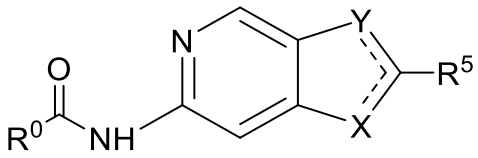
SUMMARY

[0007] Provided herein are compounds and compositions that selectively inhibit Bcr-Abl tyrosine kinases and that are useful for treating disorders mediated by Bcr-Abl tyrosine kinases.

[0007a] In an aspect of the present disclosure, there is provided a compound of formula (I):



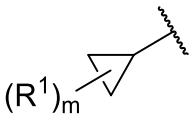
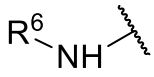
(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is $NR^{3'}$ or CR^3,

Y is NR^2 or CR^4,

wherein when X is $NR^{3'}$ then Y is CR^4, Y has a double bond to CR^5, and X has a single bond to CR^5; or when X is CR^3 then Y is NR^2, Y has a single bond to CR^5, and X has a double bond to CR^5;

R^0 is a group  or ;

m is an integer from 0 to 3;

each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^7R^8, C_1-C_3 alkylene-$NR^{7'}R^{8'}$, C_1-C_3 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1

are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

R^2 is -H, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms;

R^3 is -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, halogen, or -CN;

$R^{3'}$ is -H, C_1-C_3 alkyl, -C_3-C_6 cycloalkyl, or -CN;

R^4 is -H, C_1-C_3 alkyl, or halogen, wherein said C_1-C_3 alkyl is optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms;

R^5 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said C_6-C_{14} aryl or said 5-to-10-membered heteroaryl is optionally substituted with 1-5 R^9 groups;

R^6 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^7R^8, C_1-C_6 alkylene-$NR^{7'}R^{8'}$, C_1-C_6 alkylene-OH, C_1-C_6 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, and heterocycloalkylene moieties in R^6 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^7 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

each R^8 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

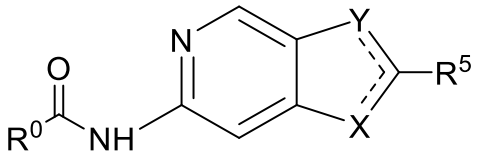
each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 3- to 8-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^9 is independently halogen, $-OR^{10}$, $-NR^7R^8$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

wherein n is an integer from 0 to 2; and

each R^{10} is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with hydroxyl, C_1-C_3 alkoxy, and/or 1-6 deuterium atoms.

[0007b] In another aspect of the present disclosure, there is provided a compound of formula (I):



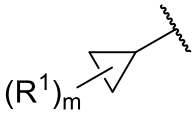
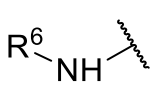
(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is $NR^{3'}$ or CR^3,

Y is NR^2 or CR^4,

wherein when X is $NR^{3'}$ then Y is CR^4, Y has a double bond to CR^5, and X has a single bond to CR^5; or when X is CR^3 then Y is NR^2, Y has a single bond to CR^5, and X has a double bond to CR^5;

R^0 is a group  or ;

m is an integer from 0 to 3;

each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^7R^8, C_1-C_3 alkylene-$NR^{7'}R^{8'}$, C_1-C_3 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

R^2 is -H, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms;

R^3 is -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, halogen, or -CN;

$R^{3'}$ is -H, C_1-C_3 alkyl, -C_3-C_6 cycloalkyl, or -CN;

R^4 is -H, C_1-C_3 alkyl, or halogen, wherein said C_1-C_3 alkyl is optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms;

R^5 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said C_6-C_{14} aryl or said 5-to-10-membered heteroaryl is optionally substituted with 1-5 R^9 groups;

R^6 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^7R^8, C_1-C_6 alkylene-$NR^{7'}R^{8'}$, C_1-C_6 alkylene-OH, C_1-C_6 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, and heterocycloalkylene moieties in R^6 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^7 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

each R^8 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

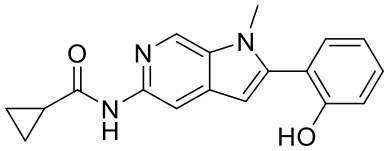
each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

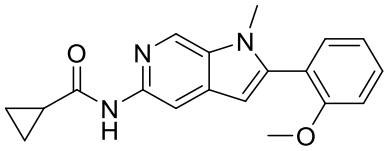
each R^9 is independently halogen, $-OR^{10}$, $-NR^7R^8$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

wherein n is an integer from 0 to 2; and

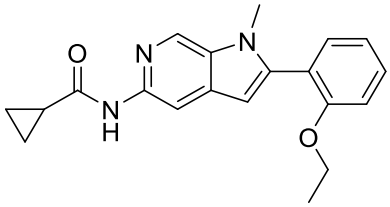
each R^{10} is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with hydroxyl, C_1-C_3 alkoxy, and/or 1-6 deuterium atoms.

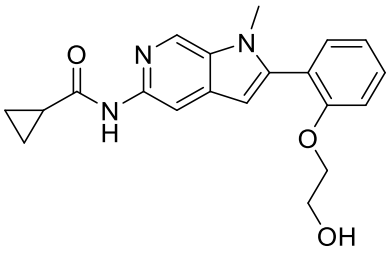
[0007c] In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of:



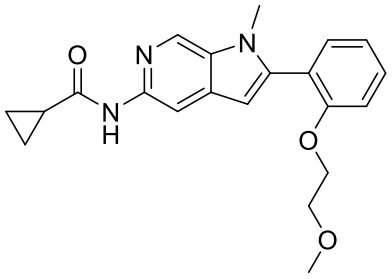
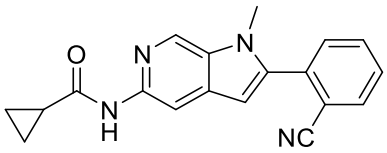
;


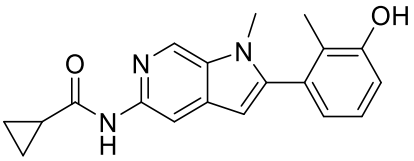
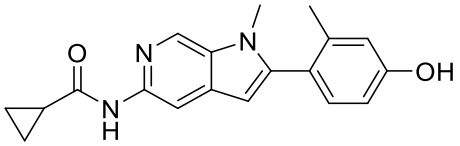
;

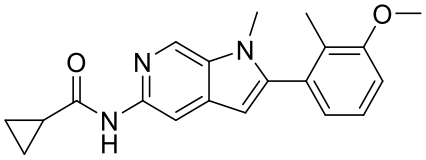
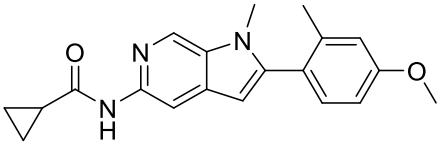


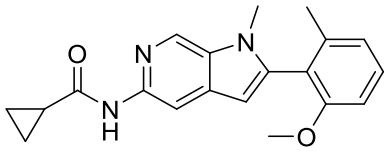
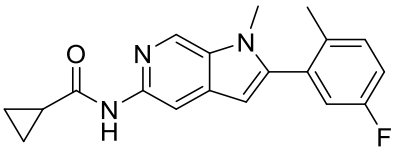
;


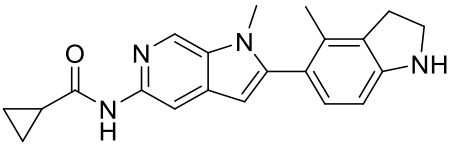
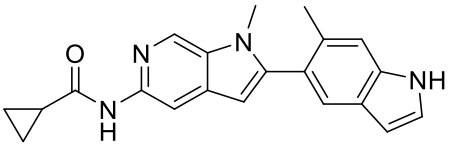
;

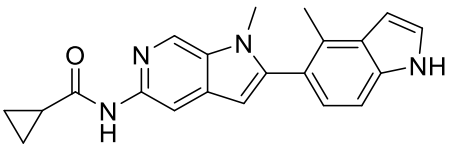
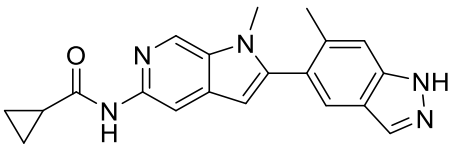

O
N
N
H
O
O
;

O
N
N
H
NC
;

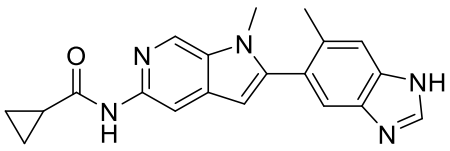
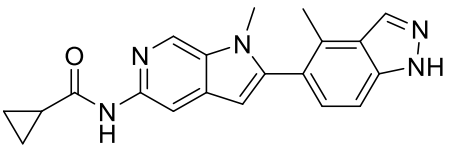

OH
O
N
N
H
;

O
N
N
H
OH
;

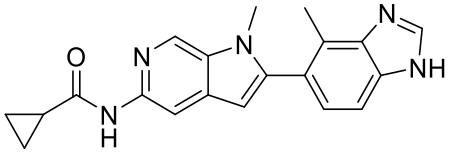
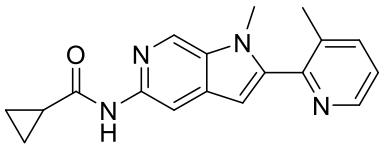
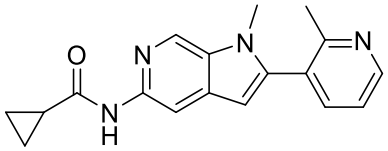
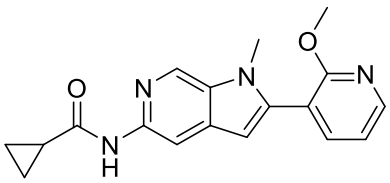
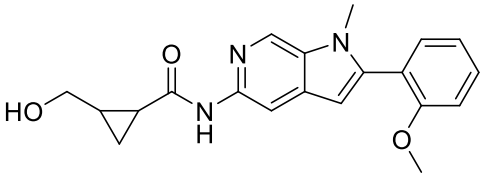
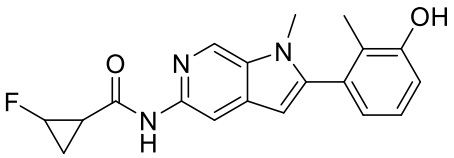
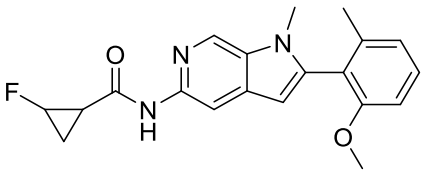
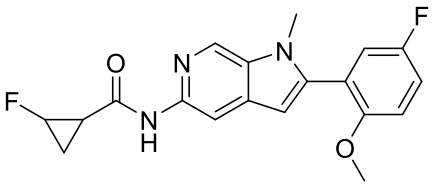
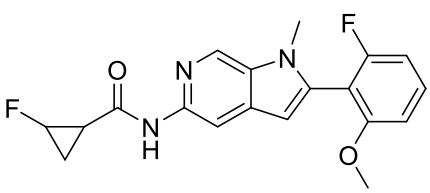
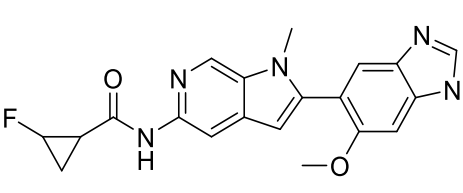
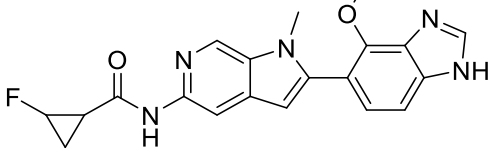
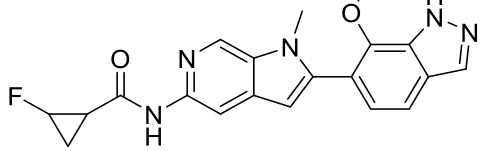

O—
O
N
N
H
;

O
N
N
H
O
;


O
N
N
H
—O
;

O
N
N
H
F
;


O
N
N
H
NH
;

O
N
N
H
NH
;

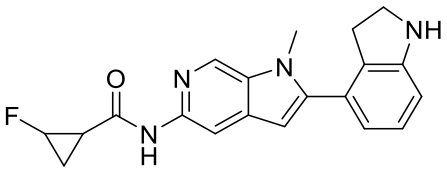
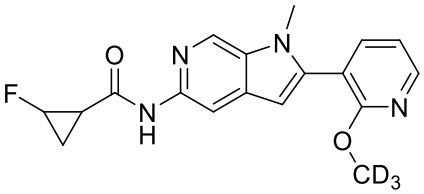

O
N
N
H
NH
;

O
N
N
H
NH
N
;

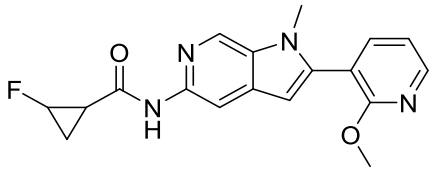
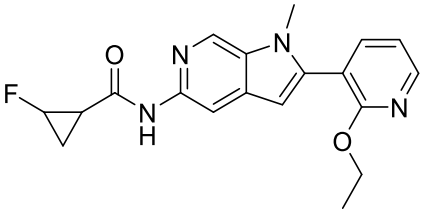

O
N
N
H
NH
N
;

N
NH
O
N
N
H
;

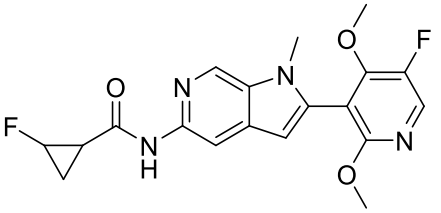
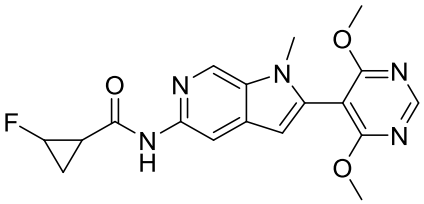

;

;

;

;

;

;

;

;

;

;

;

;

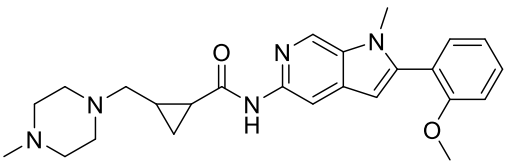
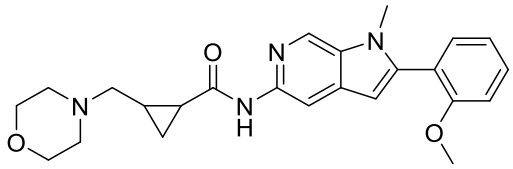
;

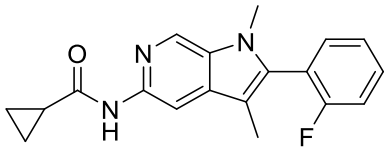
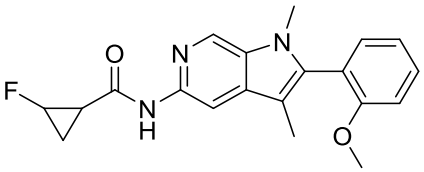
;

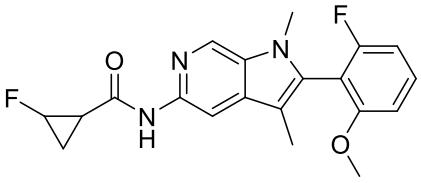
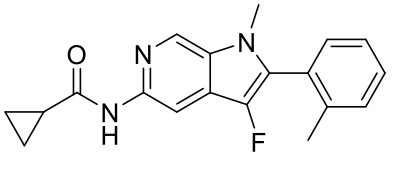

F
O
N
H
N
N
NH
;

F
O
N
H
N
N
O
CD3
;

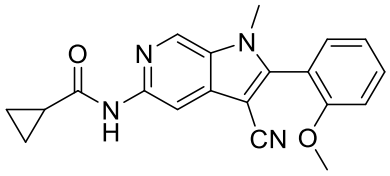
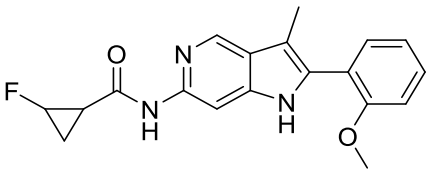
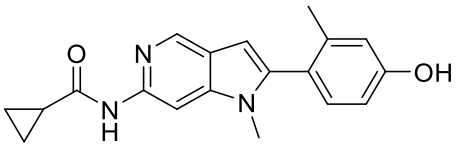
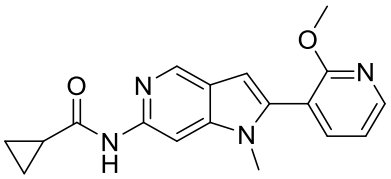
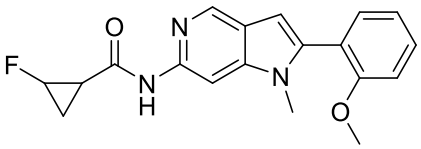
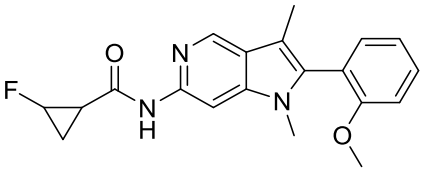
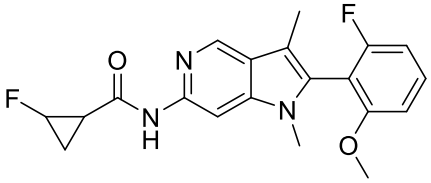
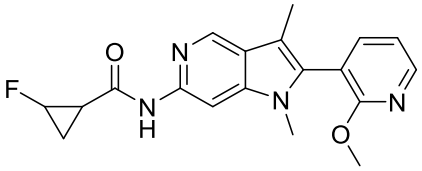
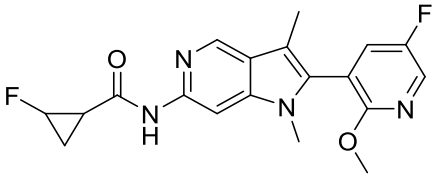
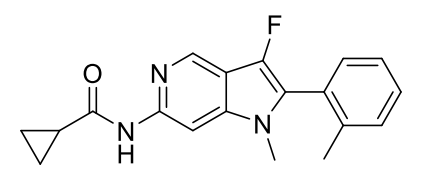
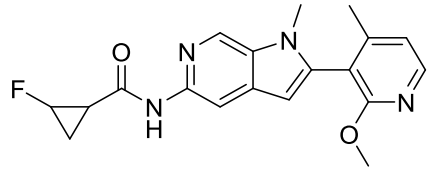
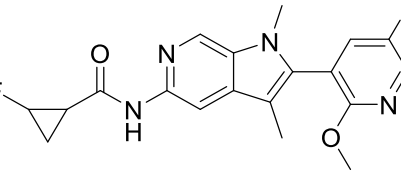

F
O
N
H
N
N
O
;

F
O
N
H
N
N
O
;


F
O
N
H
N
O
F
N
O
;

F
O
N
H
N
O
N
N
O
;


N
O
N
H
N
O
;

O
N
H
N
N
O
;

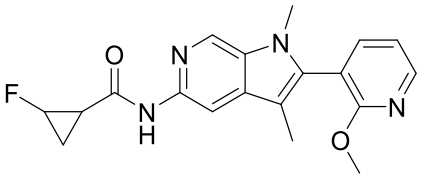
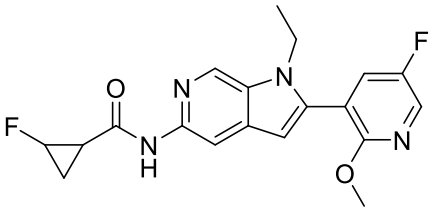

O
N
H
N
F
;

F
O
N
H
N
O
;

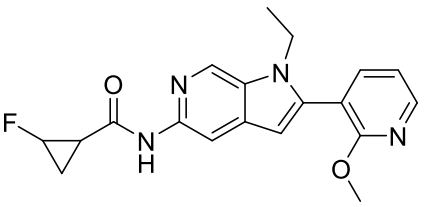
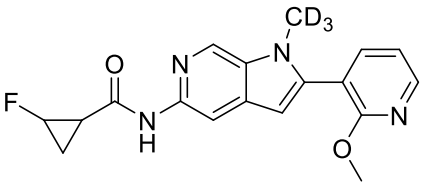

F
O
N
H
N
F
O
;

O
N
H
N
F
;

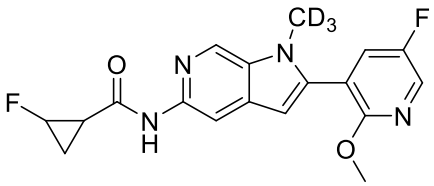
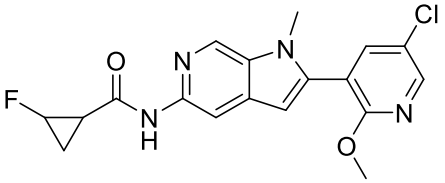

