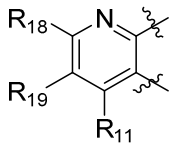
or a pharmaceutically acceptable salt thereof, wherein:

Y is O;

ring A is  and X is N or CH, wherein

R_{18} and R_{19} are each independently selected from halo, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, (C_6-C_{10}) aryl, (C_3-C_{10}) cycloalkyl, 4-14 membered heterocycloalkyl, phenyl, 5-14 membered heteroaryl, -CN, -NO_2, -OR^a, -SR^a, -C(O)R^a, -C(O)NR^aR^a, -C(O)OR^a, -NHR^a, -NR^aR^a, and -$NR^aC(O)R^a$, wherein the (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, (C_6-C_{10}) aryl, (C_3-C_{10}) cycloalkyl, 4-14 membered heterocycloalkyl, phenyl, and 5-14 membered heteroaryl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, (C_1-C_6) alkyl, -CN, and -OH; or

R_{10} and R_{11} are H;

 is optionally substituted with one, two, three, or four groups independently selected from the group consisting of halo, and C_1-C_6 alkyl, wherein "〰" indicate points of attachment;

R_5 and R_6 are each independently selected from the group consisting of H, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_6 heterocycloalkyl, and optionally substituted C_1-C_6 cycloalkyl;

Y is O, S, SO, SO_2, NH, or N-(C_1-C_6 alkyl); and

m and n are each independently 1 or 2.

[00010] In one aspect, the disclosure includes a pharmaceutical composition comprising a compound described herein, and a pharmaceutically acceptable carrier or excipient.

[00011] In another example, the disclosure includes a method of treating a disease, disorder, or syndrome mediated at least in part by modulating in vivo activity of a protein kinase, comprising administering to a subject in need thereof a therapeutically effective amount of a compound described herein, or a pharmaceutical composition thereof.

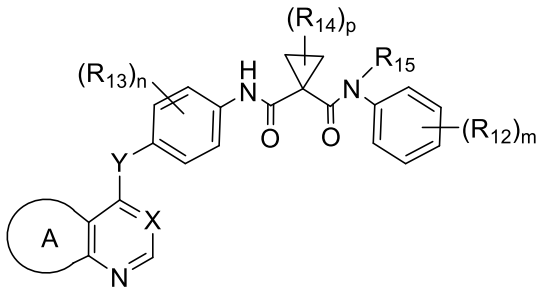
Detailed Description of the Invention

[00012] Abbreviations and Definitions

[00013] The following abbreviations and terms have the indicated meanings throughout:

Claims

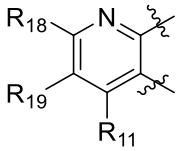
1. A compound of Formula I':



(I')

or a pharmaceutically acceptable salt thereof, wherein:

Y is O;

ring A is  and X is N or CH, wherein

R_{18} and R_{19} are each independently selected from halo, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, (C_6-C_{10}) aryl, (C_3-C_{10}) cycloalkyl, 4-14 membered heterocycloalkyl, phenyl, 5-14 membered heteroaryl, -CN, -NO_2, -OR^a, -SR^a, -C(O)R^a, -C(O)NR^aR^a, -C(O)OR^a, -NHR^a, -NR^aR^a, and -$NR^aC(O)R^a$, wherein the (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, (C_6-C_{10}) aryl, (C_3-C_{10}) cycloalkyl, 4-14 membered heterocycloalkyl, phenyl, and 5-14 membered heteroaryl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from halo, (C_1-C_6) alkyl, -CN, and -OH; or

R_{10} and R_{11} are H;

each R_{13} is independently selected from the group consisting of -H; halo; -OH; -CN; optionally substituted (C_1-C_6) alkyl; (C_1-C_6) alkoxy; (C_1-C_6) haloalkoxy; -NH_2; --NH(C_1-C_6)alkyl; -N(C_1-C_6 alkyl)$_2$; and (C_3-C_6) cycloalkyl;

each R_{14} is independently selected from the group consisting of H, halo, and (C_1-C_6) alkyl

R_{15} is H;

each R_{12} is independently selected from the group consisting of -H and halo;

each R^a is independently selected from the group consisting of -H, (C_1-C_6) alkyl, (C_3-C_{10}) cycloalkyl, 4-14 membered heterocycloalkyl, and (4-14 membered heterocycloalkyl)-(C_1-C_4) alkylene-, wherein the (C_1-C_6) alkyl, (C_3-C_{10}) cycloalkyl, 4-14 membered heterocycloalkyl, and

