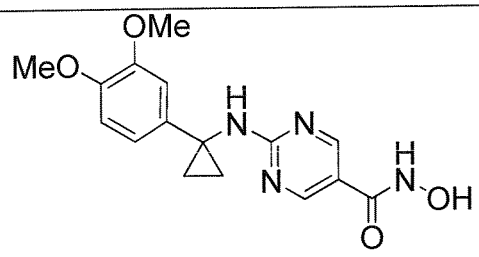
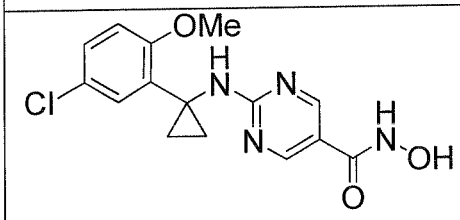
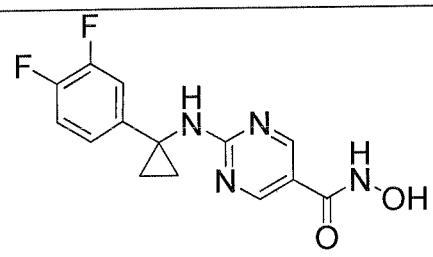
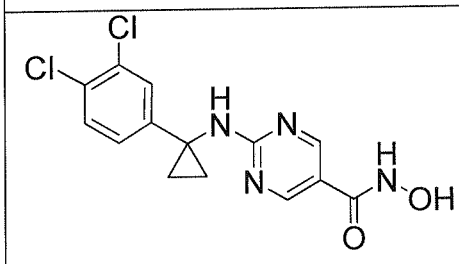
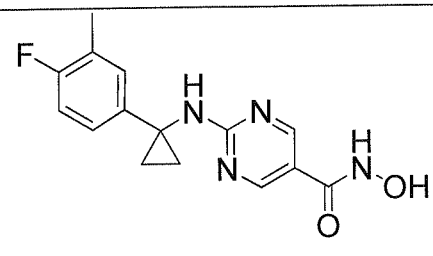
 65	 66
 67	 68
 69	 70
 71	 72
 73	 74
 75	 76
 77	 78