;

;

;

;

;

;

;

;

;

;

;

;

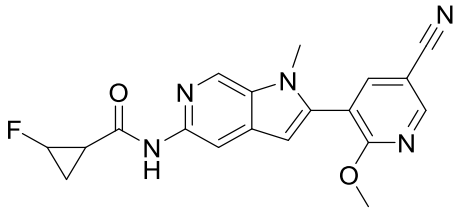
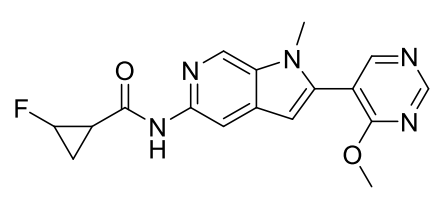
;

;


;

;

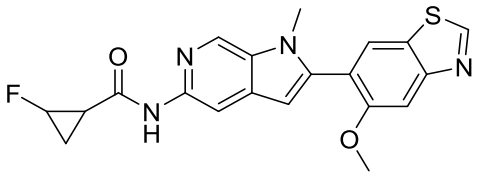
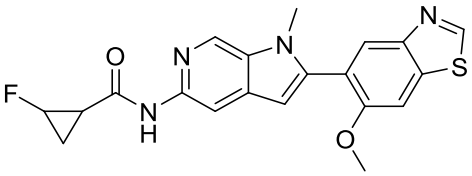

;

;

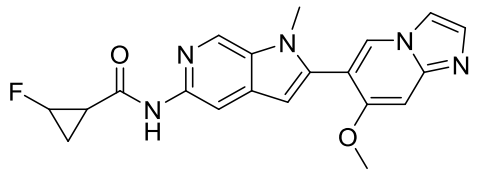
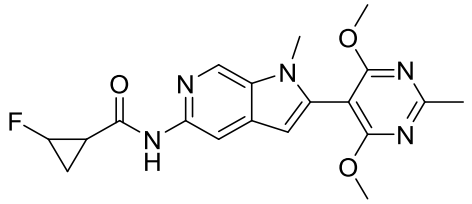

;

;

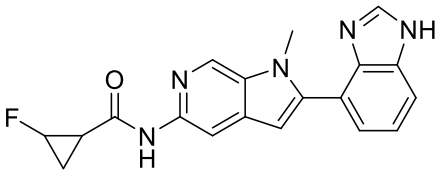
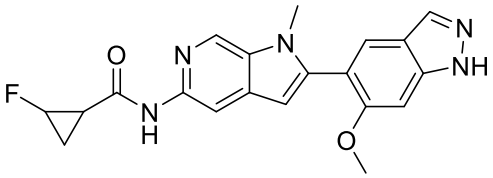

;

;

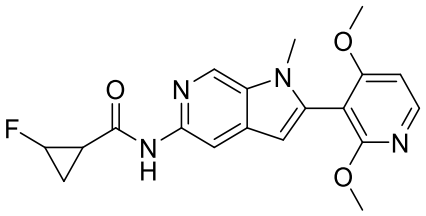
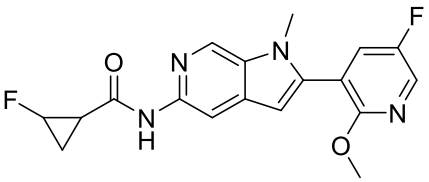
;

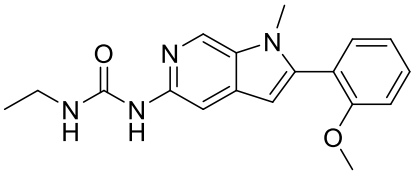
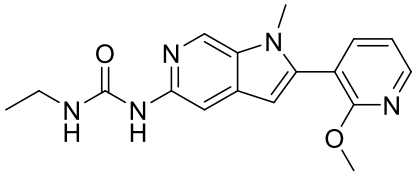
;

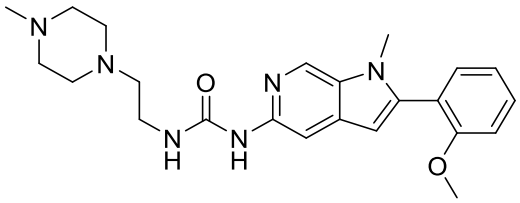
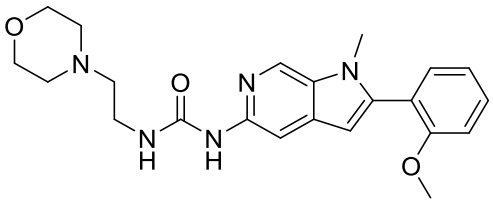

;

;

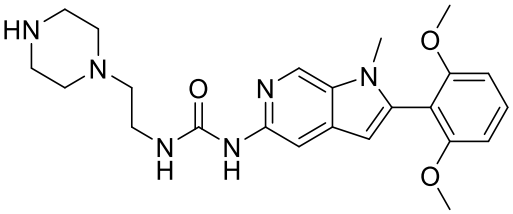
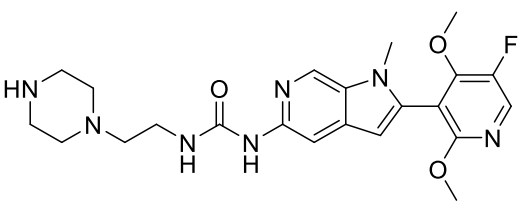

;

;

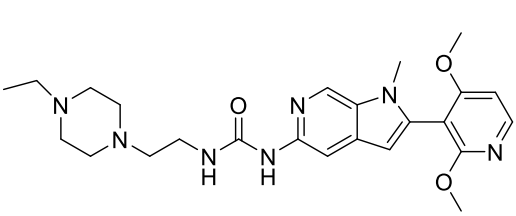
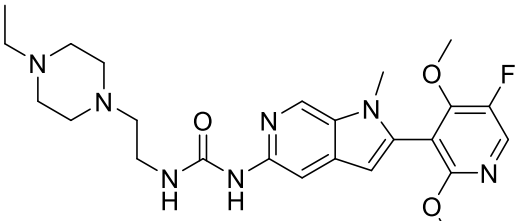

;

;


;

;


;

;

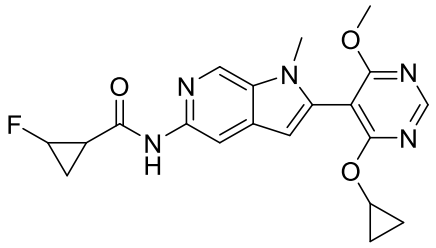
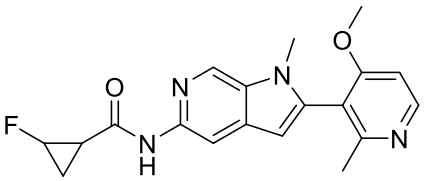
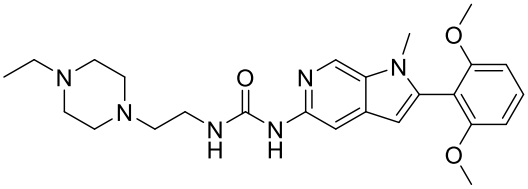
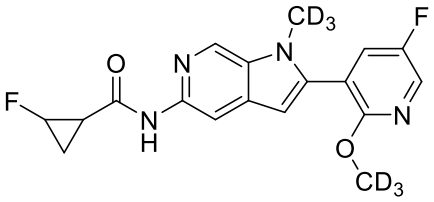
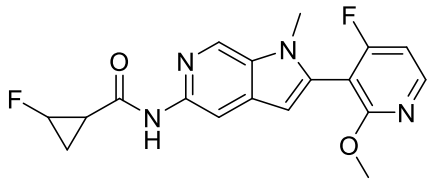
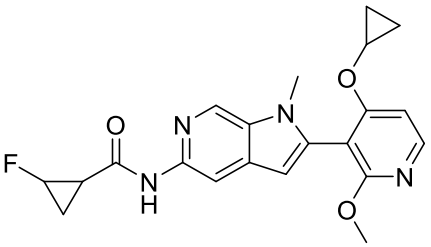
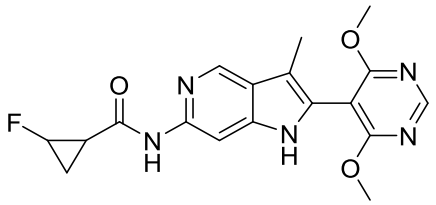
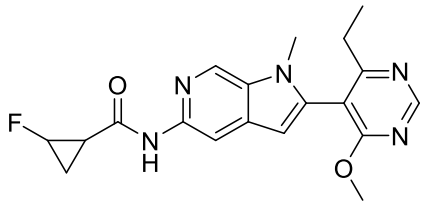
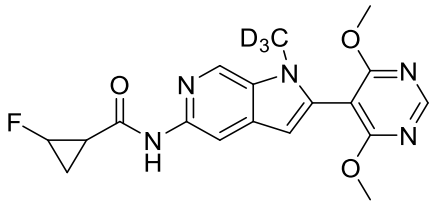
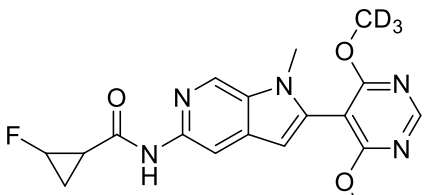

;

;


;

;


;

;

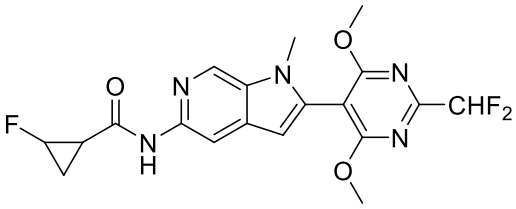
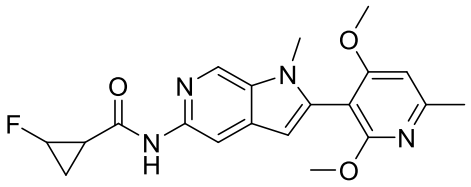
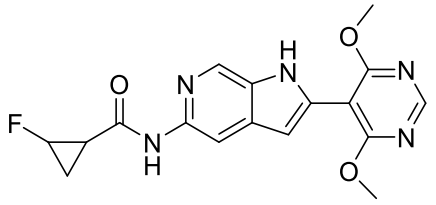
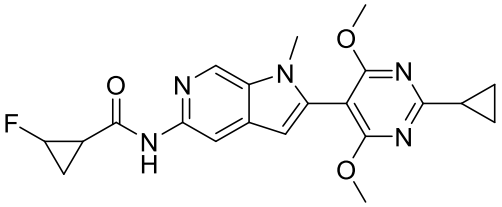
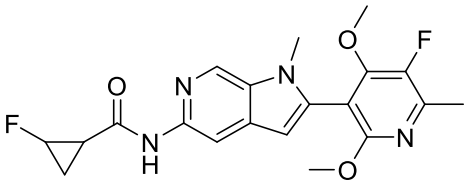
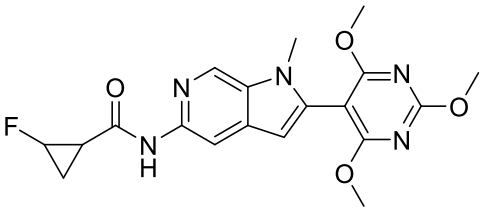
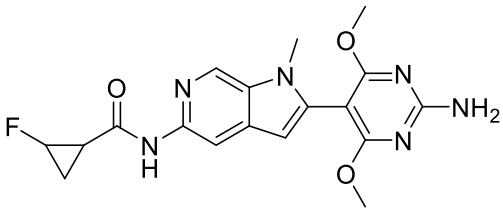
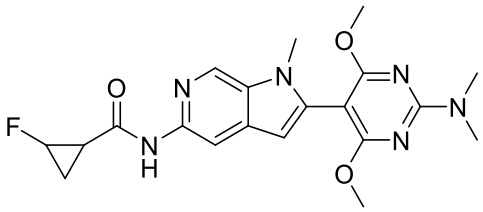
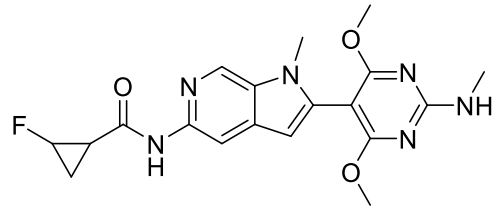
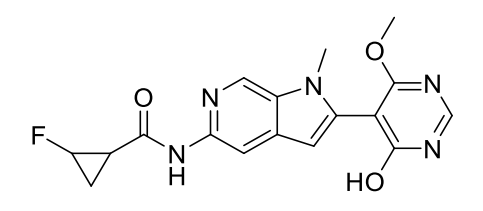
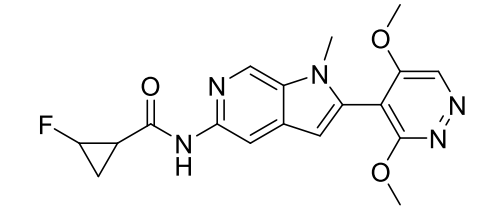
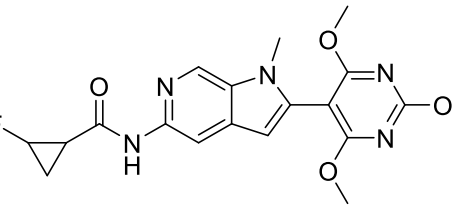
;

,


;

;

;

;

;

;

;

;

;

;

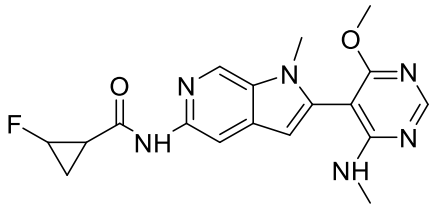
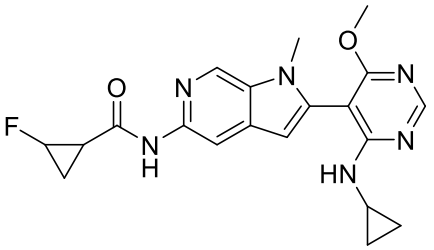
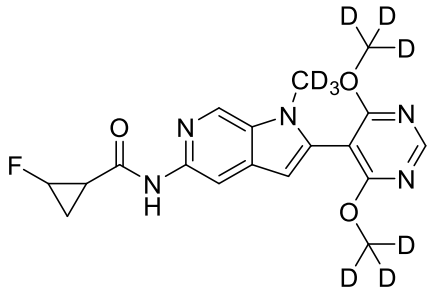
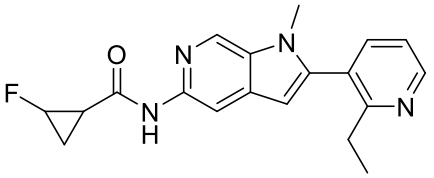
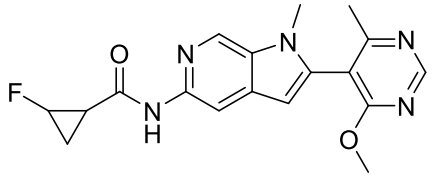
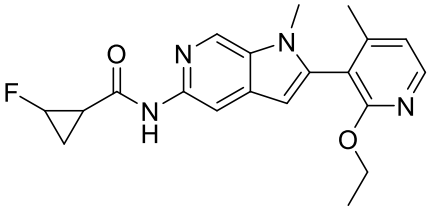
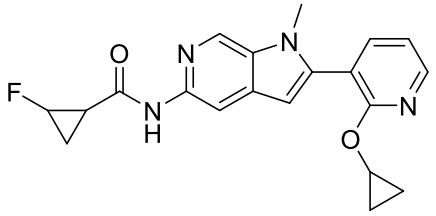
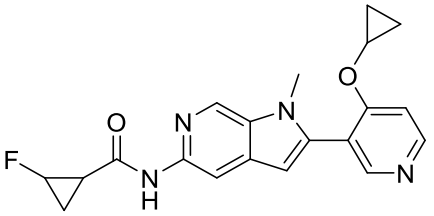
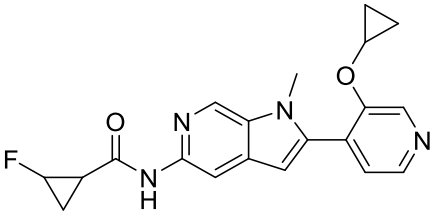
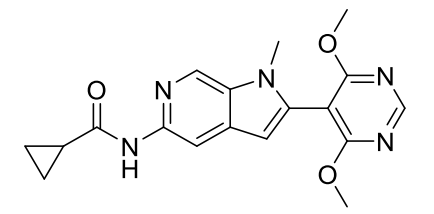
;

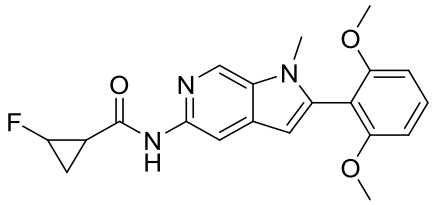
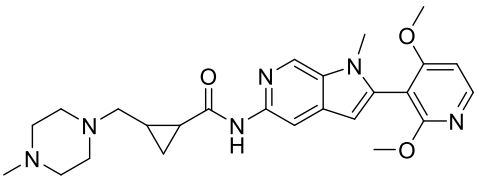
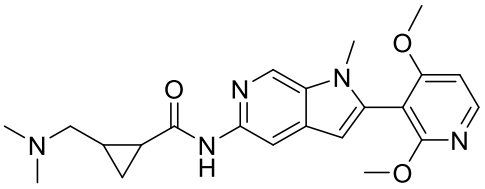
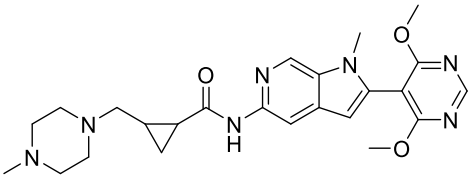
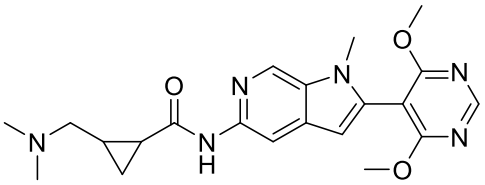
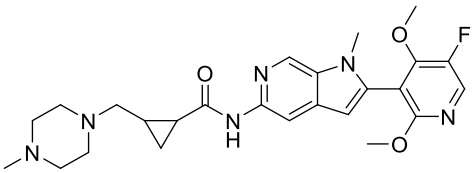
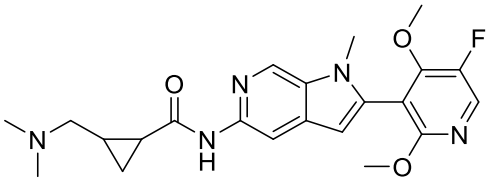
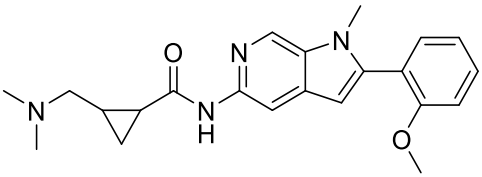
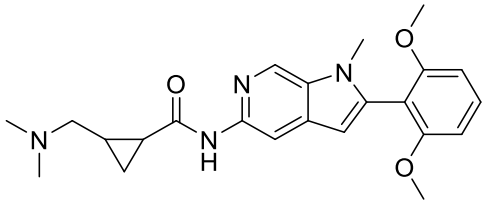
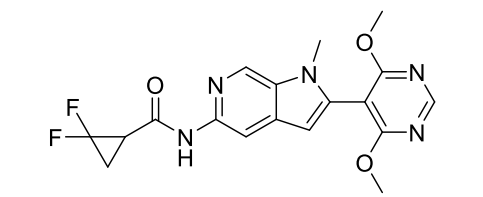
;


;

;

;

;

;

;

;

;

;

;

;

;

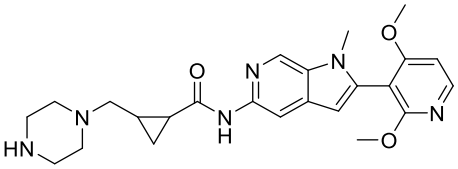
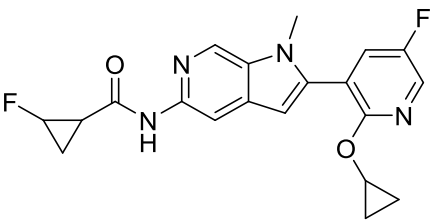
;

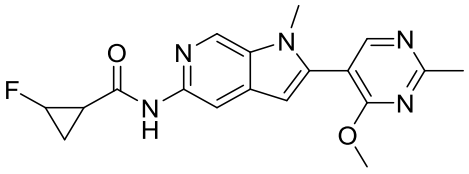
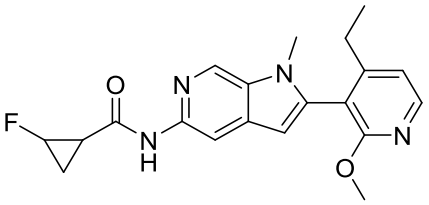
;