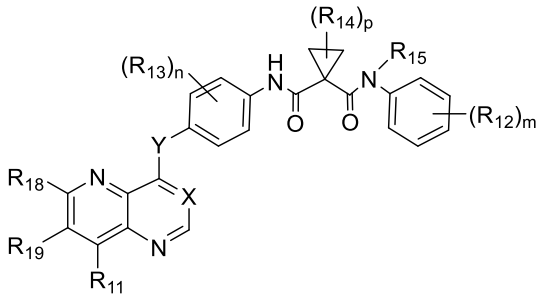
(4-14 membered heterocycloalkyl)-(C_1-C_4) alkylene- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from (C_1-C_6) alkyl, (C_1-C_6) alkoxy, and -C(O)O(C_1-C_4) alkyl;

the subscript n is an integer of 1, 2, 3, or 4;

the subscript m is an integer of 1, 2, 3, 4, or 5; and

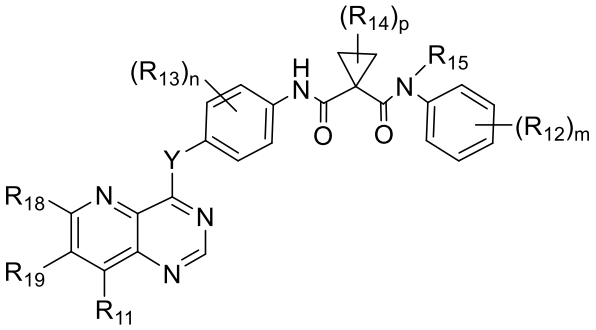
the subscript p is an integer of 0, 1, 2, 3, or 4.

2. The compound of claim 1, having Formula I'b:



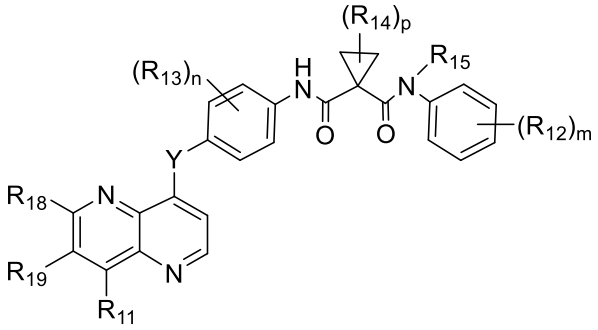
(I'b).

3. The compound of claim 1 or 2, having Formula (I'b-1):



(I'b-1).

4. The compound of claim 1 or 2, having Formula (I'b-2):



(I'b-2).

5. The compound of any of claims 1-4, wherein R_{18} and R_{19} are each independently selected from halo, (C_1-C_6) alkyl, phenyl, (C_3-C_{10}) cycloalkyl, 4-14 membered heterocycloalkyl, 5-14 membered heteroaryl, -CN, -O(C_1-C_6) alkyl, -C(O)(C_1-C_6) alkyl, -C(O)NH_2, -C(O)NH(C_1-C_6) alkyl, -C(O)N((C_1-C_6) alkyl)$_2$, -C(O)O(C_1-C_6) alkyl, -NH(C_1-C_6) alkyl, -N((C_1-C_6) alkyl)$_2$, -NHC(O)(C_1-C_6) alkyl, -O(C_1-C_4 alkylene-(4-14 membered heterocycloalkyl)), and –NH_2

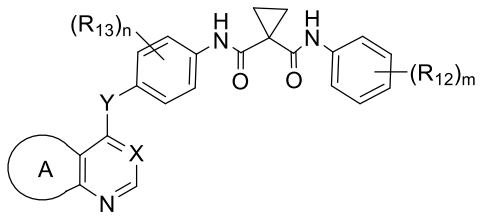
6. The compound of any of claims 1-4, wherein R_{18} and R_{19} are each independently halo, CN, R^aNHC(O)-, –OR^a or 5- or 6-membered heteroaryl optionally substituted with (C_1-C_6) alkyl.

7. The compound of any of claims 1-6, wherein the subscript m is 1.

8. The compound of any of claims 1-6, wherein the subscript n is 1.

9. The compound of any of claims 1-6, wherein the subscript p is 1.

10. The compound of claim 1, having Formula I:



I

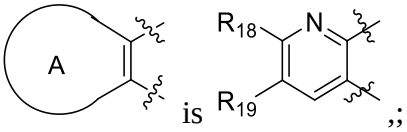
wherein:

X is selected from N and C-H;

Y is O;

R_{13} is selected from –H, halo, -CN, and optionally substituted $C_{1\text{-}6}$ alkyl;

R_{12} is -H or halo;



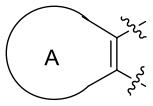
is ,;