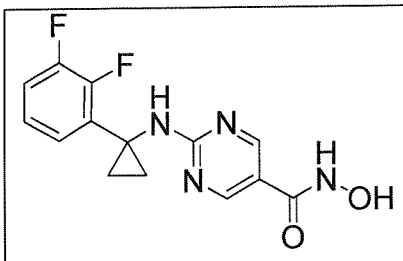
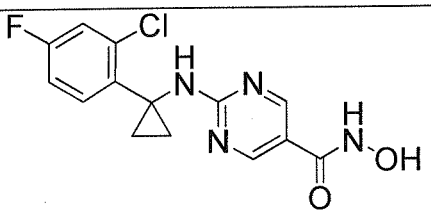
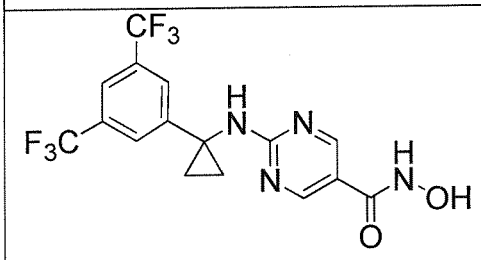
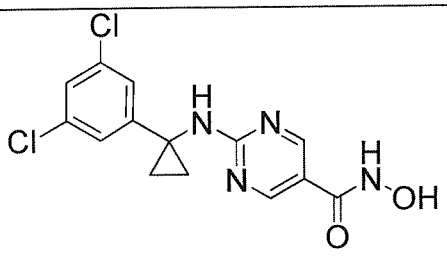
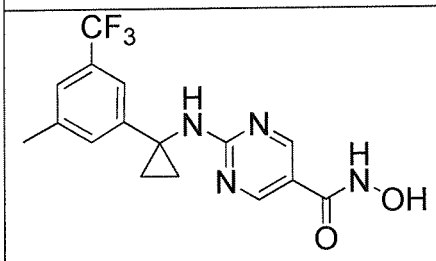
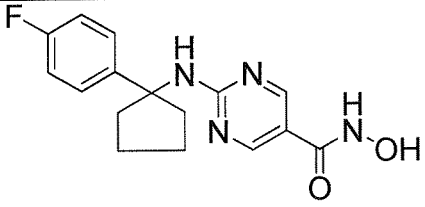
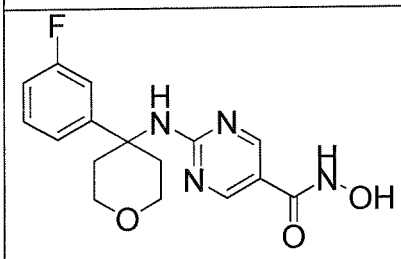
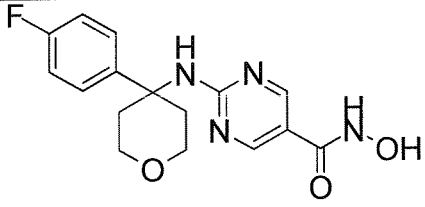
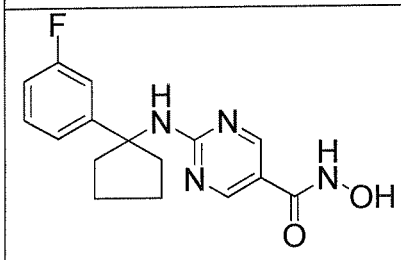
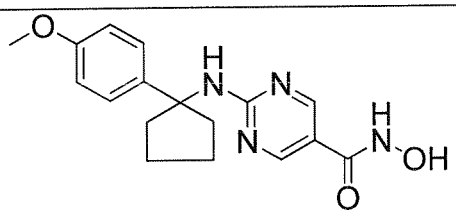
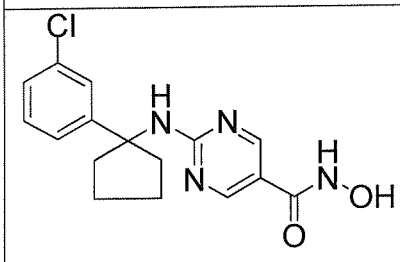
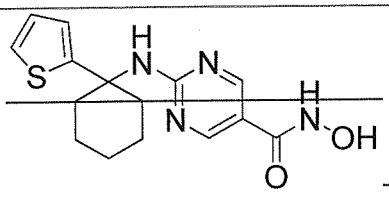
 79	 80
 81	 82
 83	 84
 85	 86
 97	 87
 88	 89
 90	 91

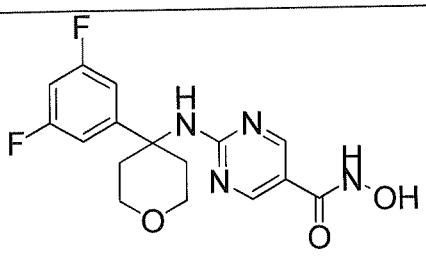
 92	 93
 94	 95
 96	 98
 99	 100
 101	 102
 103	 104
 105	 106