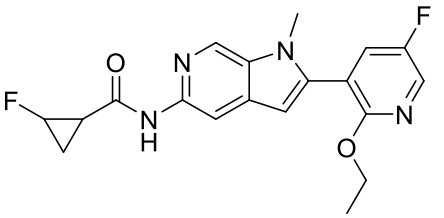
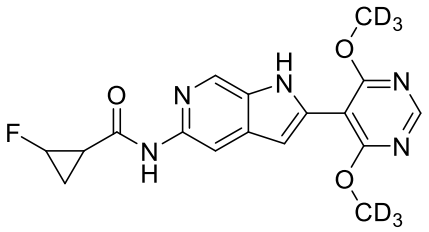

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

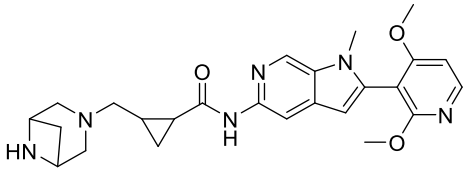
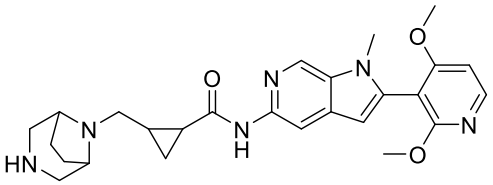
;

;

;

;


;

;

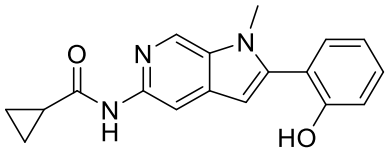
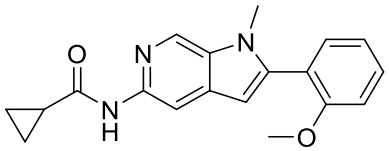

;

;

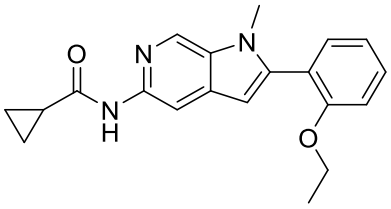
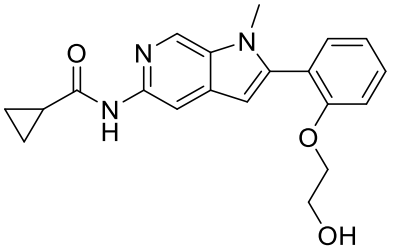
and

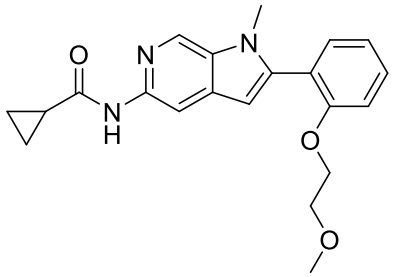
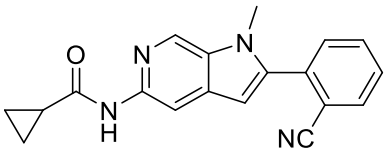
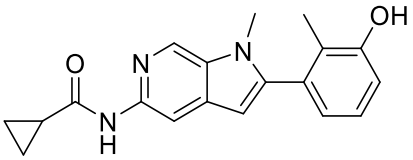
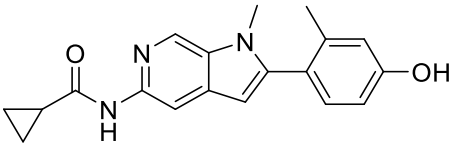
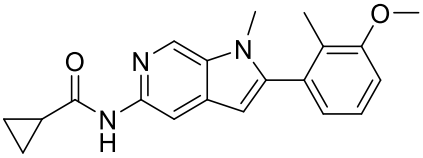
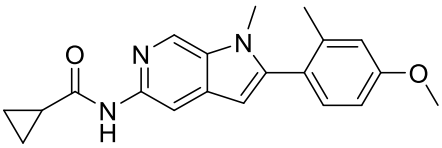
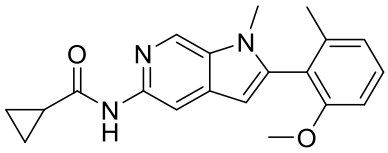
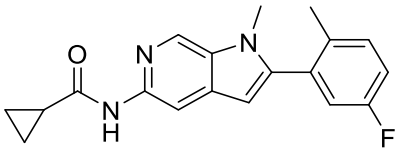
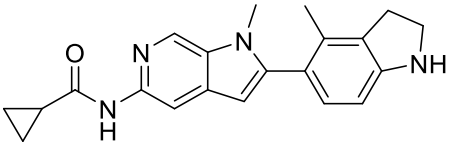
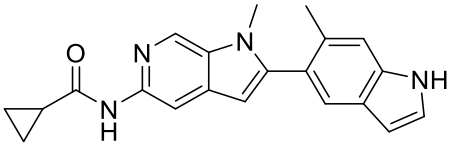
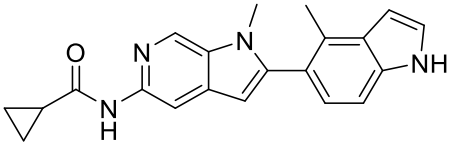
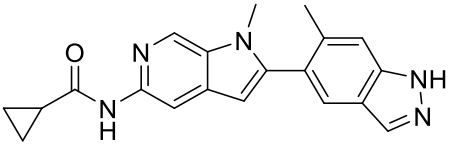
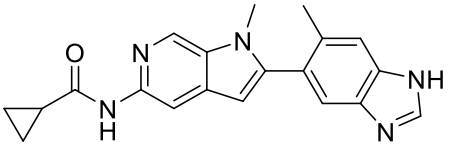
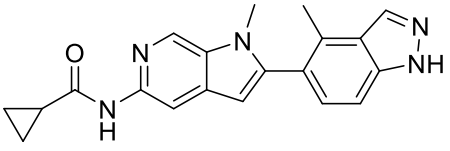

;

,

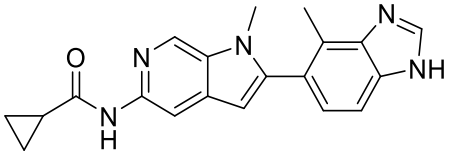
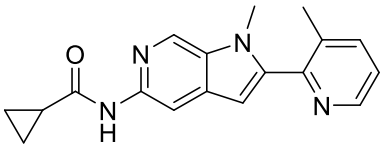
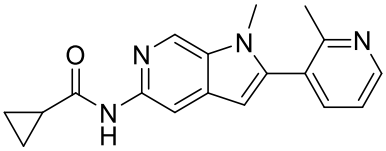
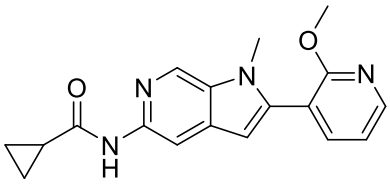
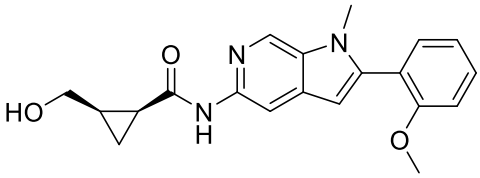
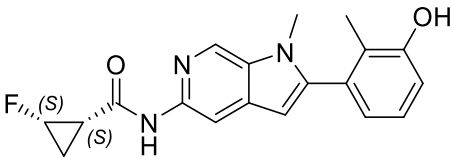
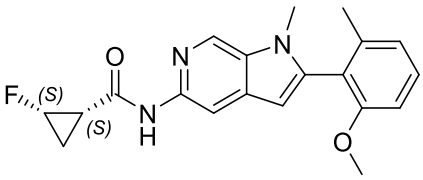
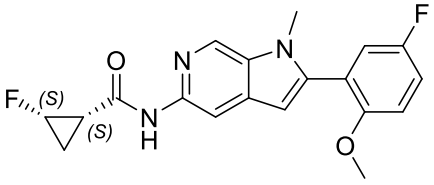
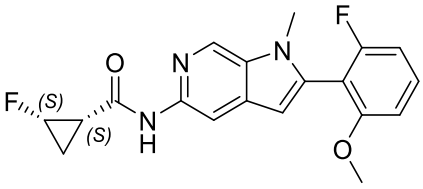
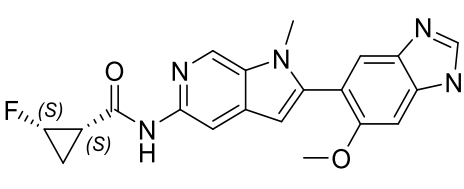
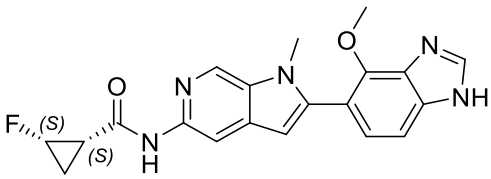
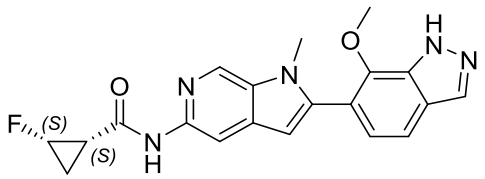
or a pharmaceutically acceptable salt thereof.

[0007d] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:


;

;

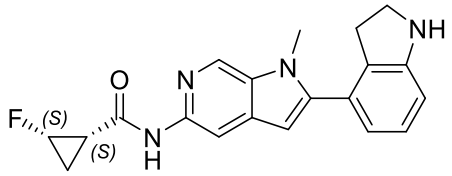
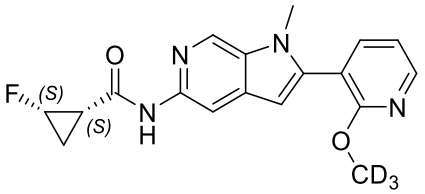

;

;

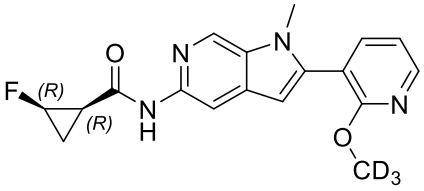
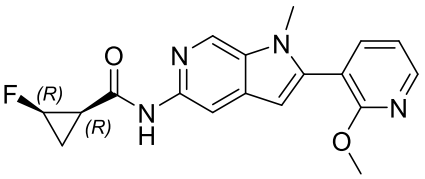

;

;

;

;

;

;

;

;

;

;

;

;

;

;

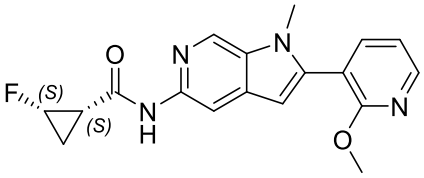
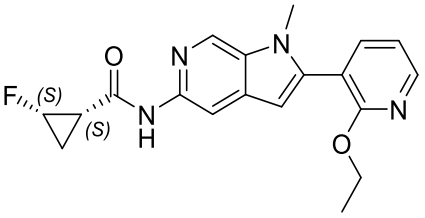

;

;

;

;

;

;

;

;

;

;

;

;

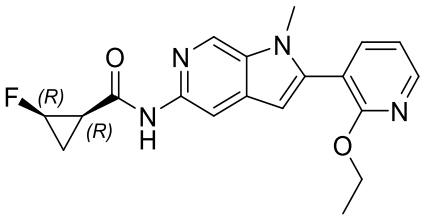
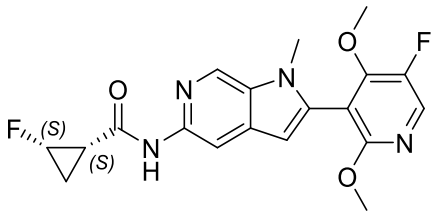
;

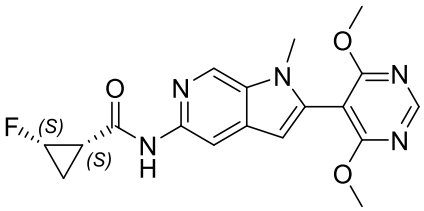
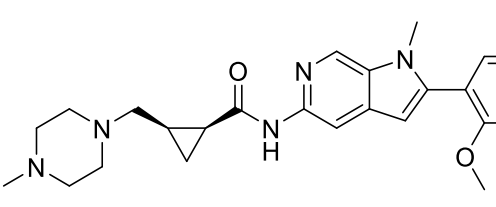
;


;

;


;

;

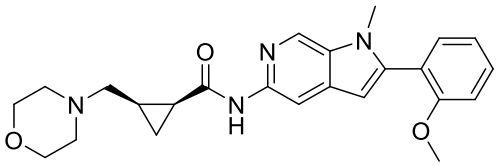
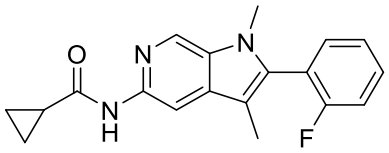

;

;

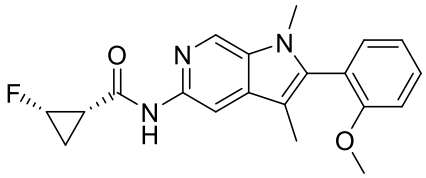
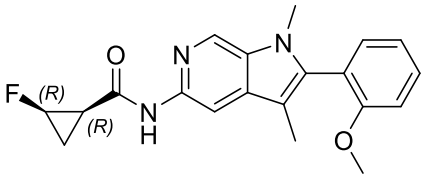
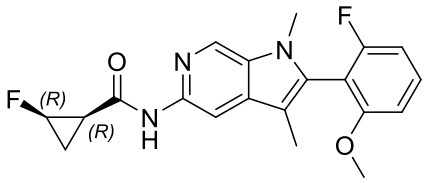
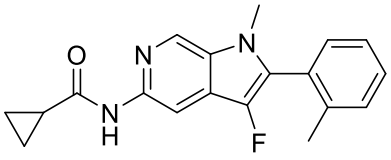
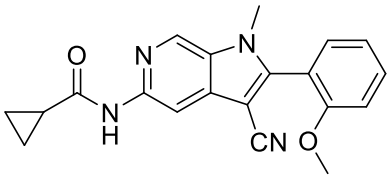
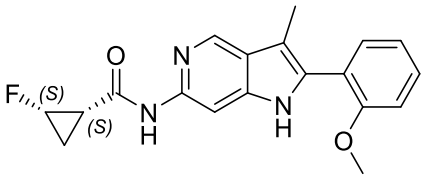
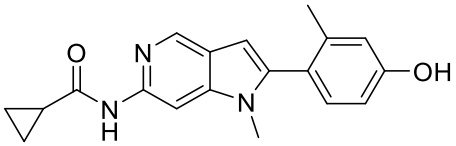
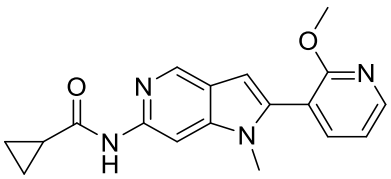
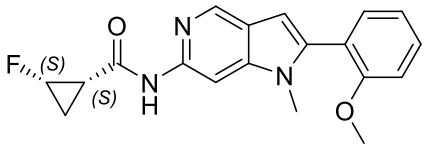
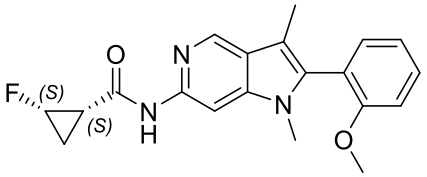
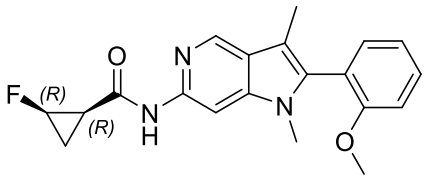
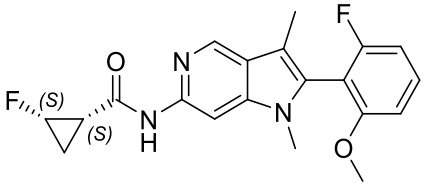

;

;


;

;

;

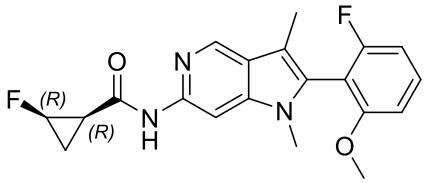
;

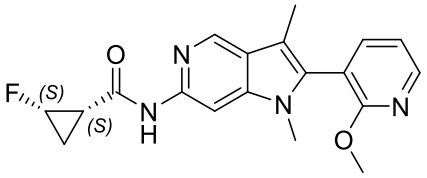

;

;

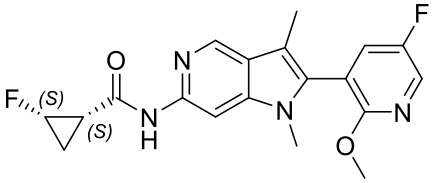

;

;

;

;

;

;

;

;

;

;

;

;

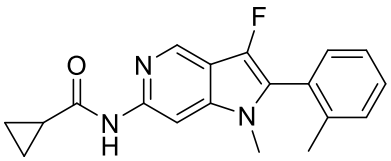
;

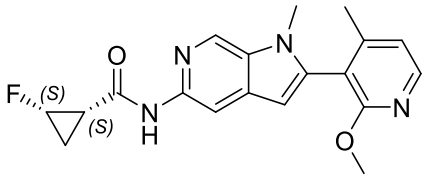
;

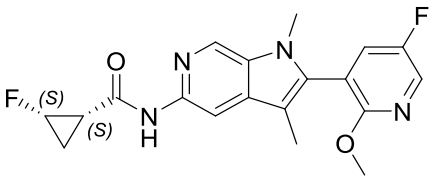

F
(R)
(R)
O
N
H
N
N
F
O
;

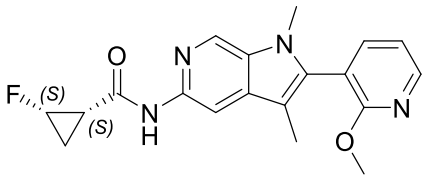

F
(S)
(S)
O
N
H
N
N
O
;

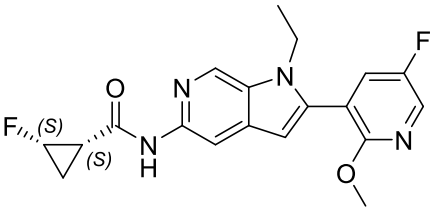

F
(S)
(S)
O
N
H
N
N
F
O
;

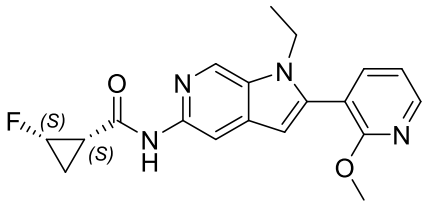

F
O
N
H
N
N
;

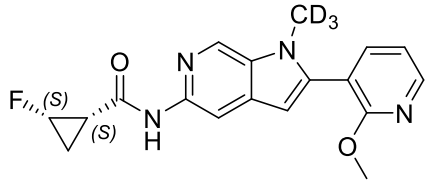

F
(S)
(S)
O
N
H
N
N
O
;

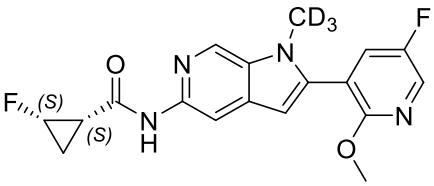

F
(S)
(S)
O
N
H
N
N
F
O
;

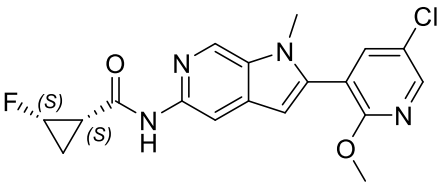

F
(S)
(S)
O
N
H
N
N
O
;