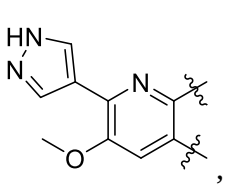
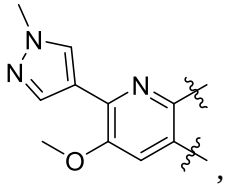
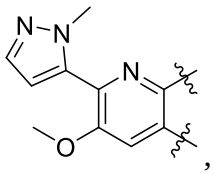
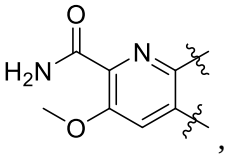
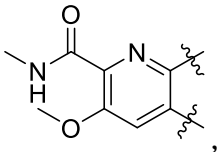
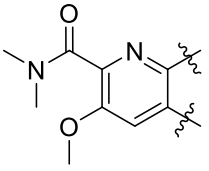
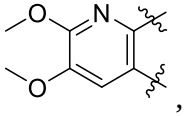
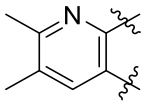
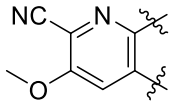
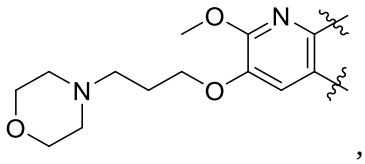
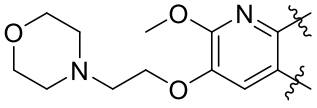
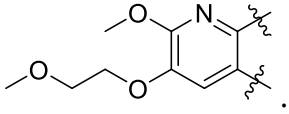
wherein R_{18} and R_{19} are selected from the group consisting of halo, -CN, optionally substituted C_1-C_6 alkyl, $C(O)NR_5R_6$, optionally substituted 5 or 6-membered heteroaryl, and optionally substituted C_1-C_6 alkoxy; or

R_5 and R_6 are selected from the group consisting of H, optionally substituted $C_{1\text{-}6}$ alkyl; and

m and n are each independently 1 or 2.

11. The compound of claim 10, wherein R_{19} is selected from the group consisting of optionally substituted C_1-C_6 alkoxy and –CN.

12. The compound of claims 1-2, wherein 

is 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, or 
.

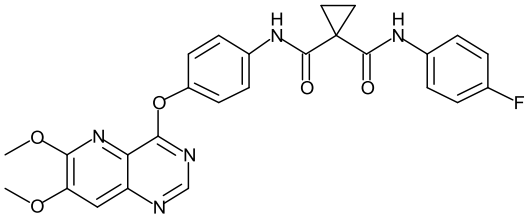
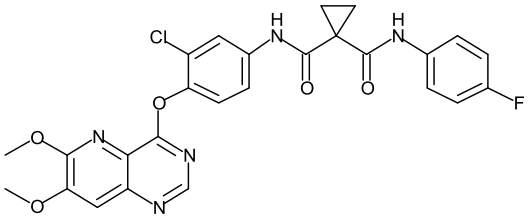
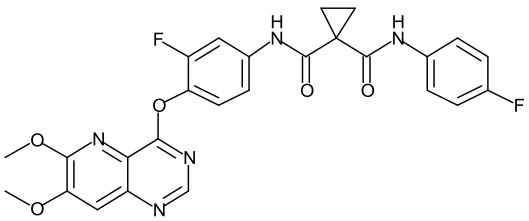
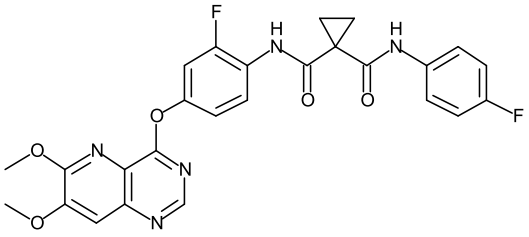
13. The compound of any of claims 10-12, wherein X is N.