 107	 108
 109	 110
 111	 112
 113	 114
 115	 116
 117	 118

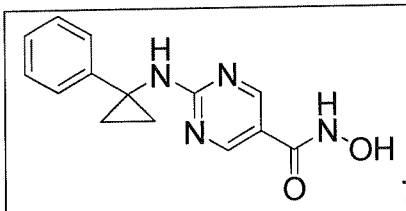
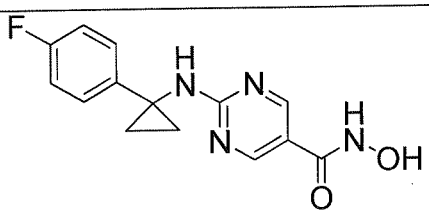
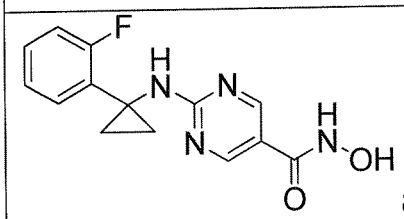
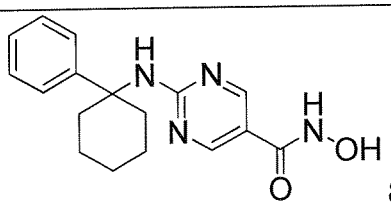
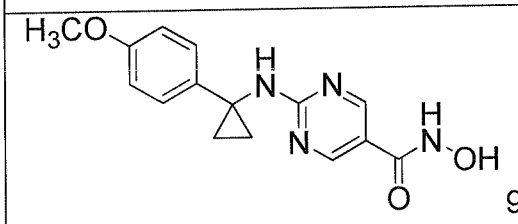
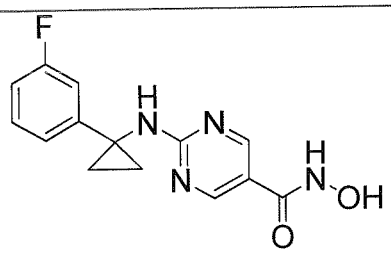
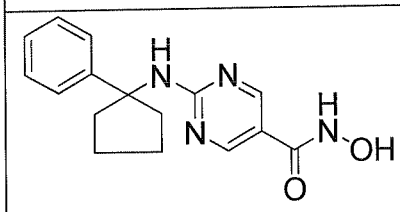
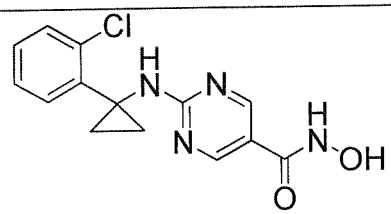
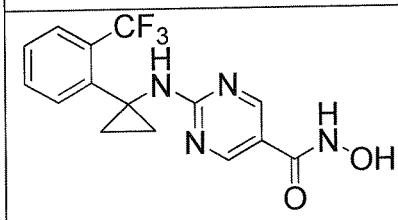
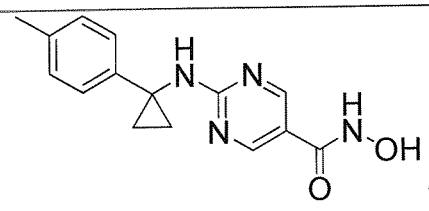
 ~~119~~	 120
 121	 122
 123	 124
 125	 126
 127	 ~~128~~
 129	 130

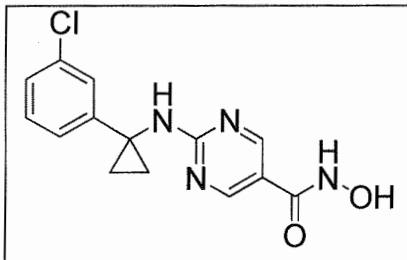
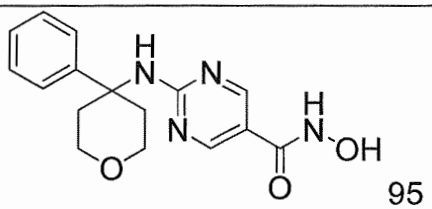
 131	 132
 133	 134
 135	 136
 137	 138
 139	 140
 141	 142

 143	 144
 145	 146
 147	 148
 149	 150
 151	 152
 153	 ~~154~~

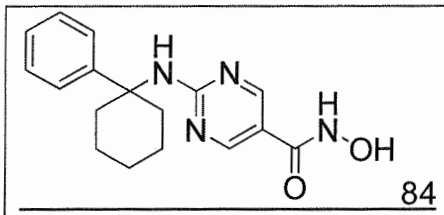
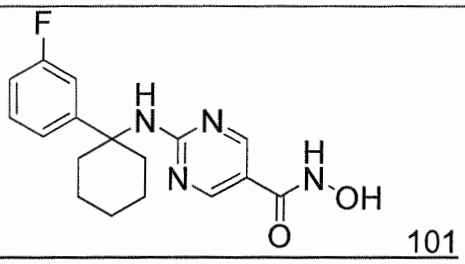
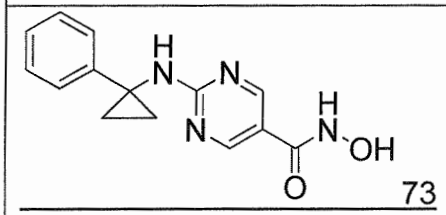
 155	