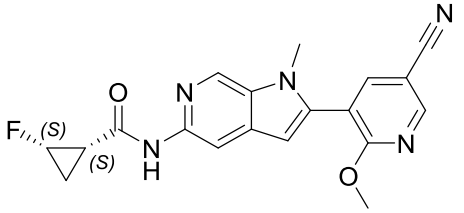
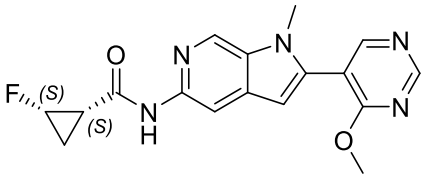
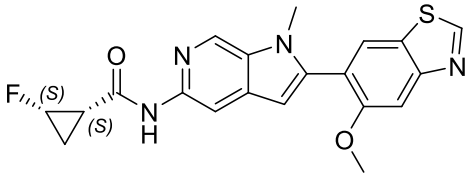
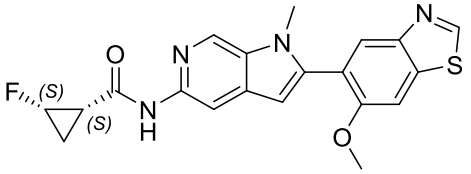
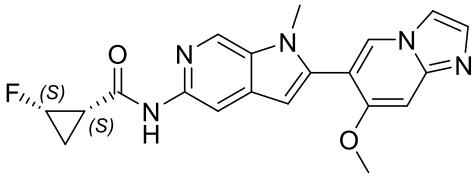
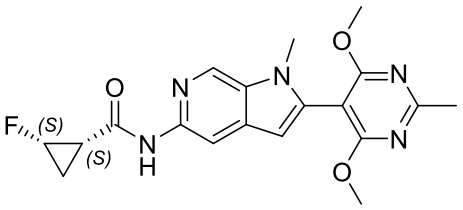
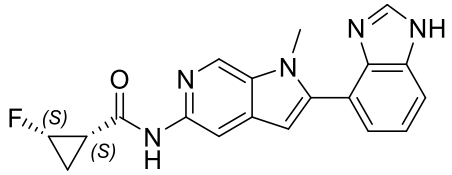
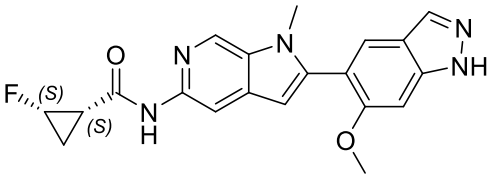
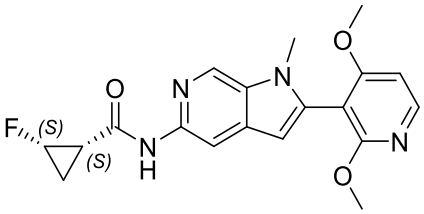
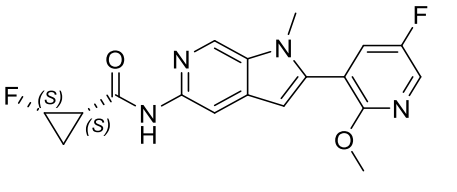
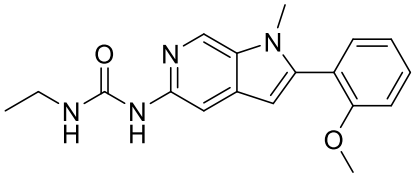
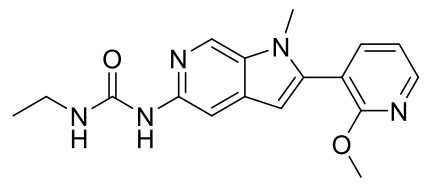

F
(S)
(S)
O
N
H
N
N
F
O
;


F
(S)
(S)
O
N
H
N
N
O
;


CD3
F
(S)
(S)
O
N
H
N
N
O
;

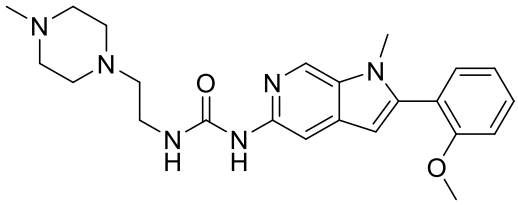
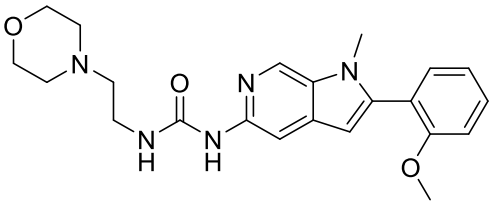
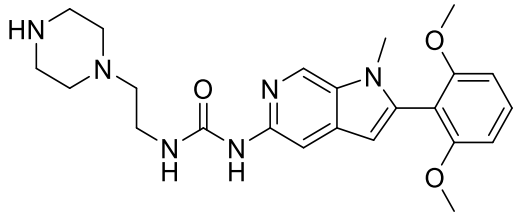
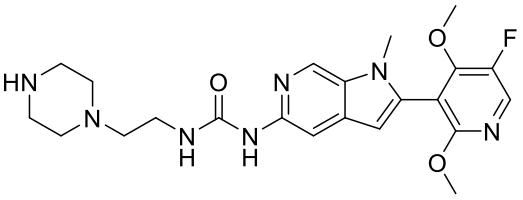
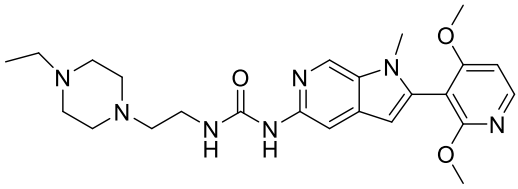
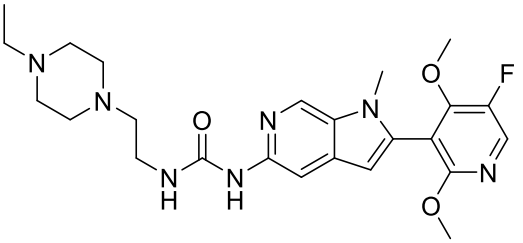
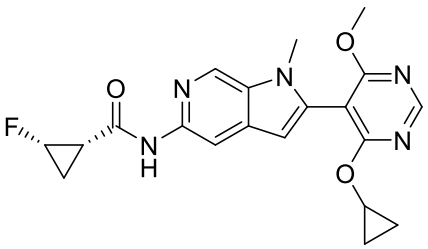
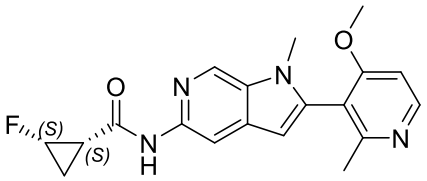
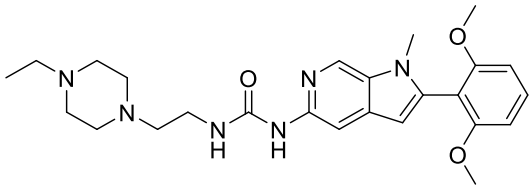
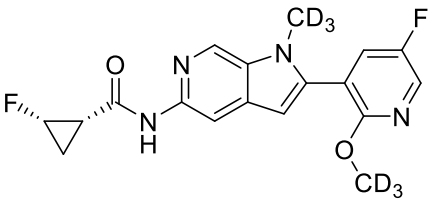

CD3
F
(S)
(S)
O
N
H
N
N
F
O
;


Cl
F
(S)
(S)
O
N
H
N
N
O
;


;

;

;

;

;

;

;

;

;

;

;

;

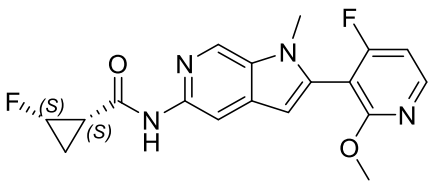
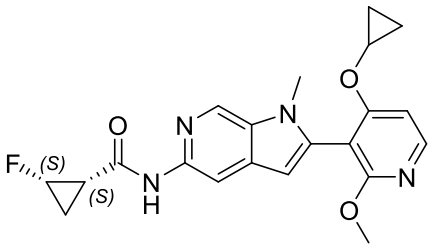
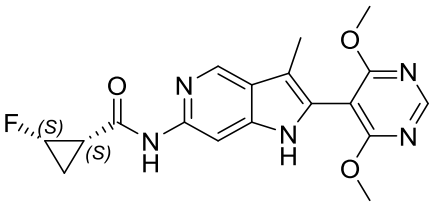
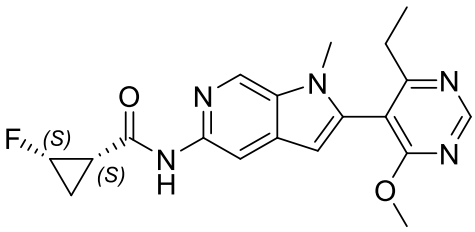
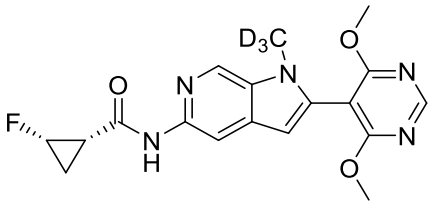
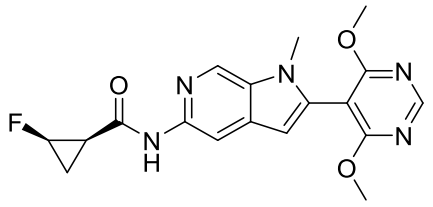
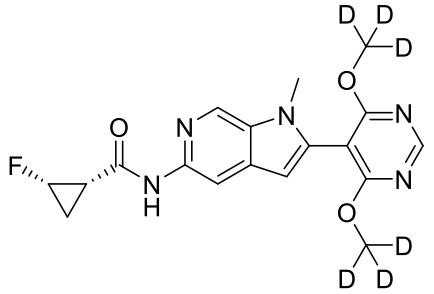
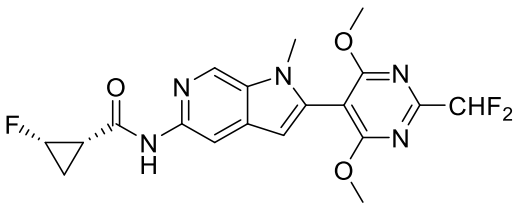
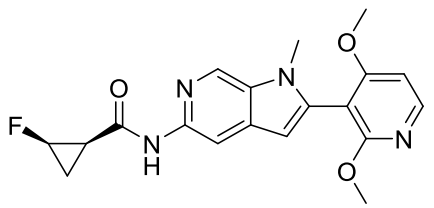
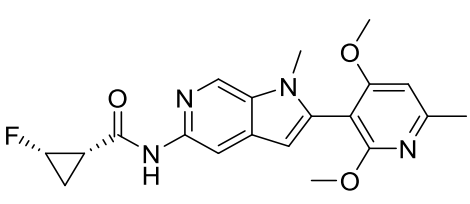
;

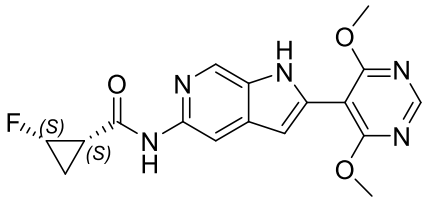
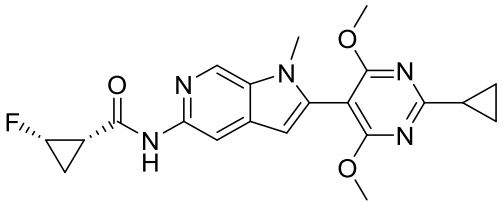
;

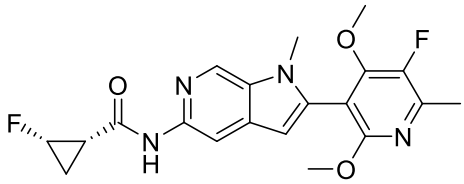
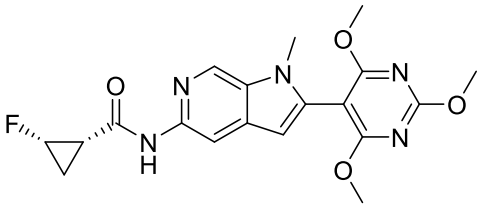

;

;

;

;

;

,

;

;

;

;

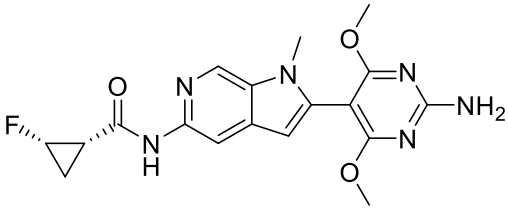
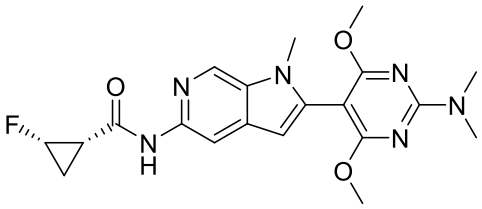
;

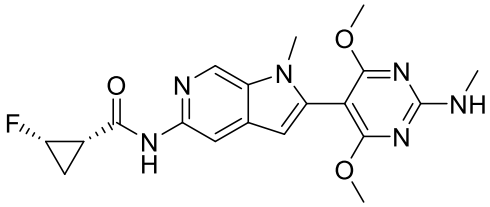
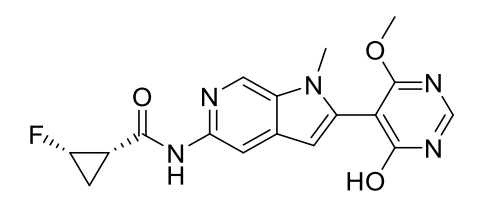
;

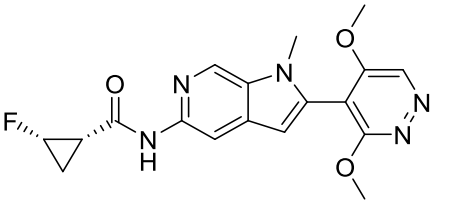
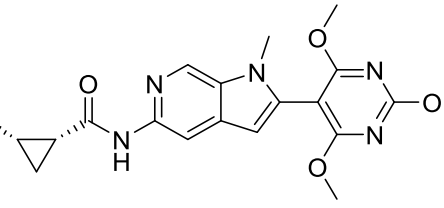

;

;

;

;

;

;

;

;

;

;

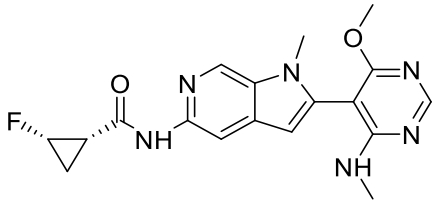
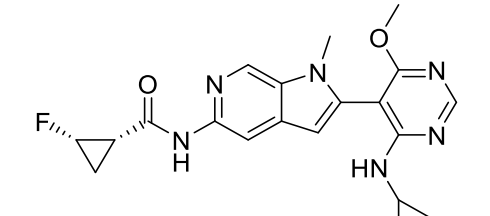

;

;


;

;


;

;

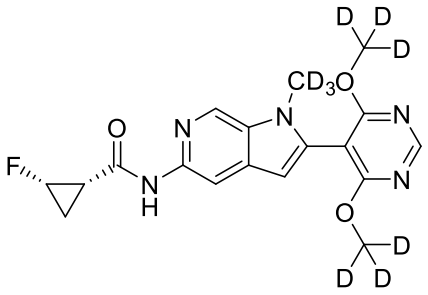
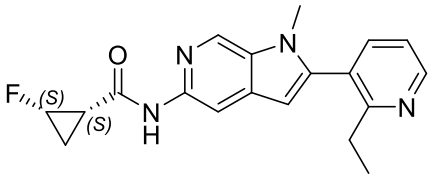
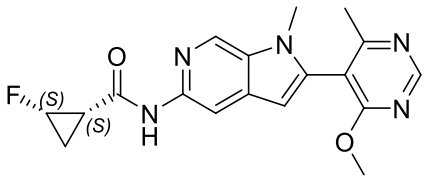
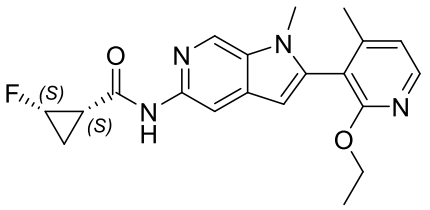
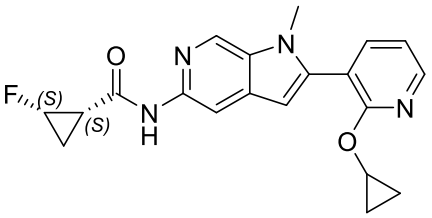
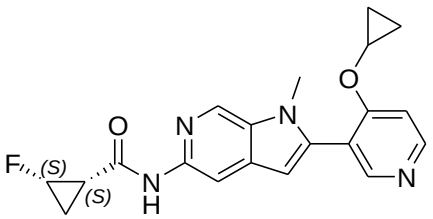
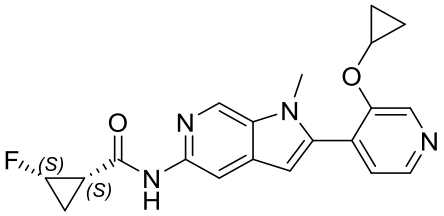
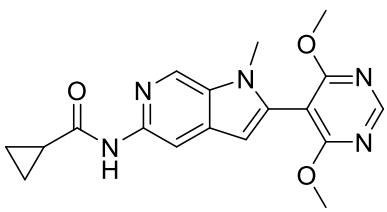
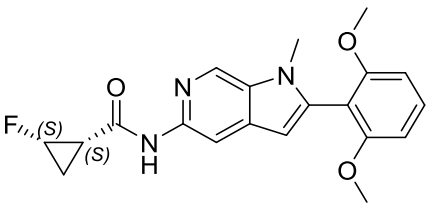

;

;

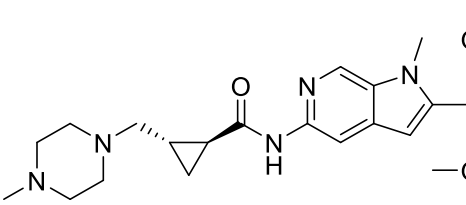

;

;


;

;

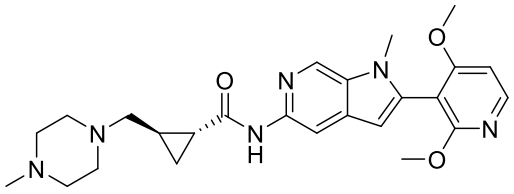
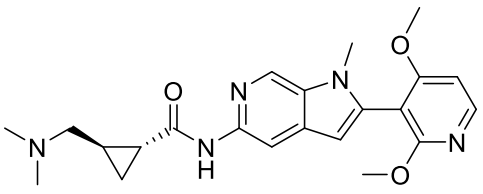
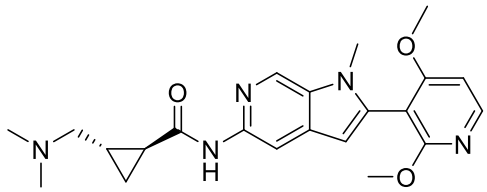
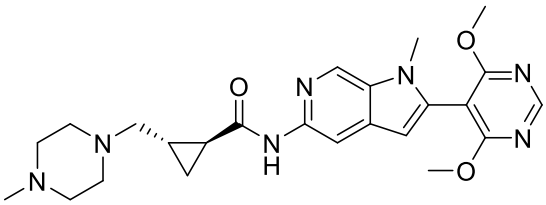
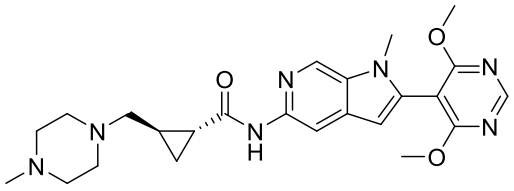
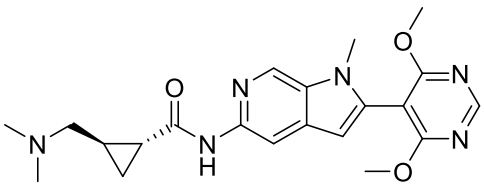
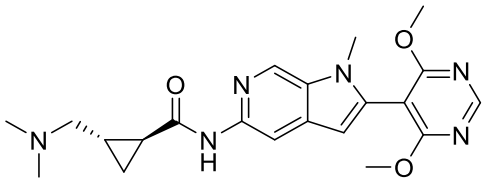
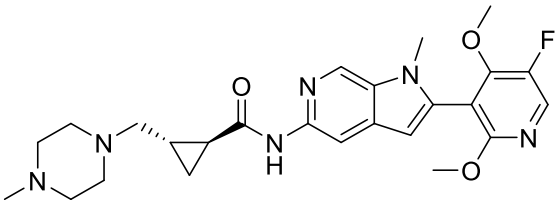
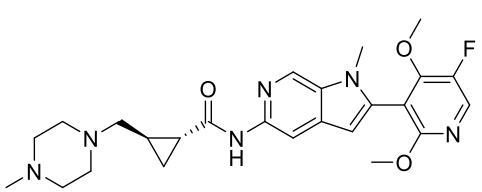
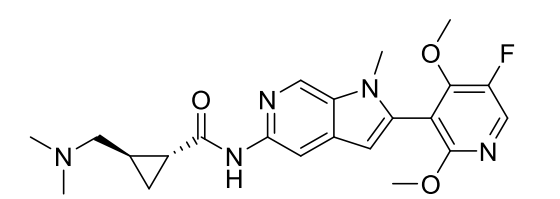
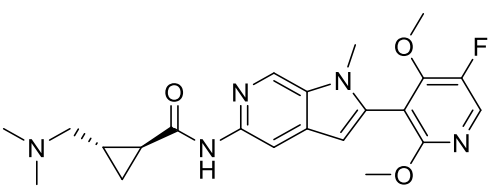
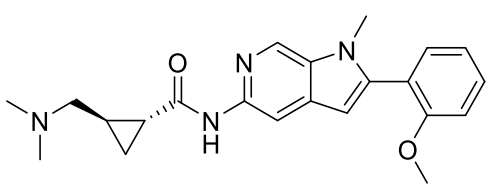
;