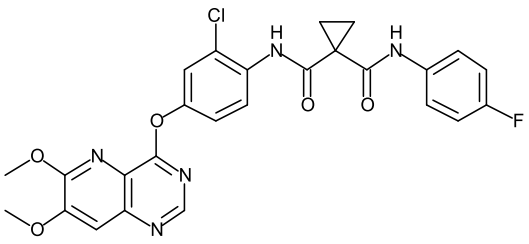
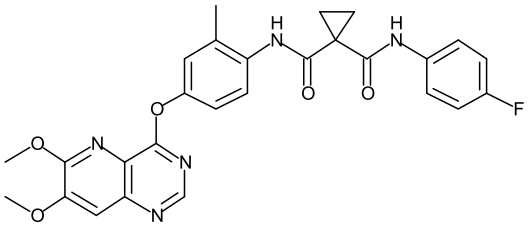
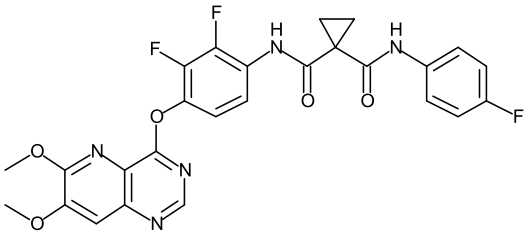
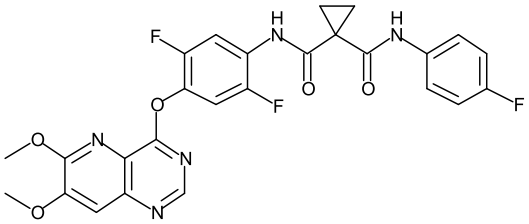
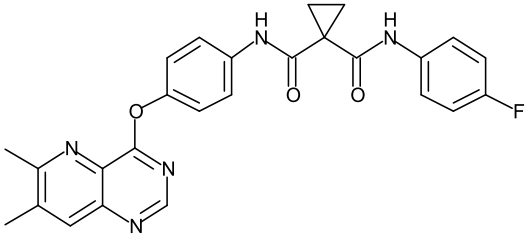
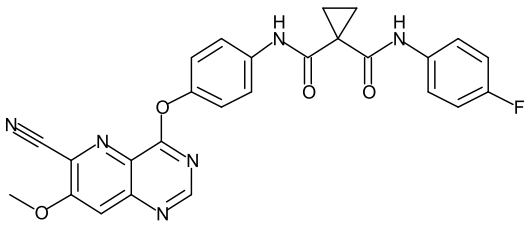
14. The compound of any of claims 10-13, wherein R_{13} is H.

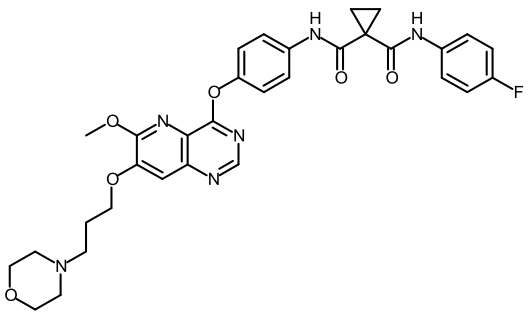
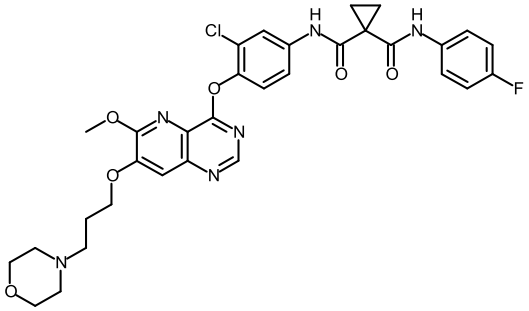
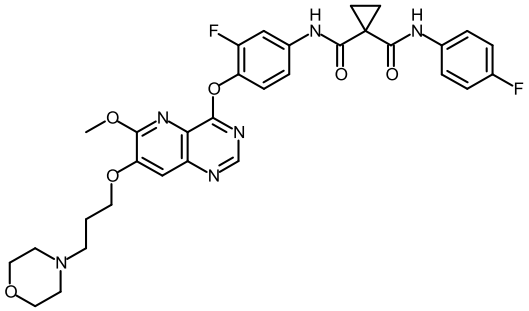
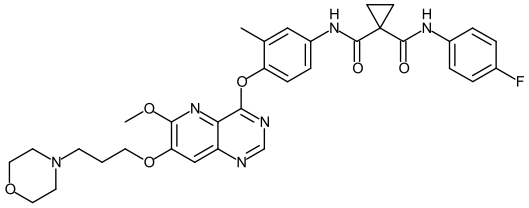
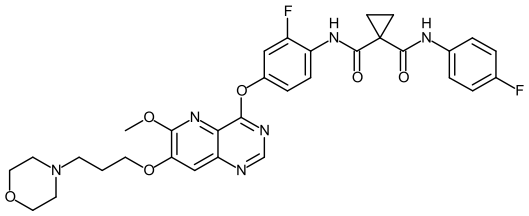
15. The compound of any of claims 10-14, wherein R_{12} is halo.