5811. The compound of claim ~~57~~ 10, selected from the following:

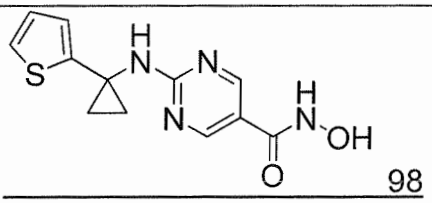
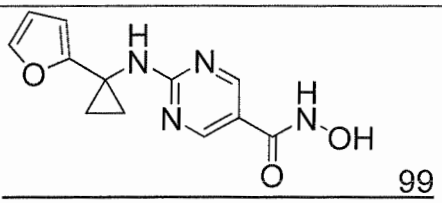
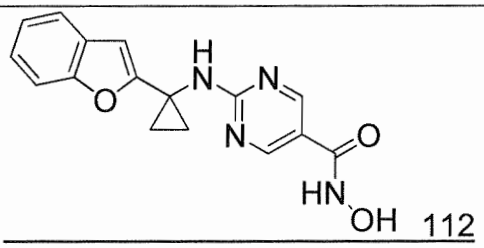
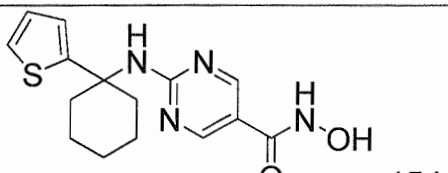
 73	 81
 82	 84
 97	 87
 88	 90
 91	 93

 94	 95

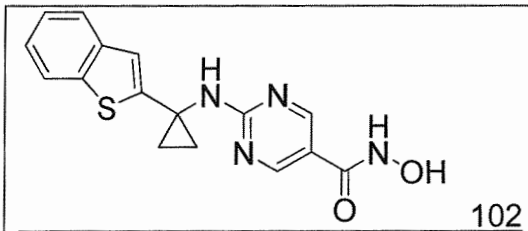
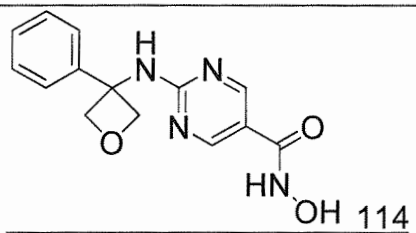
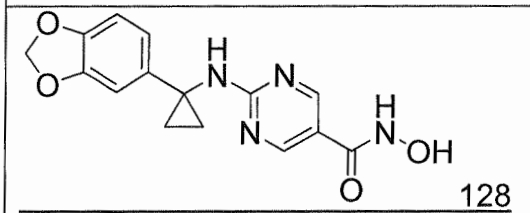
12. The compound of claim 10, selected from the following:

 84	 101
 73	

13. The compound of claim 5, selected from the following:

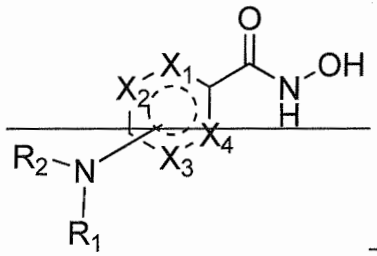
 98	 99
 112	 154

14. A compound selected from the following:

 102	 114
 128	

15~~9~~. A pharmaceutical composition comprising a compound of any one of claims 1-14, or a pharmaceutically acceptable ester~~,~~ or salt~~, or~~ prodrug thereof, together with a pharmaceutically acceptable carrier.

16~~0~~. Use of a compound of any one of claims 1-14, or a pharmaceutically acceptable ester or salt thereof, in the preparation of a medicament for selectively inhibiting HDAC6 over other HDACs in a subject. ~~A method of selectively inhibiting HDAC6 over other HDACs in a subject, comprising administering to the subject a compound of formula I:~~



~~(I);~~

~~or a pharmaceutically acceptable salt, ester or prodrug thereof,~~

~~wherein,~~

~~each of X_1, X_2, X_3, or X_4 is independently N or CR', wherein 2 of X_1, X_2, X_3, or X_4 are N;~~

~~each R' is independently H, optionally substituted alkyl, optionally substituted aryl, or halo;~~

~~R_1 is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, carbocyclic, $-C(O)R_5$, or $-S(O)_pR_5$; each of which may be optionally substituted; and~~

~~R_2 is H, alkyl, haloalkyl, alkenyl, arylalkyl, aryl, heteroaryl, heterocyclic, carbocyclic, $-C(O)R_5$, or $-S(O)_pR_5$, each of which may be optionally substituted;~~

~~p is 0, 1, or 2;~~

~~each R_5 is independently H; optionally substituted alkyl, optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl;~~

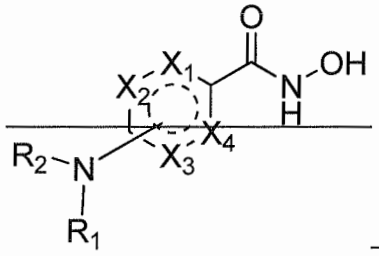
~~wherein R_1 and R_2 are both not simultaneously H.~~

~~6~~17. The ~~method~~ use of claim 16~~0~~, wherein the compound of ~~formula I~~ any one of claims 1-14, or a pharmaceutically acceptable ester or salt thereof has a selectivity for HDAC6 of 5 to 1000 fold over HDAC1, HDAC2, and/or HDAC3.