;


D
D
D
CD3O
O
N
N
F
O
N
H
N
N
O
D
D
D
;

N
N
F
(S)
O
(S)
N
H
N
;

N
N
F
(S)
O
(S)
N
H
N
O
;

N
N
F
(S)
O
(S)
N
H
N
O
;

N
N
F
(S)
O
(S)
N
H
N
O
;

O
N
N
F
(S)
O
(S)
N
H
N
;

O
N
N
F
(S)
O
(S)
N
H
N
;

O
N
N
O
N
N
O
;

O
N
N
F
(S)
O
(S)
N
H
N
;

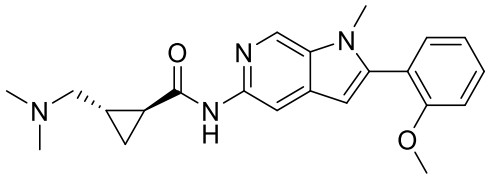
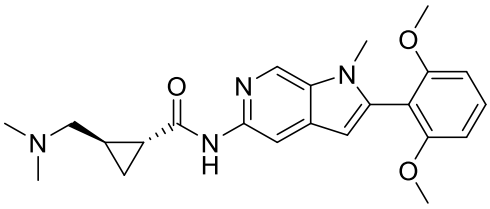
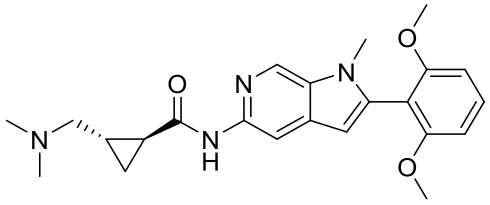
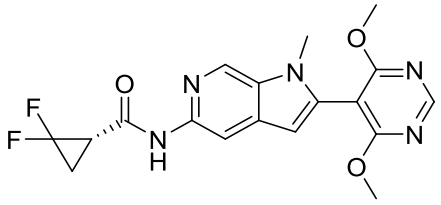
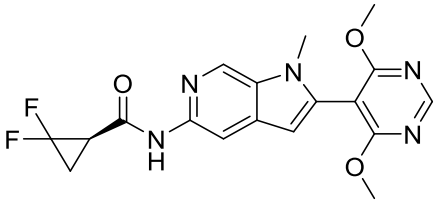
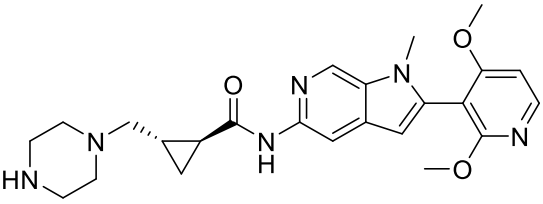
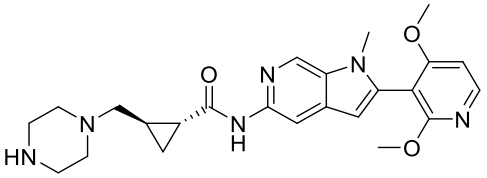
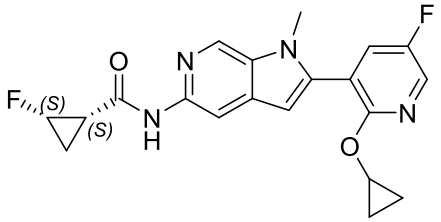
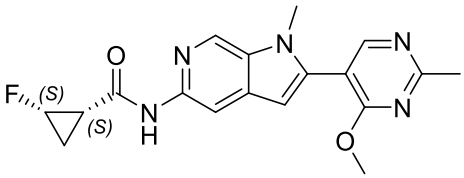
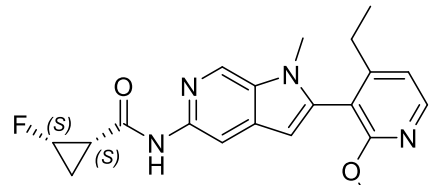
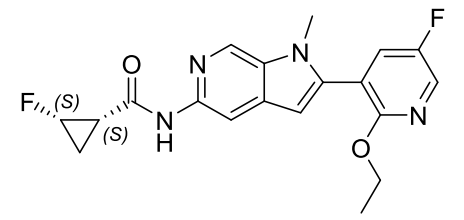
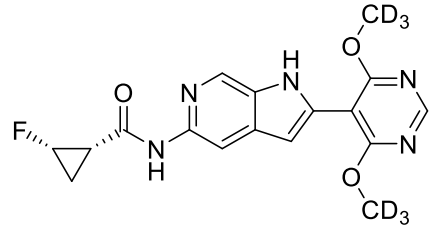
O
N
N
O
F
(S)
O
(S)
N
H
N
;

O
N
N
O
N
N
O
;

O
N
N
O
N
N
O
N
N
;


;

;

;

;

;

;

;

;

;

;

;

;

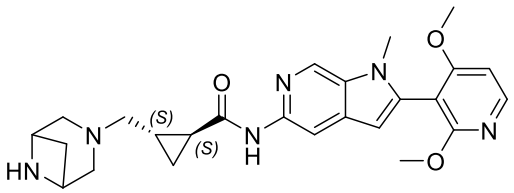
;

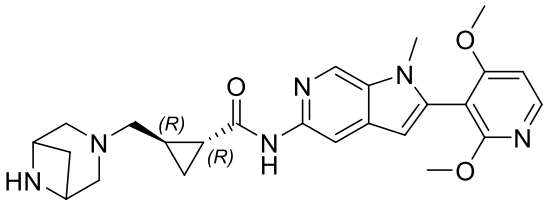
;


;

;

;

;

;

;

;

;

;

;

;

;

;

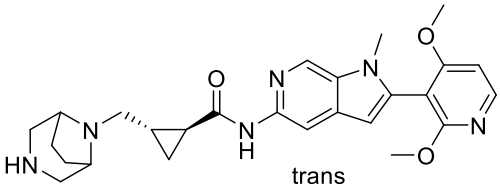
;



;


;

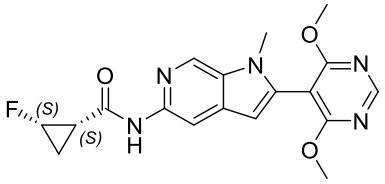
and



,

or a pharmaceutically acceptable salt thereof.

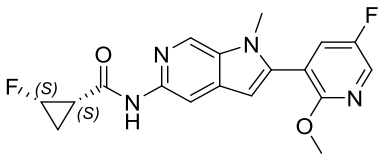
[0007e] In a further aspect of the present disclosure, there is provided a compound having the structure



,

or a pharmaceutically acceptable salt thereof.

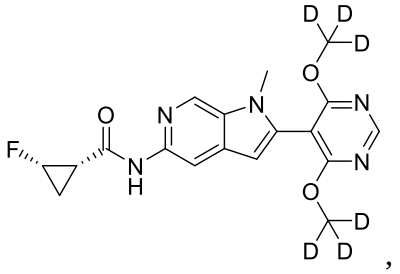
[0007f] In another aspect of the present disclosure, there is provided a compound having the structure



,

or a pharmaceutically acceptable salt thereof.

[0007g] In a further aspect of the present disclosure, there is provided a compound having the structure



or a pharmaceutically acceptable salt thereof.

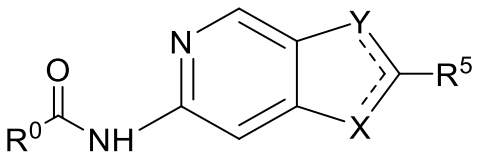
[0007h] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0007i] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for inhibiting Bcr-Abl enzymatic activity in a cell.

[0007j] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or a mixed phenotype acute leukemia, in a human in need thereof.

[0007k] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, for use in therapy.

[0008] In one example, provided herein is a compound of formula (I),



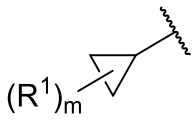
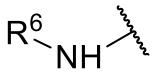
(I)

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

X is $NR^{3'}$ or CR^3,

Y is NR^2 or CR^4,

wherein when X is $NR^{3'}$ then Y is CR^4, Y has a double bond to CR^5, and X has a single bond to CR^5; or when X is CR^3 then Y is NR^2, Y has a single bond to CR^5, and X has a double bond to CR^5;

R^0 is a group  or ;

m is an integer from 0 to 3;

each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^7R^8, C_1-C_3 alkylene-$NR^{7'}R^{8'}$, C_1-C_3 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-

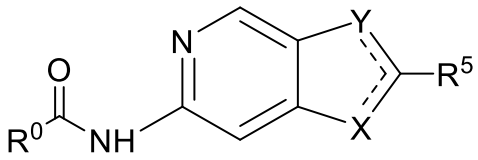
each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 3- to 8-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^9 is independently halogen, $-OR^{10}$, $-NR^7R^8$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

wherein n is an integer from 0 to 2; and

each R^{10} is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with hydroxyl, C_1-C_3 alkoxy, and/or 1-6 deuterium atoms.

[0009] In another example, provided herein is a compound of formula (I),



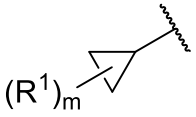
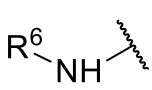
(I)

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, wherein:

X is $NR^{3'}$ or CR^3,

Y is NR^2 or CR^4,

wherein when X is $NR^{3'}$ then Y is CR^4, Y has a double bond to CR^5, and X has a single bond to CR^5; or when X is CR^3 then Y is NR^2, Y has a single bond to CR^5, and X has a double bond to CR^5;

R^0 is a group  or ;

each R^7 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

each R^8 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

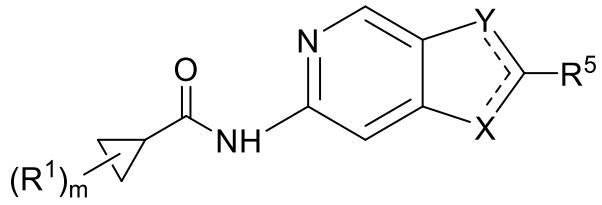
each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^9 is independently halogen, $-OR^{10}$, $-NR^7R^8$, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

wherein n is an integer from 0 to 2; and

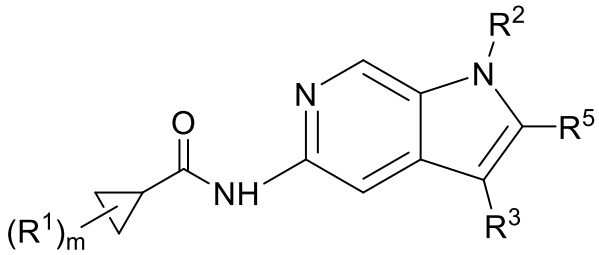
each R^{10} is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with hydroxyl, C_1-C_3 alkoxy, and/or 1-6 deuterium atoms.

[0010] In some examples, the compound of formula (I) is a compound of formula (I-A):

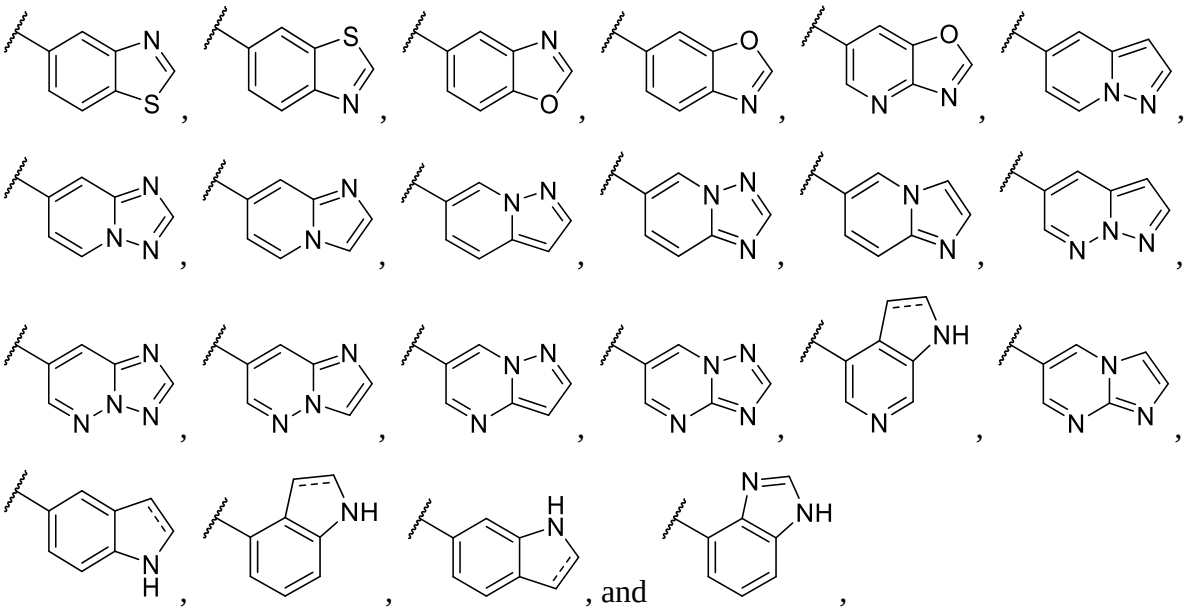


(I-A).

[0011] In some examples, the compound of formula (I) is a compound of formula (I-A-i) or formula (I-A-ii):



(I-A-i), or



wherein ⚌ indicates a single or double bond, and wherein said C_6-C_{14} aryl or said 5-to-10-membered heteroaryl is optionally substituted with 1-5 R^9 groups;

each R^7 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkyl-CN, or C_2-C_3 heteroalkyl;

each R^8 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkyl-CN, or C_2-C_3 heteroalkyl;

each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

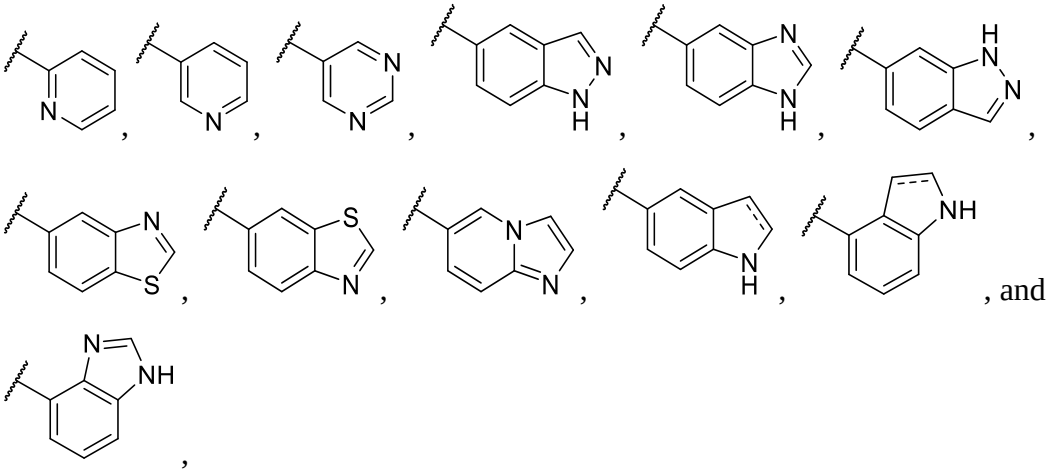
each R^9 is independently halogen, -OR^{10}, C_1-C_3 alkyl, -CF_2H, -CF_3, C_3-C_6 cycloalkyl, or

-CN, and

each R^{10} is independently -H, C_1-C_3 alkyl, -CD_3, -CF_2H, -CF_3, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with hydroxyl and/or C_1-C_3 alkoxy and/or 1-6 deuterium atoms.

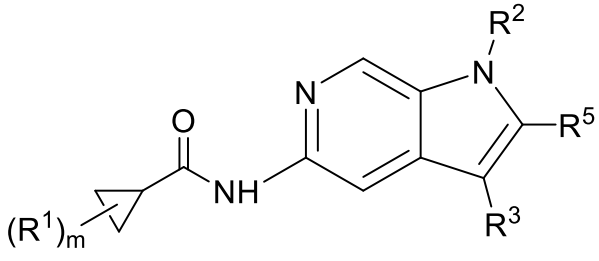
[0012] In some examples, which may be combined with any of the preceding examples, each R^1 is independently -F, C_1-C_3 alkylene-$NR^{7'}R^{8'}$, or C_1-C_3 alkylene-OH; and wherein each pair of $R^{7'}$ and $R^{8'}$ of R^1 taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the

heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein the nitrogen atom of any primary or secondary amine present in the heterocyclic ring is optionally substituted by H, or C_1-C_3 alkyl. In other examples, which may be combined with any of the preceding examples, R^5 is phenyl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:



wherein ⎓ indicates a single or double bond, and wherein said phenyl or said 5-to-10-membered heteroaryl is optionally substituted with 1-3 R^9 groups. In still other examples, which may be combined with any of the preceding examples, R^2 is -CH_3, CD_3, or -CH_2CH_3; R^3 is -H, -F, -CH_3, or -CN; $R^{3'}$ is -H or -CH_3; and R^4 is -H, -F or -CH_3. In yet further examples, which may be combined with any of the preceding examples, each R^9 is independently -F, -Cl, -OR^{10}, -CH_3, or -CN, and each R^{10} is independently -H, -CH_3, -CD_3, or -CH_2CH_3, wherein said -CH_3 or said -CH_2CH_3 is optionally substituted with hydroxyl and/or -OCH_3.

[0013] In yet other examples, which may be combined with any of the preceding examples, the compound of formula (I) is a compound of formula (I-A-i) or formula (I-A-ii):

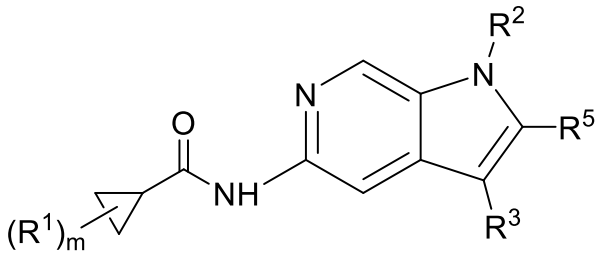


(I-A-i), or

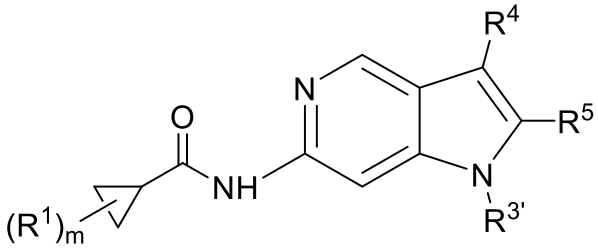
optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein the nitrogen atom of any primary or secondary amine present in the heterocyclic ring is optionally substituted by H, or C_1-C_3 alkyl;

each R^9 is independently -F, -Cl, $-OR^{10}$, $-CH_3$, or -CN, and

each R^{10} is independently -H, $-CH_3$, $-CD_3$, or $-CH_2CH_3$, wherein said $-CH_3$ or said $-CH_2CH_3$ is optionally substituted with hydroxyl and/or $-OCH_3$. In still yet other examples, which may be combined with any of the preceding examples, the compound of formula (I) is a compound of formula (I-A-i) or formula (I-A-ii):



(I-A-i), or



(I-A-ii),

wherein

m is an integer 0 or 1;

R^1 is -F;

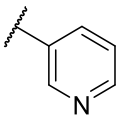
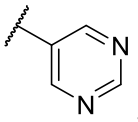
R^2 is $-CH_3$;

R^3 is -H or $-CH_3$;

$R^{3'}$ is -H or $-CH_3$;

R^4 is $-CH_3$;

R^5 is a 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:

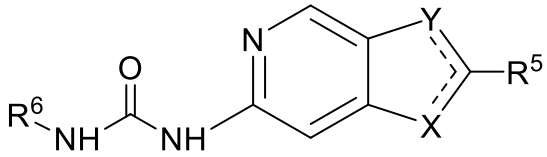
 and ,

wherein said 5-to-10-membered heteroaryl is optionally substituted with 1-3 R^9 groups;

each R^9 is independently -F or $-OR^{10}$, and

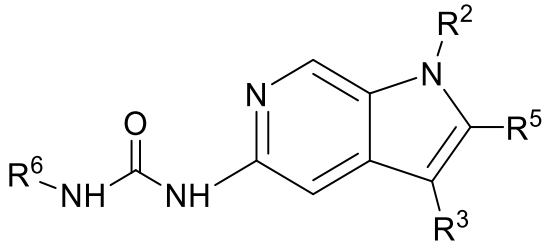
each R^{10} is independently -H or $-CH_3$.