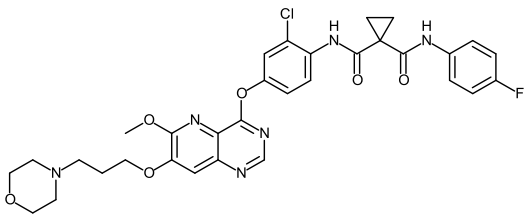
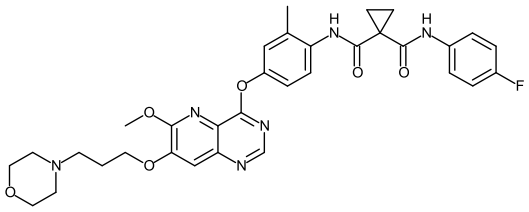
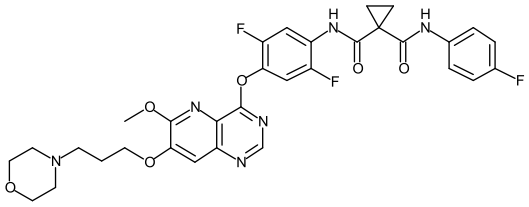
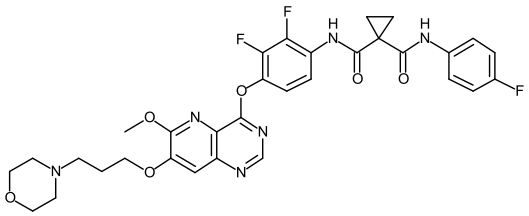
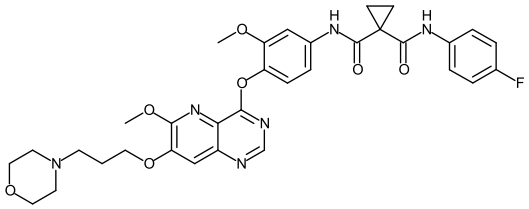
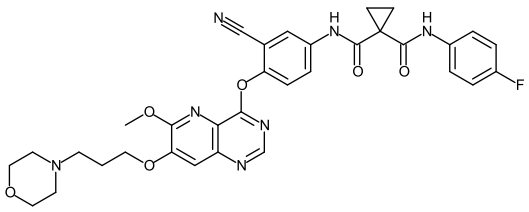
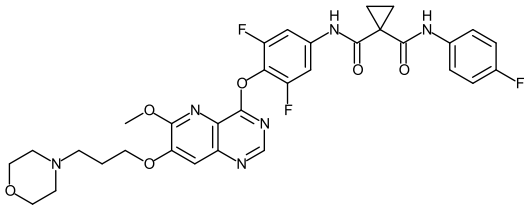
16. The compound of any of claims 10-15, wherein R_{12} is para fluoro.

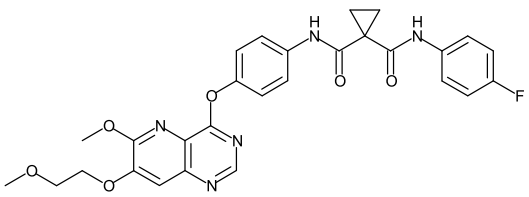
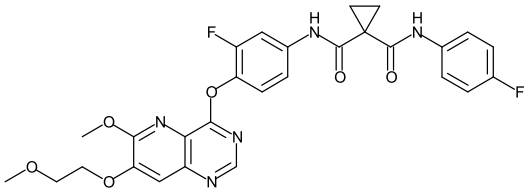
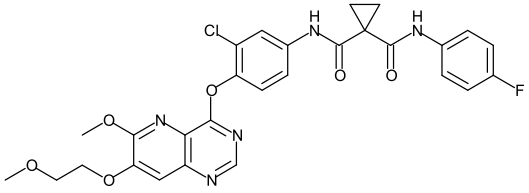
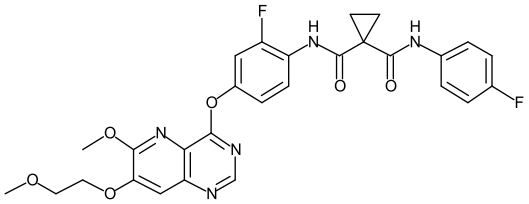
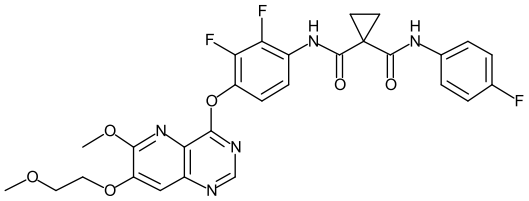
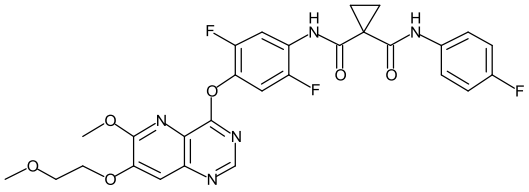
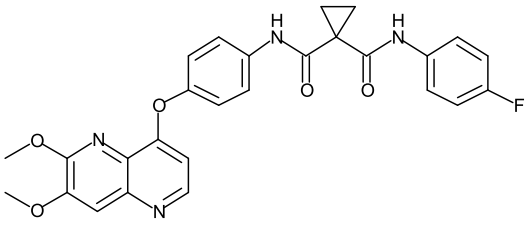
17. The compound of claim 1, wherein the compound is selected from:

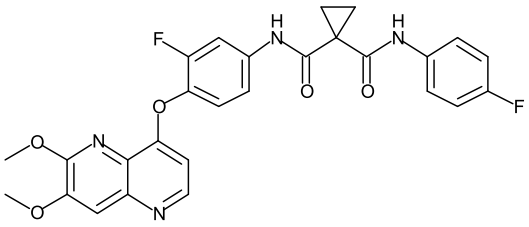
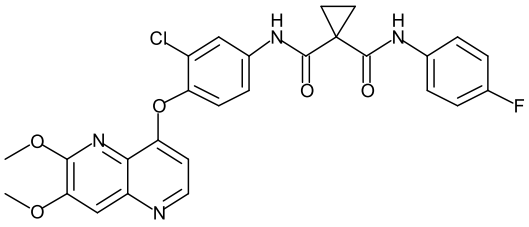
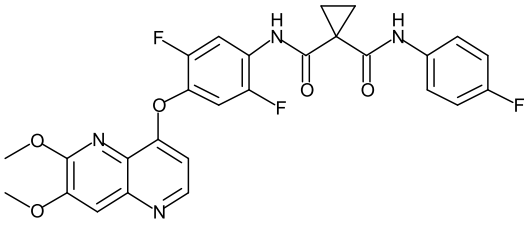
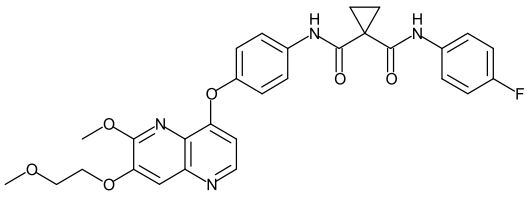
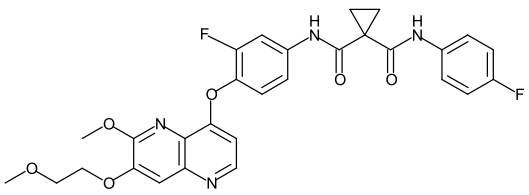
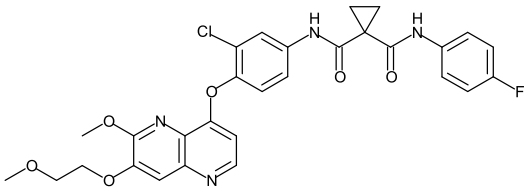
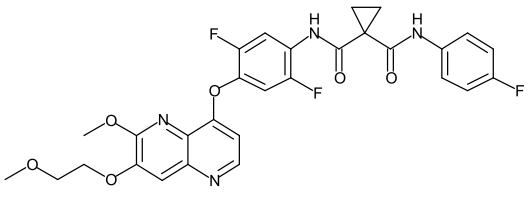
Comp.	Structure	IUPAC Name
28		1-N-[4-(6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
29		1-N'-[3-chloro-4-(6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
30		1-N'-[4-(6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy-3-fluorophenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
31		1-N'-[4-(6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy-2-fluorophenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