~~62~~18. The ~~method~~ use of claim ~~6~~17, wherein the compound of ~~formula I~~ any one of claims 1-14, or a pharmaceutically acceptable ester or salt thereof has a selectivity for HDAC6 when tested in a HDAC enzyme assay of about 5 to 1000 fold over HDAC1, HDAC2, and/or HDAC3.

~~63~~19. The ~~method~~ use of claim ~~61~~17 or ~~62~~ 18, wherein the compound has a selectivity for HDAC6 of 15 to 40 fold over HDAC1, HDAC2, and/or HDAC3.

~~64~~20. A compound of any one of claims 1-14, or a pharmaceutically acceptable ester or salt thereof, for use in medicine. ~~A method of treating a disease mediated by HDAC6 in a subject comprising administering to the subject a compound of formula I:~~



~~(I);~~

~~or a pharmaceutically acceptable salt, ester or prodrug thereof,~~

~~wherein,~~

~~each of X_1, X_2, X_3, or X_4 is independently N or CR', wherein 2 of X_1, X_2, X_3, or X_4 are N;~~

~~each R' is independently H, optionally substituted alkyl, optionally substituted aryl, or halo;~~

~~R_1 is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, carbocyclic, $C(O)R_5$, or $S(O)_pR_5$; each of which may be optionally substituted; and~~

~~R_2 is H, alkyl, haloalkyl, alkenyl, arylalkyl, aryl, heteroaryl, heterocyclic, carbocyclic, $C(O)R_5$, or $S(O)_pR_5$, each of which may be optionally substituted;~~

~~p is 0, 1, or 2;~~

~~each R_5 is independently H; optionally substituted alkyl, optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl;~~

~~wherein R_1 and R_2 are both not simultaneously H.~~

21. A compound of any one of claims 1-14, or a pharmaceutically acceptable ester or salt thereof, for use in the preparation of a medicament to treat a disease.

~~65~~22. The ~~method~~ use of claim ~~64~~ 21, wherein the disease is cancer or a proliferation disease.

~~66~~23. The ~~method~~ use of claim ~~65~~ 22, wherein the disease is lung cancer, colon cancer, breast cancer, prostate cancer, liver cancer, brain cancer, kidney cancer, ovarian cancer, stomach cancer, skin cancer, bone cancer, gastric cancer, pancreatic cancer, glioma, gliobastoma, hepatocellular carcinoma, papillary renal carcinoma, head and neck squamous cell carcinoma, leukemias, lymphomas, myelomas, and solid tumors.

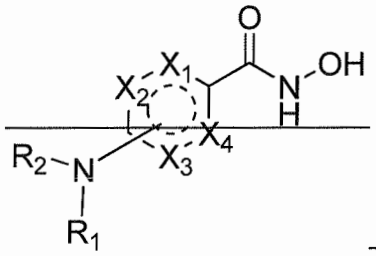
~~67~~24. The ~~method~~ use of claim ~~66~~ 23, wherein the cancer is multiple myeloma.

~~68~~25. The ~~method~~ use of claim ~~64~~ 21, wherein the disease is Wilson's disease, spinocerebellar ataxia, prion disease, Parkinson's disease, Huntington's disease, amytrophic lateral sclerosis, amyloidosis, Alzheimer's disease, Alexander's disease, alcoholic liver disease, cystic fibrosis, Pick's Disease, spinal muscular dystrophy or Lewy body dementia.