[0014] In other examples, the compound of formula (I) is a compound of formula (I-B):

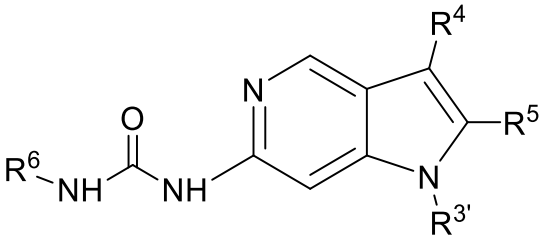


(I-B).

[0015] In some examples of the foregoing, the compound of formula (I) is a compound of formula (I-B-i) or formula (I-B-ii):



(I-B-i), or



(I-B-ii),

wherein

R^2 is -H, $-CH_3$, CD_3, $-CHF_2$, or $-CH_2CH_3$;

heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, and heterocycloalkylene moieties in R^6 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^7 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkyl-CN, or C_2-C_3 heteroalkyl;

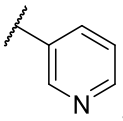
each R^8 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkyl-CN, or C_2-C_3 heteroalkyl;

each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^9 is independently halogen, $-OR^{10}$, C_1-C_3 alkyl, $-CF_2H$, $-CF_3$, C_3-C_6 cycloalkyl, or -CN, and

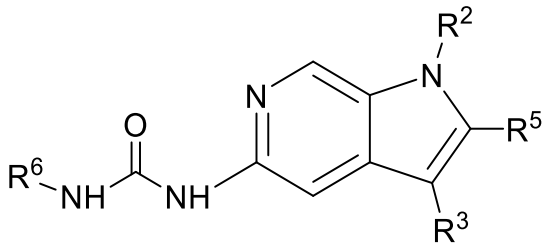
each R^{10} is independently -H, C_1-C_3 alkyl, $-CD_3$, $-CF_2H$, $-CF_3$, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with hydroxyl and/or C_1-C_3 alkoxy.

[0016] In some examples, which may be combined with any of the preceding examples, R^6 is C_1-C_3 alkyl or C_1-C_3 alkylene-$NR^{7'}R^{8'}$; and wherein each pair of $R^{7'}$ and $R^{8'}$ of R^6 taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl. In other examples, which may be combined with any of the preceding examples, R^5 is phenyl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:

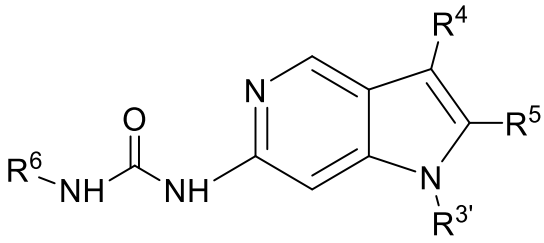


, wherein said phenyl or said 5-to-10-membered heteroaryl is optionally substituted with 1-3 R^9 groups. In still other examples, which may be combined with any of the preceding examples, each R^9 is independently -F, -OR^{10}, -CH_3, and each R^{10} is independently -H, -CH_3, -CD_3, -CF_2H, or -CF_3. In yet other examples, which may be combined with any of the preceding examples, R^2 is -H or -CH_3; R^3 is -H; $R^{3'}$ is -H; and R^4 is -H or -CH_3.

[0017] In some examples, which may be combined with any of the preceding examples, the compound of formula (I) is a compound of formula (I-B-i) or formula (I-B-ii):



(I-B-i), or



(I-B-ii),

wherein

R^2 is -H or -CH_3;

R^3 is -H;

$R^{3'}$ is -H;

R^4 is -H or -CH_3;

R^5 is phenyl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:

or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

[0019] In another example, provided herin is a pharmaceutical composition comprising a compound of formula (I) as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0020] In yet another example, the present disclosure provides a method of inhibiting Bcr-Abl enzymatic activity in a cell, comprising exposing the cell with an effective amount of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

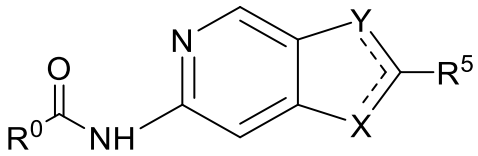
[0021] In still yet another example, provided herein is a method of treating chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or a mixed phenotype acute leukemia, in a human in need thereof, comprising administering to the human a compound of formula (I) as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) as described herein, or a pharmaceutically acceptable salt, solvate, hydrate, or co-crystal thereof, or a mixture of any of the foregoing.

[0022] In some examples, the leukemia is refractory leukemia. In certain examples of the foregoing, the refractory leukemia is associated with a mutation in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitutions selected from the group consisting of M244V, L248V, G250E, G250A, Q252H, Q252R, Y253F, Y253H, E255K, E255V, D276G, F311L, T315N, T315A, F317V, F317L, M343T, M351T, E355G, F359A, F359V, V379I, F382L, L387M, H396P, H396R, S417Y, E459K, F486S, and T315I. In still further examples of the foregoing, the refractory leukeumia is associated with a mutation in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitution T315I. In yet other examples, which may be combined with any preceding examples, the method further comprises administering one or more pharmaceutical agents including including anti-microtubular therapies,

CLAIMS

What is claimed:

Claim 1. A compound of formula (I):



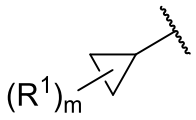
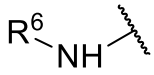
(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is $NR^{3'}$ or CR^3,

Y is NR^2 or CR^4,

wherein when X is $NR^{3'}$ then Y is CR^4, Y has a double bond to CR^5, and X has a single bond to CR^5; or when X is CR^3 then Y is NR^2, Y has a single bond to CR^5, and X has a double bond to CR^5;

R^0 is a group  or ;

m is an integer from 0 to 3;

each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^7R^8, C_1-C_3 alkylene-$NR^{7'}R^{8'}$, C_1-C_3 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein

each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

R^2 is -H, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms;

R^3 is -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, halogen, or -CN;

$R^{3'}$ is -H, C_1-C_3 alkyl, -C_3-C_6 cycloalkyl, or -CN;

R^4 is -H, C_1-C_3 alkyl, or halogen, wherein said C_1-C_3 alkyl is optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms;

R^5 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said C_6-C_{14} aryl or said 5-to-10-membered heteroaryl is optionally substituted with 1-5 R^9 groups;

R^6 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^7R^8, C_1-C_6 alkylene-$NR^{7'}R^{8'}$, C_1-C_6 alkylene-OH, C_1-C_6 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(4- to 8-membered heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_3-C_7 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, and heterocycloalkylene moieties in R^6 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^7 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

each R^8 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 3- to 8-membered heterocyclic ring, wherein the heterocyclic ring

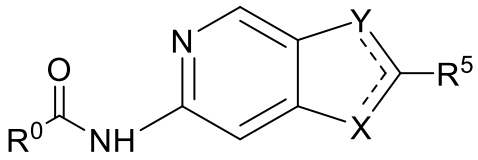
optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^9 is independently halogen, -OR^{10}, -NR^7R^8, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

wherein n is an integer from 0 to 2; and

each R^{10} is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with hydroxyl, C_1-C_3 alkoxy, and/or 1-6 deuterium atoms.

Claim 2. A compound of formula (I):



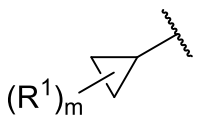
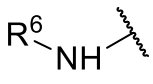
(I)

or a pharmaceutically acceptable salt thereof, wherein:

X is $NR^{3'}$ or CR^3,

Y is NR^2 or CR^4,

wherein when X is $NR^{3'}$ then Y is CR^4, Y has a double bond to CR^5, and X has a single bond to CR^5; or when X is CR^3 then Y is NR^2, Y has a single bond to CR^5, and X has a double bond to CR^5;

R^0 is a group  or ;

m is an integer from 0 to 3;

each R^1 is independently -D, -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^7R^8, C_1-C_3 alkylene-$NR^{7'}R^{8'}$, C_1-C_3 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene moieties in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

R^2 is -H, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms;

R^3 is -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, halogen, or -CN;

$R^{3'}$ is -H, C_1-C_3 alkyl, -C_3-C_6 cycloalkyl, or -CN;

R^4 is -H, C_1-C_3 alkyl, or halogen, wherein said C_1-C_3 alkyl is optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms;

R^5 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said C_6-C_{14} aryl or said 5-to-10-membered heteroaryl is optionally substituted with 1-5 R^9 groups;

R^6 is -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkylene-NR^7R^8, C_1-C_6 alkylene-$NR^{7'}R^{8'}$, C_1-C_6 alkylene-OH, C_1-C_6 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, and heterocycloalkylene moieties in R^6 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^7 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

each R^8 is independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkylene-CN, or C_1-C_6 heteroalkyl;

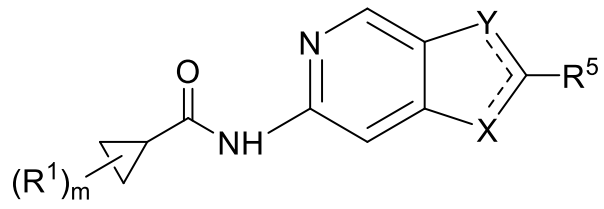
each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^9 is independently halogen, -OR^{10}, -NR^7R^8, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl, -CN, $S(O)_nC_1$-C_3 alkyl, or $S(O)_nC_3$-C_6 cycloalkyl,

wherein n is an integer from 0 to 2; and

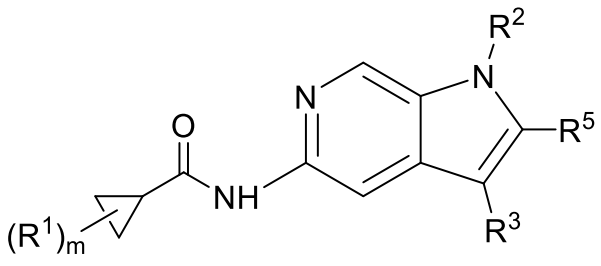
each R^{10} is independently -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with hydroxyl, C_1-C_3 alkoxy, and/or 1-6 deuterium atoms.

Claim 3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (I-A):

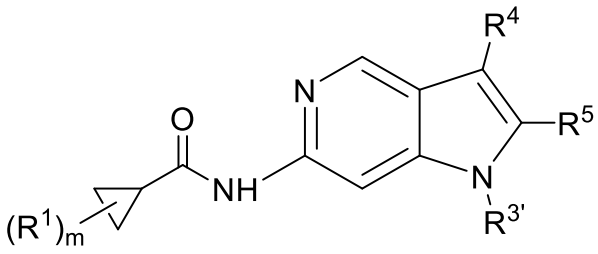


(I-A).

Claim 4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (I-A-i) or formula (I-A-ii):



(I-A-i), or



(I-A-ii),

wherein

m is an integer 0 or 2;

each R^1 is independently -F, C_1-C_3 alkyl, C_1-C_3 alkylene-NR^7R^8, C_1-C_3 alkylene-$NR^{7'}R^{8'}$, C_1-C_3 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$,C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, wherein the alkyl, alkylene, cycloalkylene, and heterocycloalkylene in R^1 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

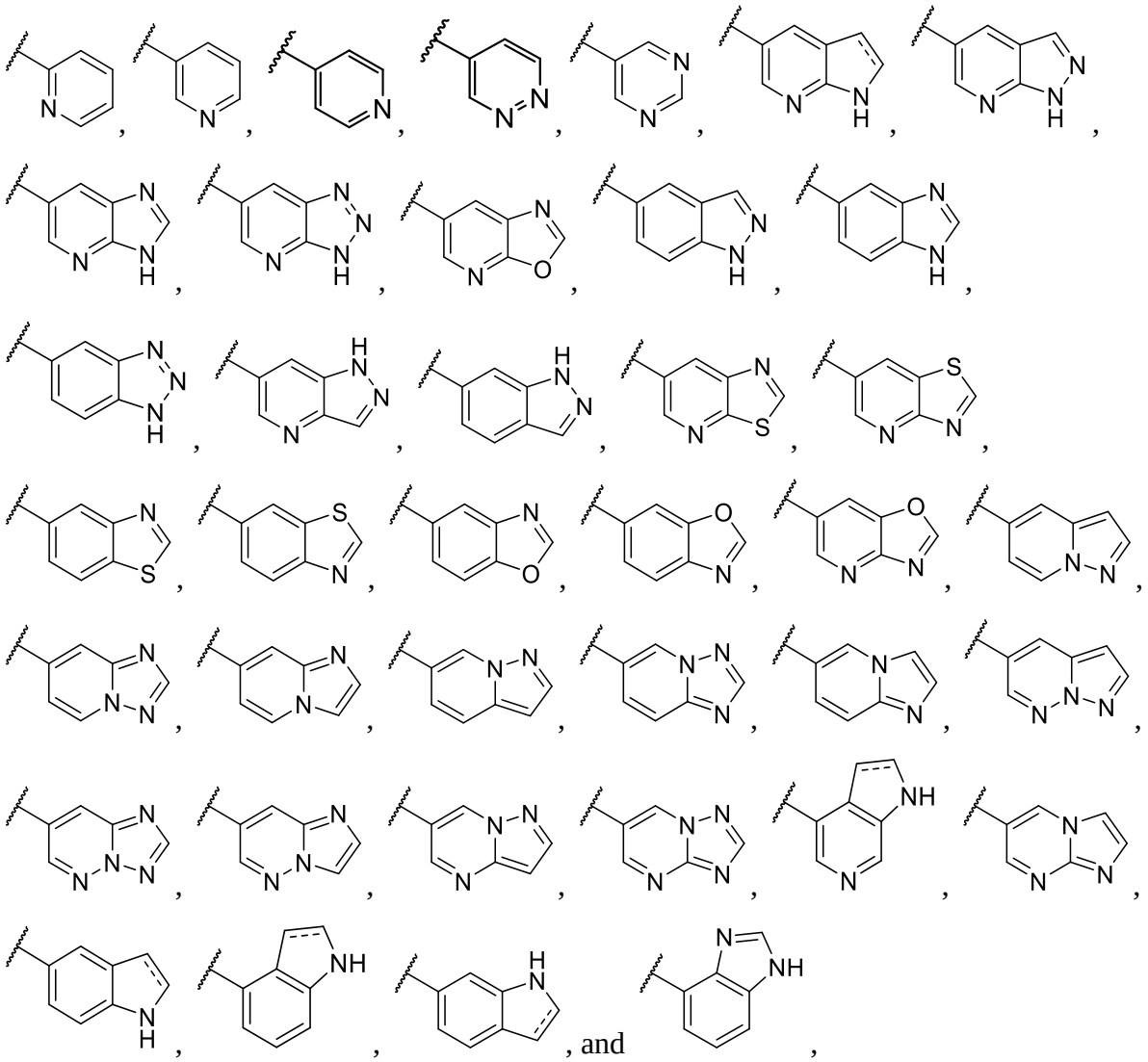
R^2 is -H, $-CH_3$, CD_3, $-CHF_2$, or $-CH_2CH_3$;

R^3 is -H, C_1-C_3 alkyl, C_3-cycloalkyl, halogen, or -CN;

$R^{3'}$ is -H, C_1-C_3 alkyl, C_3-cycloalkyl, or -CN;

R^4 is -H, $-CH_3$, $-CD_3$, $-CHF_2$, $-CH_2CH_3$, or halogen;

R^5 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:



wherein ⁼⁼⁼ indicates a single or double bond, and wherein said C_6-C_{14} aryl or said 5-to-10-membered heteroaryl is optionally substituted with 1-5 R^9 groups;

each R^7 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkyl-CN, or C_2-C_3 heteroalkyl;

each R^8 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkyl-CN, or C_2-C_3 heteroalkyl;

each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally

substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^9 is independently halogen, -OR^{10}, C_1-C_3 alkyl, -CF_2H, -CF_3, C_3-C_6 cycloalkyl, or
-CN, and

each R^{10} is independently -H, C_1-C_3 alkyl, -CD_3, -CF_2H, -CF_3, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with hydroxyl and/or C_1-C_3 alkoxy and/or 1-6 deuterium atoms.

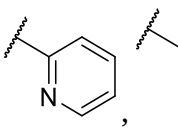
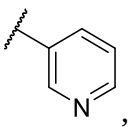
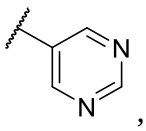
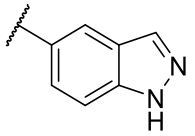
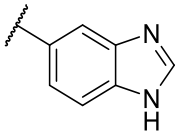
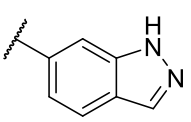
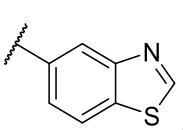
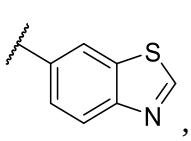
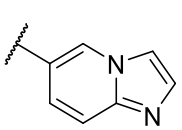
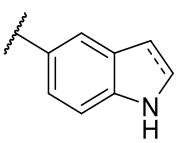
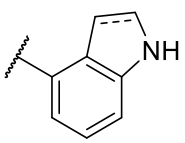
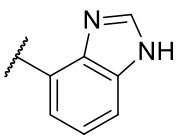
Claim 5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein

each R^1 is independently -F, C_1-C_3 alkylene-$NR^{7'}R^{8'}$, or C_1-C_3 alkylene-OH; and

wherein each pair of $R^{7'}$ and $R^{8'}$ of R^1 taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein the nitrogen atom of any primary or secondary amine present in the heterocyclic ring is optionally substituted by -H or C_1-C_3 alkyl.

Claim 6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein

R^5 is phenyl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:


,

,

,

,

,

,

,

,

,

,

, and

,

wherein ⎓ indicates a single or double bond, and wherein said phenyl or said 5-to-10-membered heteroaryl is optionally substituted with 1-3 R^9 groups.

Claim 7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein

R^2 is -CH_3, -CD_3, or -CH_2CH_3;

R^3 is -H, -F, -CH_3, or -CN;

$R^{3'}$ is -H or -CH_3; and

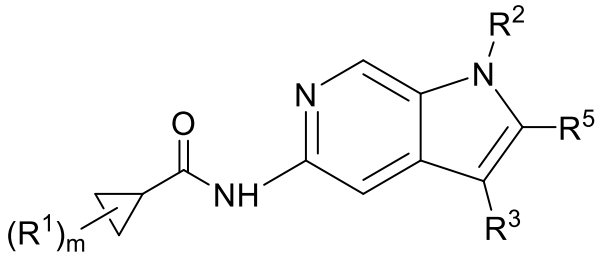
R^4 is -H, -F or -CH_3.

Claim 8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein

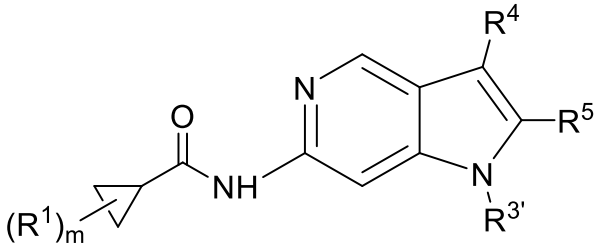
each R^9 is independently -F, -Cl, -OR^{10}, -CH_3, or -CN, and

each R^{10} is independently -H, -CH_3, -CD_3, or -CH_2CH_3, wherein said -CH_3 or said -CH_2CH_3 is optionally substituted with hydroxyl and/or -OCH_3.

Claim 9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (I-A-i) or formula (I-A-ii):



(I-A-i), or



(I-A-ii),

wherein

m is an integer 0 or 1;

R^1 is -F, C_1-C_3 alkylene-$NR^{7'}R^{8'}$, or C_1-C_3 alkylene-OH;

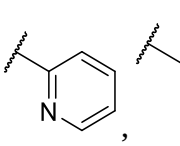
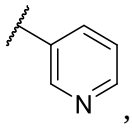
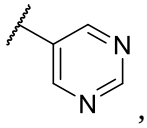
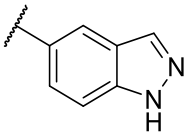
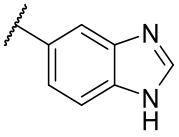
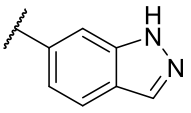
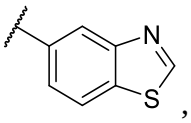
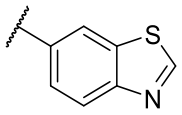
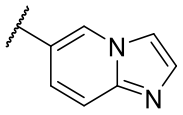
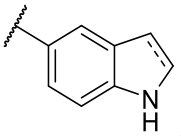
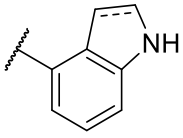
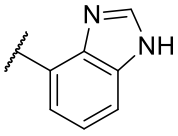
R^2 is $-CH_3$, $-CD_3$, or $-CH_2CH_3$;

R^3 is -H, -F, $-CH_3$, or -CN;

$R^{3'}$ is -H or $-CH_3$;

R^4 is -H, -F or $-CH_3$;

R^5 is phenyl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:


,

,

,

,

,

,

,

,

,

,

, and

,

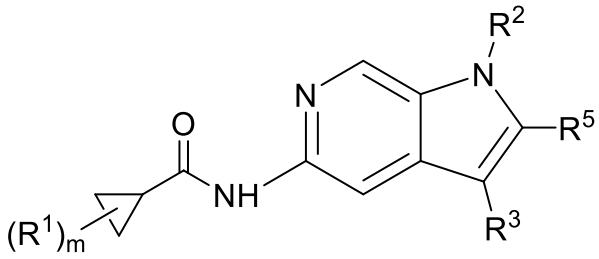
wherein ⁻⁻⁻ indicates a single or double bond, and wherein said phenyl or said 5-to-10-membered heteroaryl is optionally substituted with 1-3 R^9 groups;

each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N and O, and wherein the nitrogen atom of any primary or secondary amine present in the heterocyclic ring is optionally substituted by -H or C_1-C_3 alkyl;

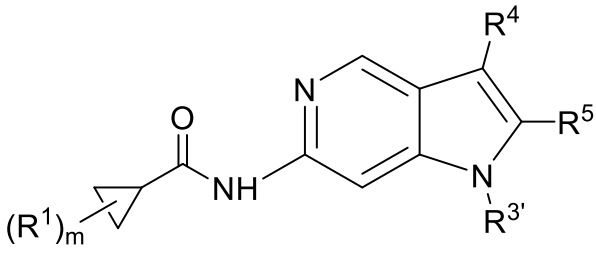
each R^9 is independently -F, -Cl, $-OR^{10}$, $-CH_3$, or -CN, and

each R^{10} is independently -H, $-CH_3$, $-CD_3$, or $-CH_2CH_3$, wherein said $-CH_3$ or said $-CH_2CH_3$ is optionally substituted with hydroxyl and/or $-OCH_3$.