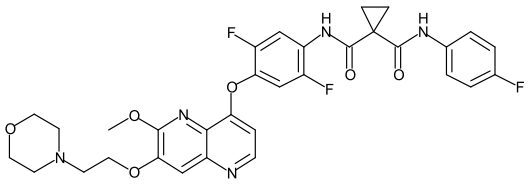
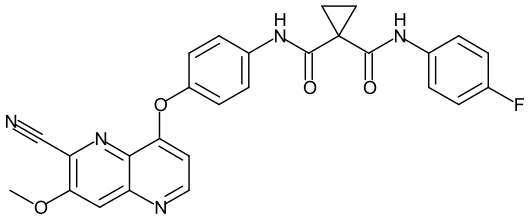
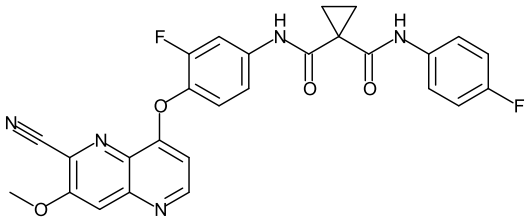
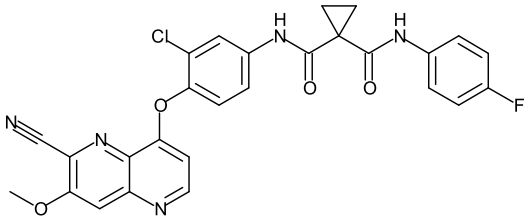
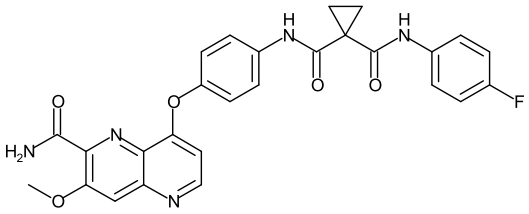
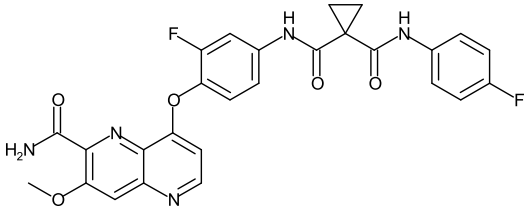
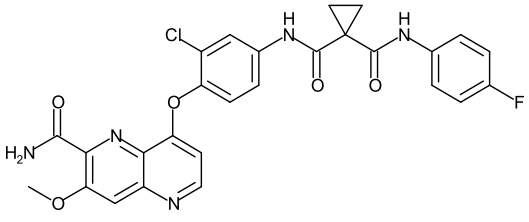
32		1-N'-[2-chloro-4-(6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
33		1-N'-[4-(6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy-2-methylphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
34		1-N'-[4-(6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy-2,3-difluorophenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
35		1-N'-[4-(6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy-2,5-difluorophenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
43		1-N-[4-(6,7-dimethylpyrido[3,2-d]pyrimidin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
57		1-N-[4-(6-cyano-7-methoxypyrido[3,2-d]pyrimidin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

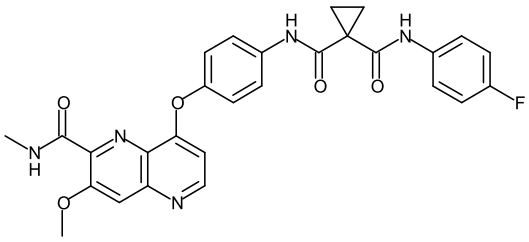
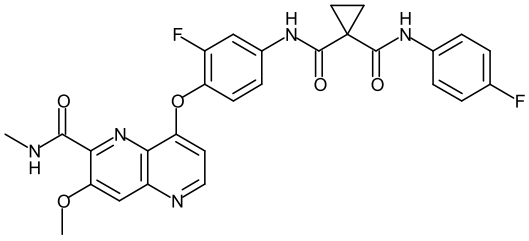
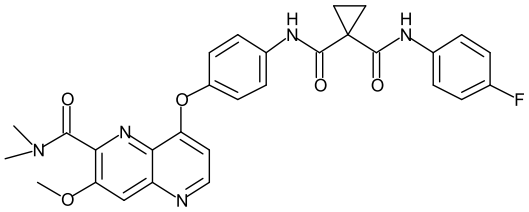
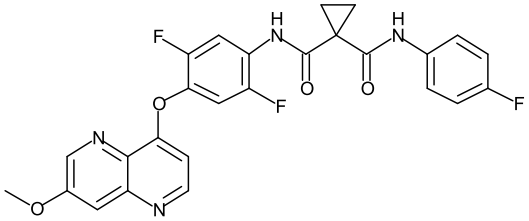
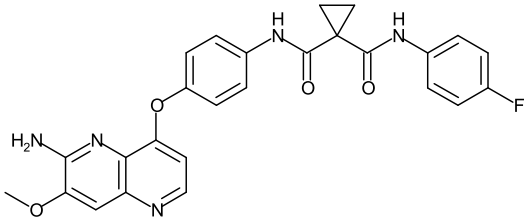
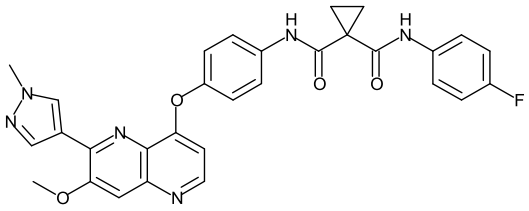
65		1-N'-(4-fluorophenyl)-1-N-[4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide
66		1-N'-[3-chloro-4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
67		1-N'-[3-fluoro-4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
68		1-N-(4-fluorophenyl)-1-N'-[4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxy-3-methylphenyl]cyclopropane-1,1-dicarboxamide
69		1-N'-[2-fluoro-4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