~~69~~26. The ~~method~~ use of claim ~~64~~ 21, wherein the disease is rheumatoid arthritis, osteoarthritis; rheumatoid spondylitis; psoriasis; post ischemic perfusion injury; inflammatory bowel disease; chronic inflammatory pulmonary disease, eczema, asthma, psoriasis,

ischemia/reperfusion injury, ulcerative colitis, acute respiratory distress syndrome, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis and spondylitis, glomerulonephritis, hemolytic anemia, aplasic anemia, idiopathic thrombocytopenia, neutropenia, ulcerative colitis, Crohn's disease, host versus graft disease, graft versus host disease, allograft rejection, chronic thyroiditis, Graves' disease, schleroderma, diabetes, active hepatitis, primary binary cirrhosis, myasthenia gravis, multiple sclerosis (MS), systemic lupus erythematosus, atopic dermatitis, contact dermatitis, skin sunburns, chronic renal insufficiency, Stevens-Johnson syndrome, idiopathic sprue, sarcoidosis, Guillain-Barre syndrome, uveitis, conjunctivitis, keratoconjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, or silicosis.

27~~0~~. A ~~method~~ compound of any one of claims 1-14, or a pharmaceutically acceptable ester or salt thereof, for use in the preparation of a medicament to treat~~ing~~ a subject suffering from or susceptible to multiple myeloma. ~~comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I:~~



~~(I);~~

~~or a pharmaceutically acceptable salt, ester or prodrug thereof,~~

~~wherein,~~

~~each of X_1, X_2, X_3, or X_4 is independently N or CR', wherein 2 of X_1, X_2, X_3, or X_4 are N;~~

~~each R' is independently H, optionally substituted alkyl, optionally substituted aryl, or halo;~~

~~R_1 is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, carbocyclic, $-C(O)R_5$, or $-S(O)_pR_5$; each of which may be optionally substituted; and~~

~~R_2 is H, alkyl, haloalkyl, alkenyl, arylalkyl, aryl, heteroaryl, heterocyclic, carbocyclic, $-C(O)R_5$, or $-S(O)_pR_5$, each of which may be optionally substituted;~~

~~p is 0, 1, or 2;~~

~~each R_5 is independently H; optionally substituted alkyl, optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl;~~

~~wherein R1 and R2 are both not simultaneously H;~~

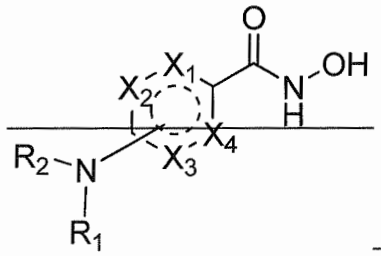
~~to thereby treat the subject suffering from or susceptible to multiple myeloma.~~

~~71~~28. The ~~method~~ use of claim 27~~0~~, wherein the use further ~~comprising~~comprises co-administering one or more of a chemotherapeutic agent, radiation agent, hormonal agent, biological agent or an anti-inflammatory agent to the subject.

~~72~~9. The ~~method~~ use of claim ~~71~~ 28, wherein the chemotherapeutic agent is tamoxifen, trastuzamab, raloxifene, doxorubicin, fluorouracil/5-fu, pamidronate disodium, anastrozole, exemestane, cyclophosphamide, epirubicin, letrozole, toremifene, fulvestrant, fluoxymesterone, trastuzumab, methotrexate, megastrol acetate, docetaxel, paclitaxel, testolactone, aziridine, vinblastine, capecitabine, goselerin acetate, zoledronic acid, taxol, vinblastine, or vincristine.

~~73. The method of any one of claims 60-72, wherein the subject is a human.~~

~~74. A kit comprising a compound capable of inhibiting HDAC activity selected from one or more compounds of formula I:~~



~~(I);~~

~~or a pharmaceutically acceptable salt, ester or prodrug thereof,~~

~~wherein,~~

~~each of X_1, X_2, X_3, or X_4 is independently N or CR', wherein 2 of X_1, X_2, X_3, or X_4 are N;~~

~~each R' is independently H, optionally substituted alkyl, optionally substituted aryl, or halo;~~

~~R_1 is H, alkyl, haloalkyl, alkenyl, aryl, arylalkyl, heteroarylalkyl, heteroaryl, heterocyclic, carbocyclic, $-C(O)R_5$, or $-S(O)_pR_5$; each of which may be optionally substituted;~~ and

~~R_2 is H, alkyl, haloalkyl, alkenyl, arylalkyl, aryl, heteroaryl, heterocyclic, carbocyclic, $-C(O)R_5$, or $-S(O)_pR_5$, each of which may be optionally substituted;~~

~~p is 0, 1, or 2;~~

~~each R_5 is independently H; optionally substituted alkyl, optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl;~~

~~wherein R1 and R2 are both not simultaneously H;~~

~~and instructions for use in treating multiple myeloma.~~