Claim 10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (I-A-i) or formula (I-A-ii):



(I-A-i), or



(I-A-ii),

wherein

m is an integer 0 or 1;

R^1 is -F;

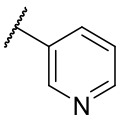
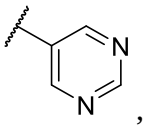
R^2 is $-CH_3$;

R^3 is -H or $-CH_3$;

$R^{3'}$ is -H or $-CH_3$;

R^4 is $-CH_3$;

R^5 is a 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:

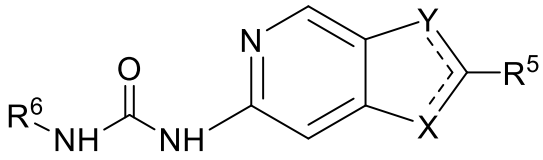
 and ,

wherein said 5-to-10-membered heteroaryl is optionally substituted with 1-3 R^9 groups;

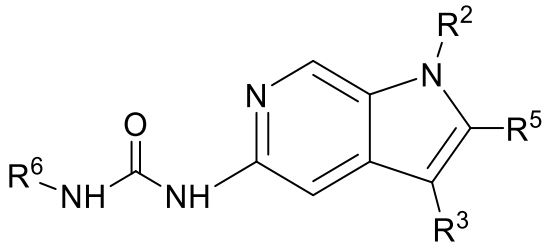
each R^9 is independently -F or $-OR^{10}$, and

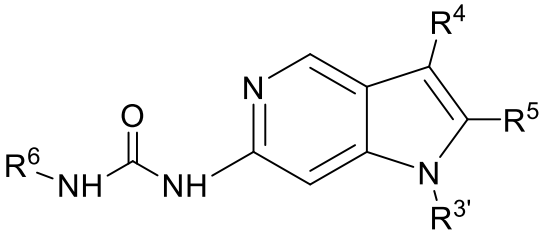
each R^{10} is independently -H or $-CH_3$.

Claim 11. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (I-B):

 (I-B).

Claim 12. The compound of any one of claims 1, 2 and 11, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (I-B-i) or formula (I-B-ii):

 (I-B-i), or

 (I-B-ii),

wherein

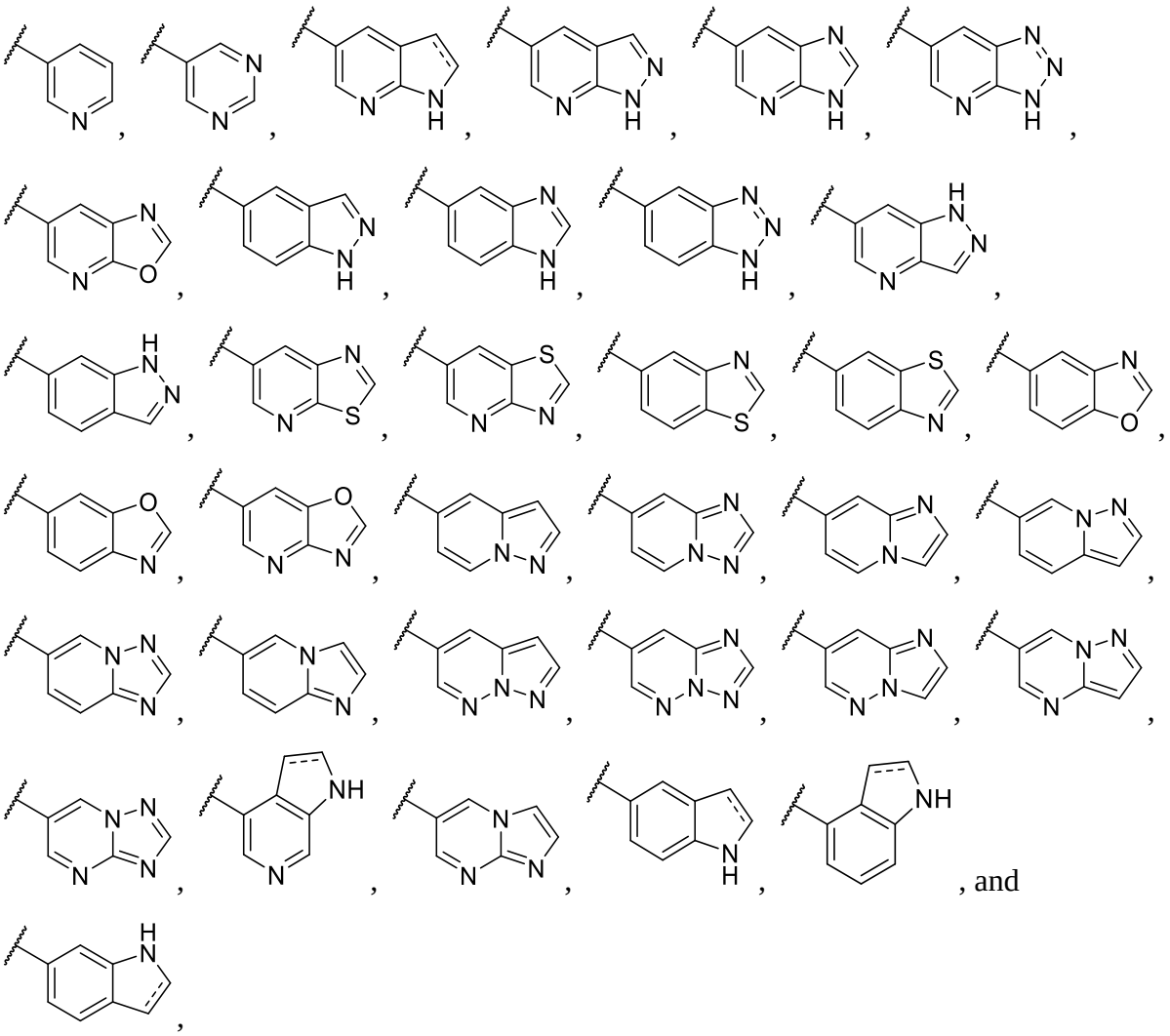
R^2 is -H, $-CH_3$, CD_3, $-CHF_2$, or $-CH_2CH_3$;

R^3 is -H, C_1-C_3 alkyl, C_3-cycloalkyl, halogen, or -CN;

$R^{3'}$ is -H, C_1-C_3 alkyl, C_3-cycloalkyl, or -CN;

R^4 is -H, $-CH_3$, $-CD_3$, $-CHF_2$, $-CH_2CH_3$, or halogen;

R^5 is C_6-C_{14} aryl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:



wherein ⚌ indicates a single or double bond, and wherein said C_6-C_{14} aryl or said 5-to-10-membered heteroaryl is optionally substituted with 1-5 R^9 groups;

R^6 is C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_1-C_3 alkylene-NR^7R^8, C_1-C_3 alkylene-$NR^{7'}R^{8'}$, C_1-C_3 alkylene-OH, C_1-C_3 alkylene-CN, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, C_1-C_2 alkylene-(C_3-C_6 cycloalkylene)-(C_0-C_2 alkylene)-OH, C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-(C_0-C_2 alkylene)-NR^7R^8, or C_1-C_2 alkylene-(C_4-C_6 heterocycloalkylene)-

(C_0-C_2 alkylene)-$NR^{7'}R^{8'}$, wherein the alkyl, alkylene, cycloalkyl, cycloalkylene, and heterocycloalkylene moieties in R^6 are optionally substituted with 1-3 fluorine atoms and/or 1-6 deuterium atoms, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^7 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkyl-CN, or C_2-C_3 heteroalkyl;

each R^8 is independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkyl-CN, or C_2-C_3 heteroalkyl;

each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^9 is independently halogen, $-OR^{10}$, C_1-C_3 alkyl, $-CF_2H$, $-CF_3$, C_3-C_6 cycloalkyl, or -CN, and

each R^{10} is independently -H, C_1-C_3 alkyl, $-CD_3$, $-CF_2H$, $-CF_3$, or C_3-C_6 cycloalkyl, wherein said C_1-C_3 alkyl is optionally substituted with hydroxyl and/or C_1-C_3 alkoxy.

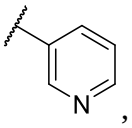
Claim 13. The compound of any one of claims 1 to 2 and 11 to 12, or a pharmaceutically acceptable salt thereof, wherein

R^6 is C_1-C_3 alkyl or C_1-C_3 alkylene-$NR^{7'}R^{8'}$; and

wherein each pair of $R^{7'}$ and $R^{8'}$ of R^6 taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl.

Claim 14. The compound of any one of claims 1 to 2 and 11 to 13, or a pharmaceutically acceptable salt thereof, wherein

R^5 is phenyl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of:



,

wherein said phenyl or said 5-to-10-membered heteroaryl is optionally substituted with 1-3 R^9 groups.

Claim 15. The compound of any one of claims 1 to 2 and 11 to 14, or a pharmaceutically acceptable salt thereof, wherein

each R^9 is independently -F, $-OR^{10}$, or $-CH_3$, and

each R^{10} is independently -H, $-CH_3$, $-CD_3$, $-CF_2H$, or $-CF_3$.

Claim 16. The compound of any one of claims 1 to 2 and 11 to 15, or a pharmaceutically acceptable salt thereof, wherein

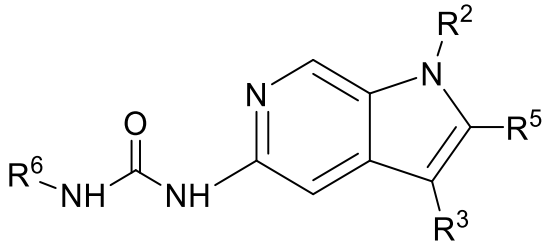
R^2 is -H or $-CH_3$;

R^3 is -H;

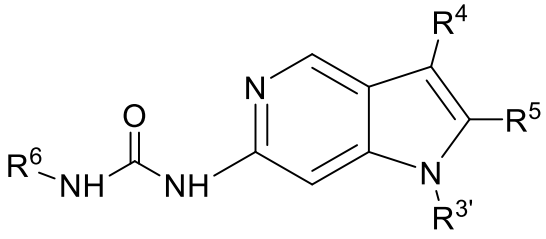
$R^{3'}$ is -H; and

R^4 is -H or $-CH_3$.

Claim 17. The compound of any one of claims 1 to 2 and 11 to 16, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (I-B-i) or formula (I-B-ii):



(I-B-i), or



(I-B-ii),

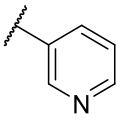
wherein

R^2 is -H or -CH_3;

R^3 is -H;

$R^{3'}$ is -H;

R^4 is -H or -CH_3;

R^5 is phenyl or 5-to-10-membered heteroaryl, wherein said 5-to-10-membered heteroaryl is selected from the group consisting of: , wherein said phenyl or said 5-to-10-membered heteroaryl is optionally substituted with 1-3 R^9 groups;

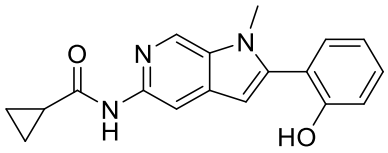
R^6 is C_1-C_3 alkyl or C_1-C_3 alkylene-$NR^{7'}R^{8'}$;

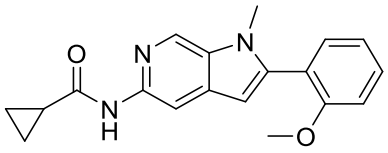
each pair of $R^{7'}$ and $R^{8'}$ taken together with the nitrogen atom to which they are attached independently form a 4-to-6-membered heterocyclic ring, wherein the heterocyclic ring optionally contains an additional 1-2 heteroatoms selected from the group consisting of N, O, and S, and wherein each heterocyclic nitrogen atom, if present, is independently optionally substituted with C_1-C_3 alkyl, C_3-C_6 cycloalkyl, C_2-C_3 haloalkyl, C_2-C_3 alkylene-CN, or C_2-C_3 heteroalkyl;

each R^9 is independently -F, -OR^{10}, or -CH_3, and

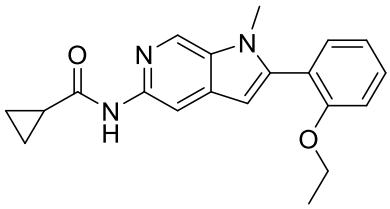
each R^{10} is independently -H, -CH_3, -CD_3, -CF_2H, or -CF_3.

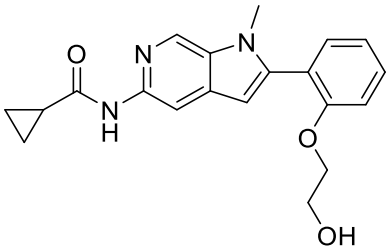
Claim 18. A compound selected from the group consisting of:



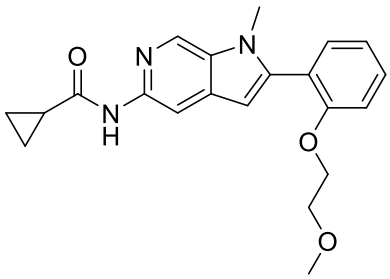
;


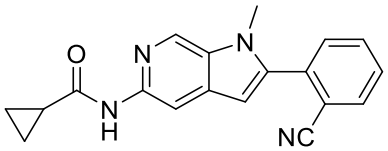
;



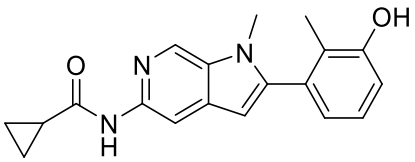
;


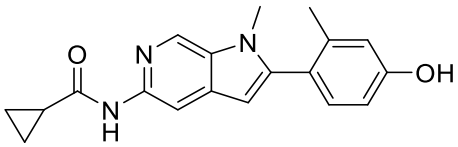
;



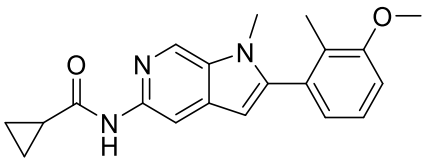
;


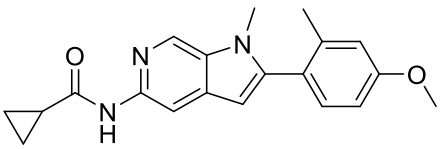
;



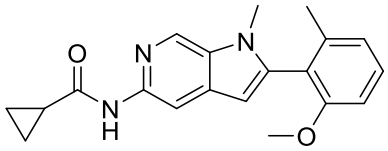
;


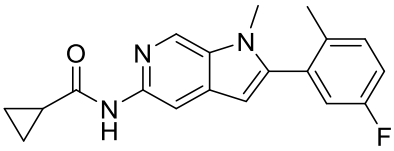
;



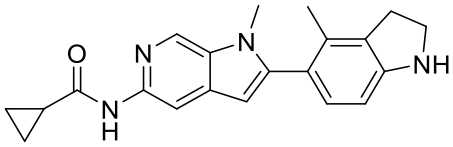
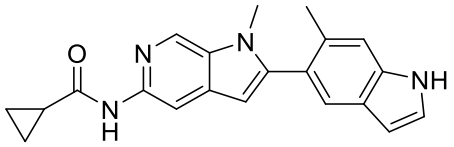
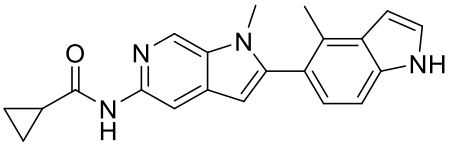
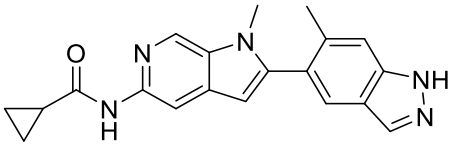
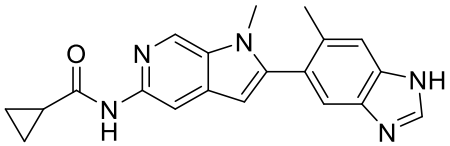
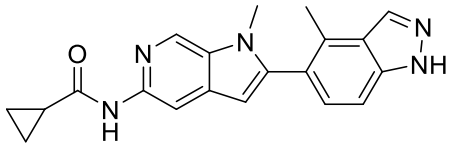
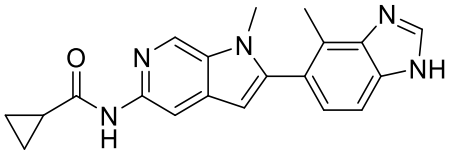
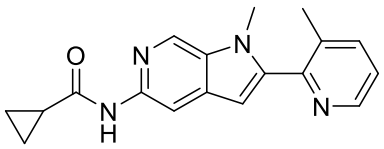
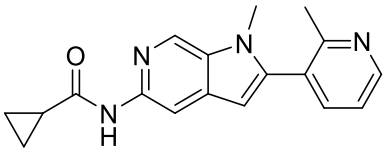
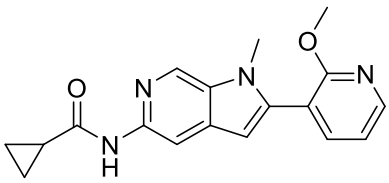
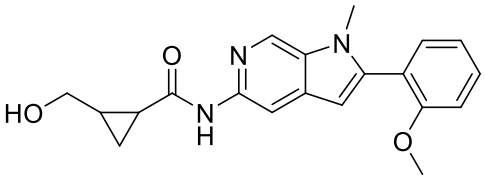
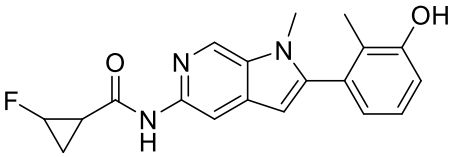
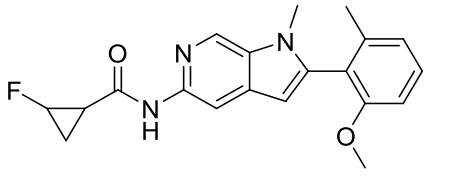
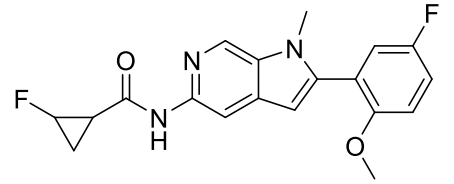
;


;