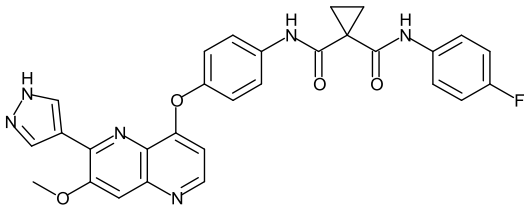
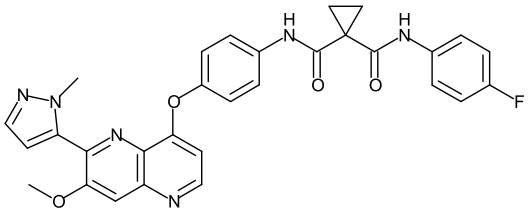
70		1-N'-[2-chloro-4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
71		1-N-(4-fluorophenyl)-1-N'-[4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxy-2-methylphenyl]cyclopropane-1,1-dicarboxamide
72		1-N'-[2,5-difluoro-4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
73		1-N'-[2,3-difluoro-4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
74		1-N-(4-fluorophenyl)-1-N'-[3-methoxy-4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide
75		1-N'-[3-cyano-4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
76		1-N'-[3,5-difluoro-4-[6-methoxy-7-(3-morpholin-4-ylpropoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

78		1-N'-(4-fluorophenyl)-1-N-[4-[6-methoxy-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide
79		1-N'-[3-fluoro-4-[6-methoxy-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
80		1-N'-[3-chloro-4-[6-methoxy-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
81		1-N'-[2-fluoro-4-[6-methoxy-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
82		1-N'-[2,3-difluoro-4-[6-methoxy-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
83		1-N'-[2,5-difluoro-4-[6-methoxy-7-(2-methoxyethoxy)pyrido[3,2-d]pyrimidin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
139		1-N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

140		1-N'-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
141		1-N'-[3-chloro-4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
142		1-N'-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-2,5-difluorophenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
149		1-N'-(4-fluorophenyl)-1-N-[4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]cyclopropane-1,1-dicarboxamide
150		1-N'-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
151		1-N'-[3-chloro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
152		1-N'-[2,5-difluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

153		1-N'-[2,5-difluoro-4-[[6-methoxy-7-(2-morpholin-4-ylethoxy)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
164		1-N-[4-[(6-cyano-7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
165		1-N'-[4-[(6-cyano-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
166		1-N'-[3-chloro-4-[(6-cyano-7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
167		1-N-[4-[(6-carbamoyl-7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
168		1-N'-[4-[(6-carbamoyl-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-fluorophenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
169		1-N'-[4-[(6-carbamoyl-7-methoxy-1,5-naphthyridin-4-yl)oxy]-3-chlorophenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

172		1-N'-(4-fluorophenyl)-1-N-[4-[[7-methoxy-6-(methylcarbamoyl)-1,5-naphthyridin-4-yl]oxy]phenyl]cyclopropane-1,1-dicarboxamide
173		1-N'-[3-fluoro-4-[[7-methoxy-6-(methylcarbamoyl)-1,5-naphthyridin-4-yl]oxy]phenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
174		1-N-[4-[[6-(dimethylcarbamoyl)-7-methoxy-1,5-naphthyridin-4-yl]oxy]phenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
176		1-N'-[2,5-difluoro-4-[(7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
181		1-N-[4-[(6-amino-7-methoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
182		1-N'-(4-fluorophenyl)-1-N-[4-[[7-methoxy-6-(1-methylpyrazol-4-yl)-1,5-naphthyridin-4-yl]oxy]phenyl]cyclopropane-1,1-dicarboxamide

183		1-N'-(4-fluorophenyl)-1-N-[4-[[7-methoxy-6-(1H-pyrazol-4-yl)-1,5-naphthyridin-4-yl]oxy]phenyl]cyclopropane-1,1-dicarboxamide
184		1-N'-(4-fluorophenyl)-1-N-[4-[[7-methoxy-6-(2-methylpyrazol-3-yl)-1,5-naphthyridin-4-yl]oxy]phenyl]cyclopropane-1,1-dicarboxamide

or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a compound of any of claims 1-17, and a pharmaceutically acceptable carrier or excipient.