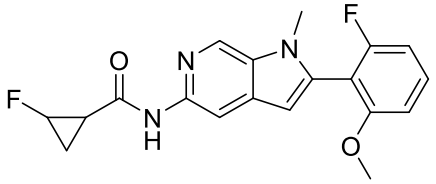
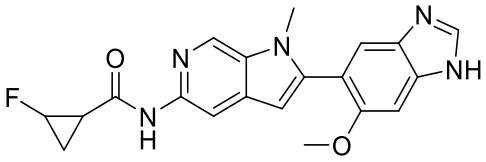
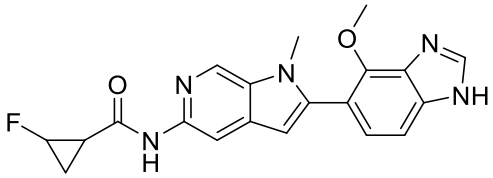
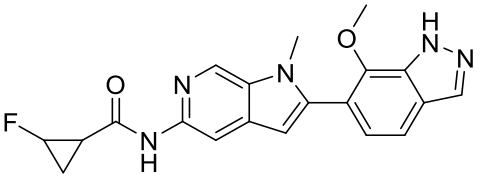
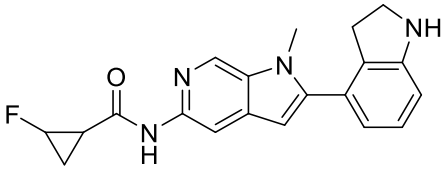
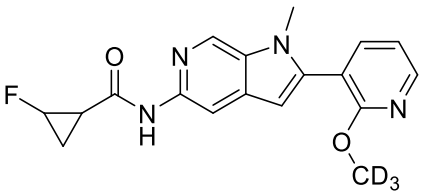
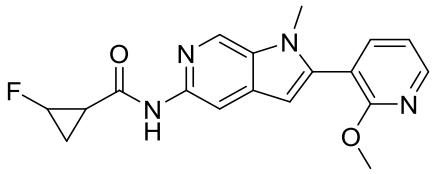
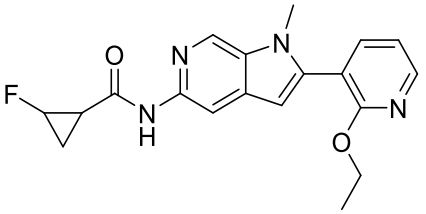
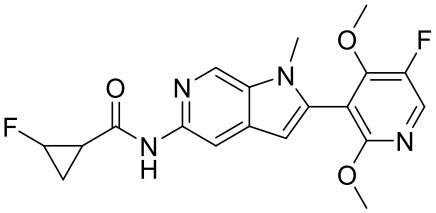
;


;

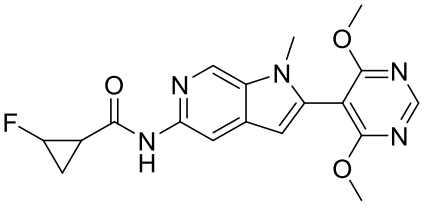

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

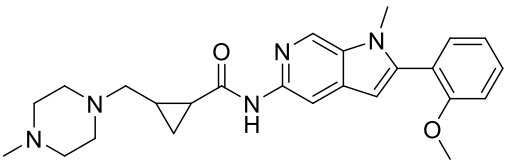
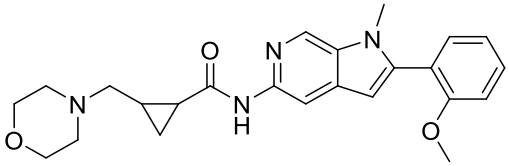
;

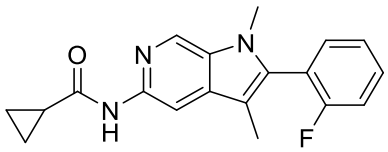
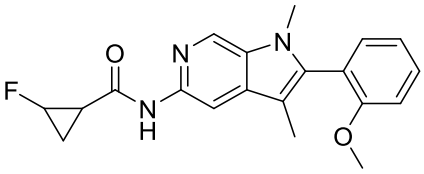
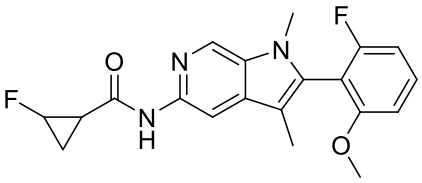
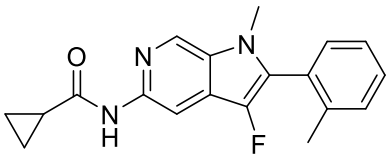
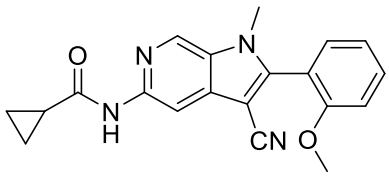
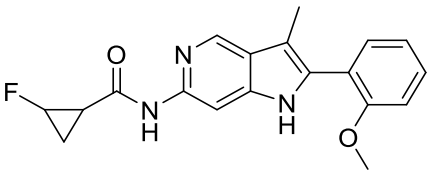
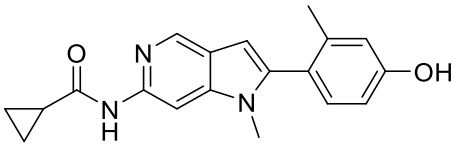
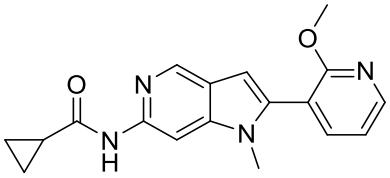
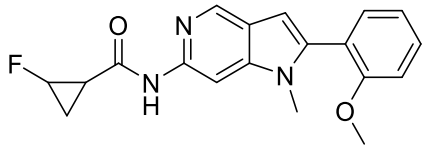
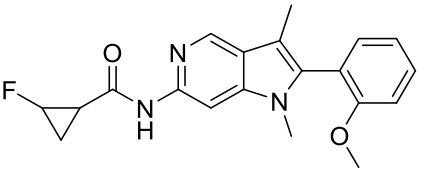
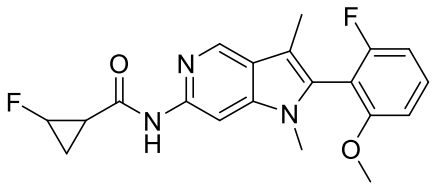
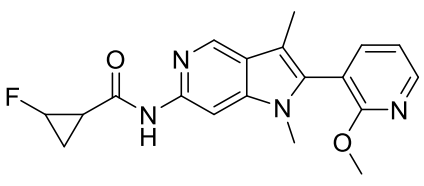
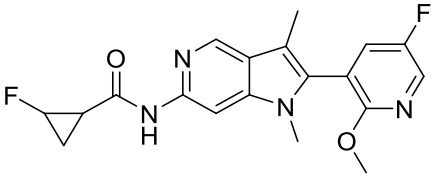
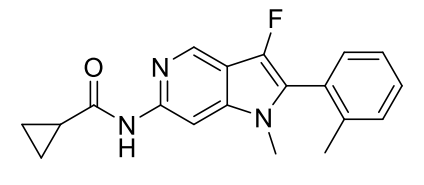

;

;

;

;

;

;

;

;

;

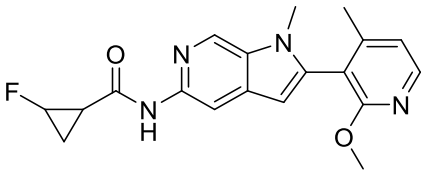
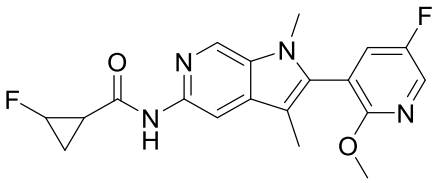
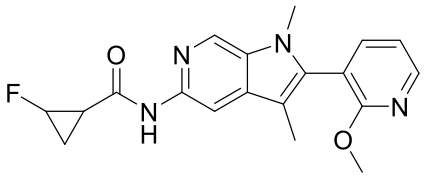
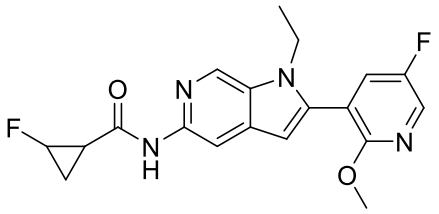
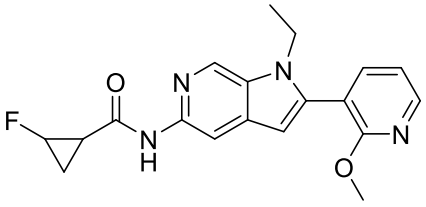
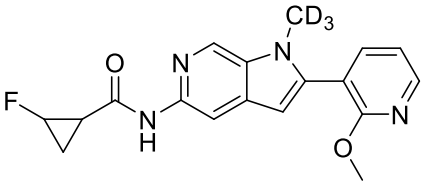
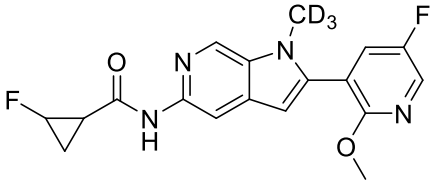
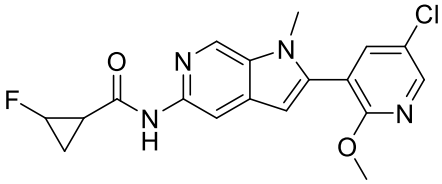
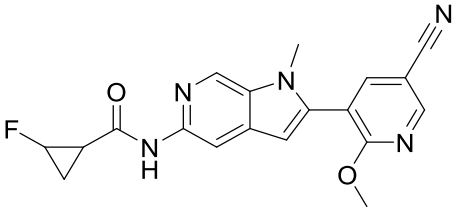
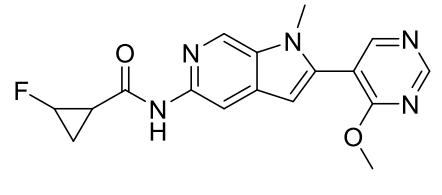
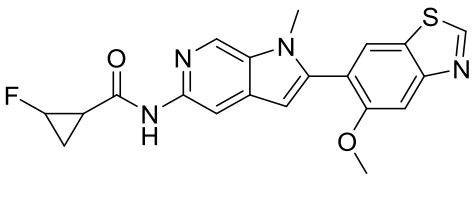
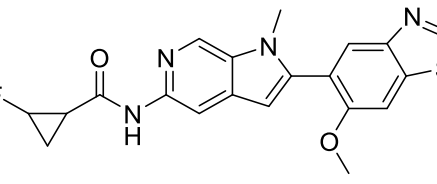
;

;

;

;

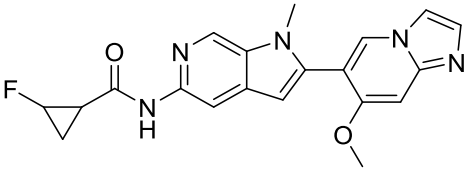
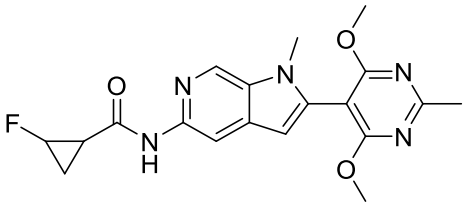
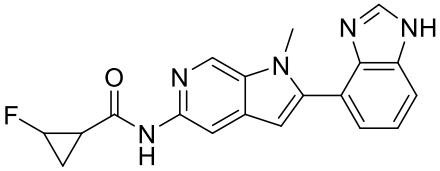
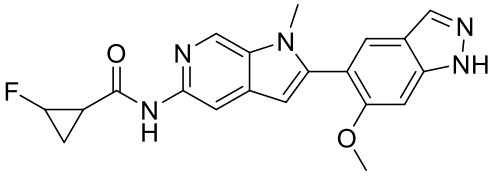
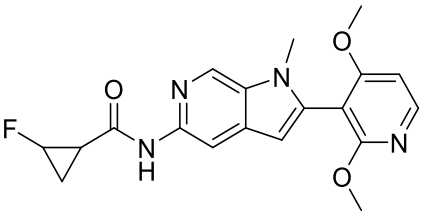
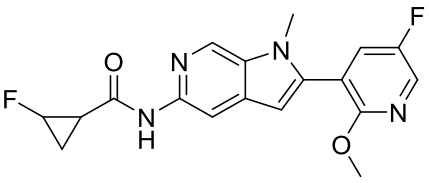
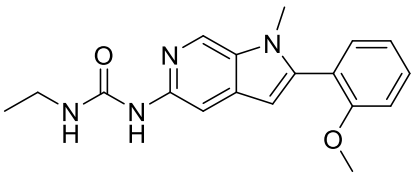
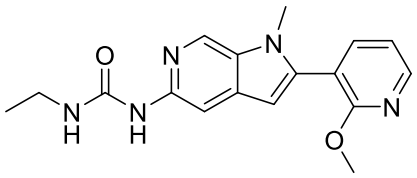
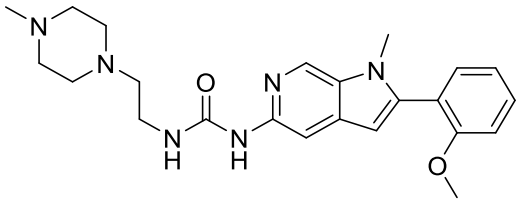
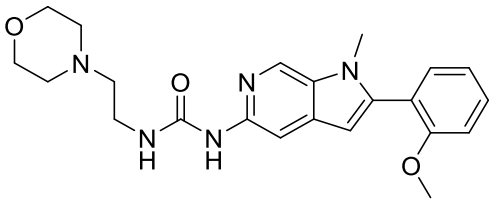
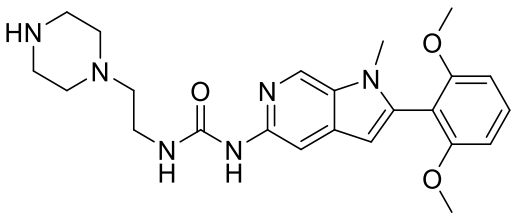
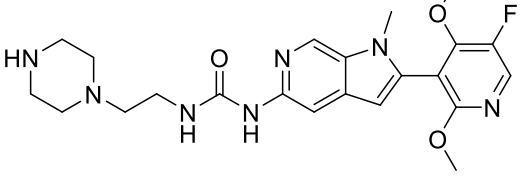
;

;

;

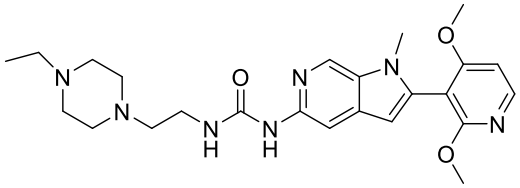
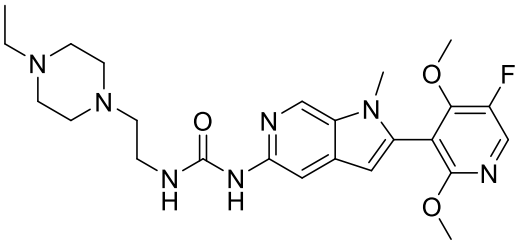
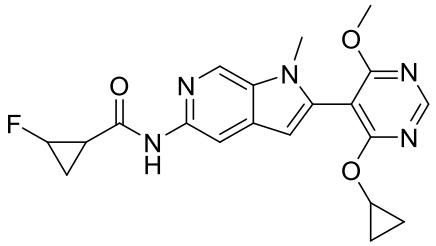
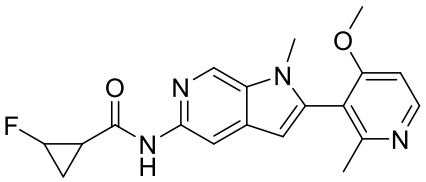
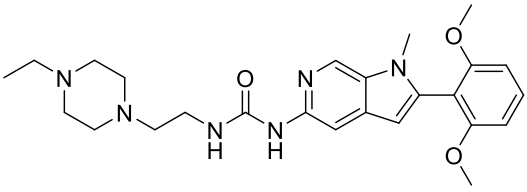
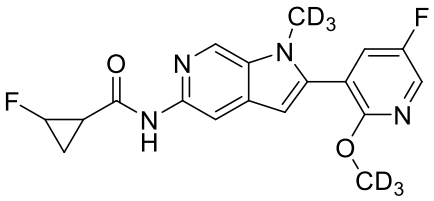
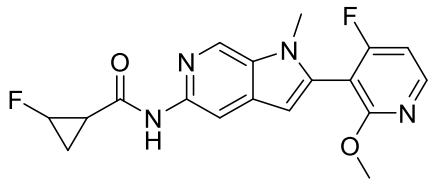
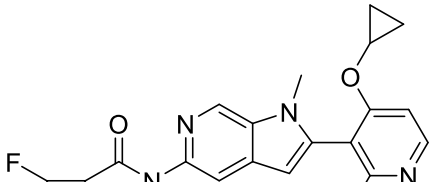
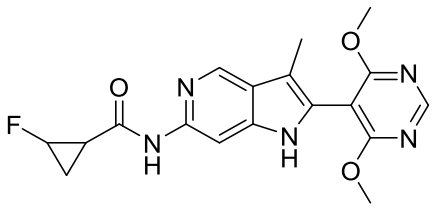
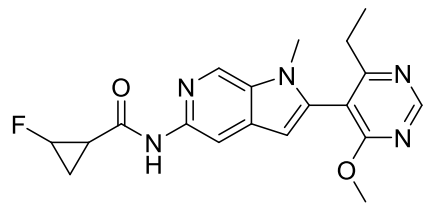

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

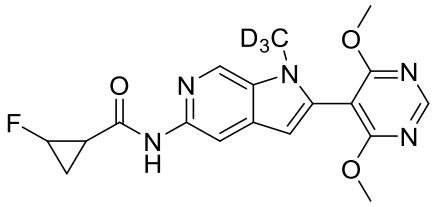
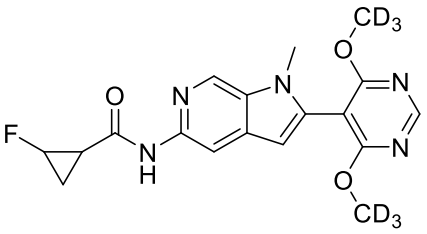
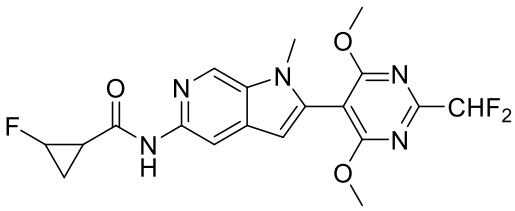
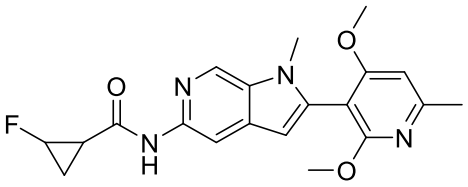
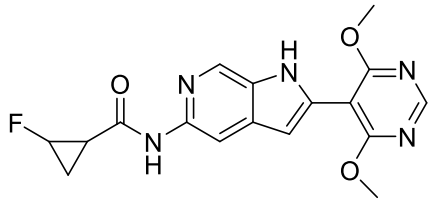
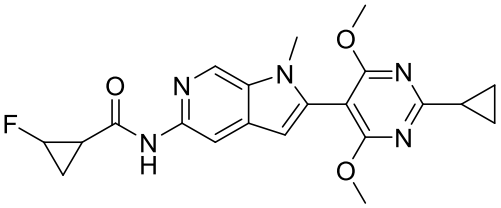
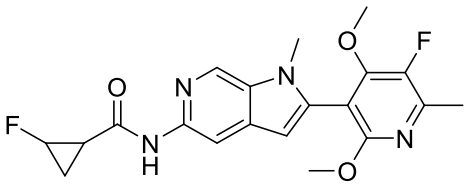
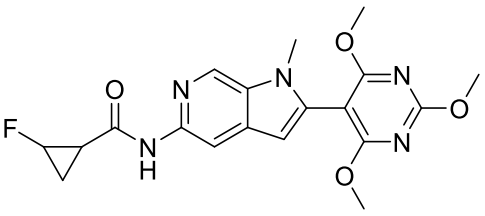
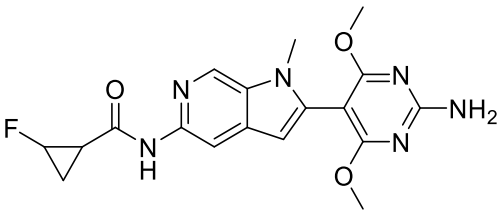
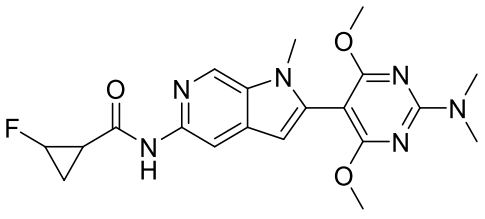
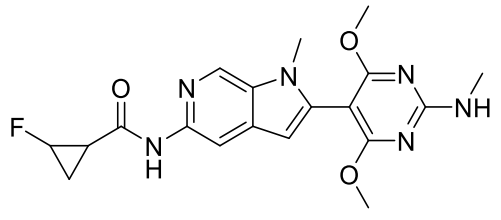
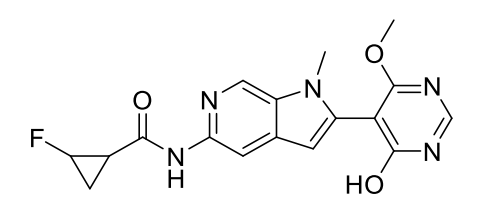
;


;

;

;

;

;

;

;

;

;

;

;

;


;

,

;

;

;

;

;

;

;

;

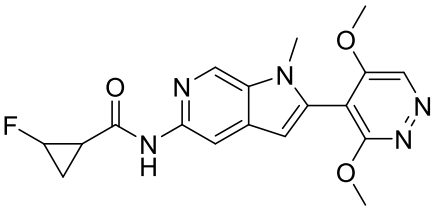
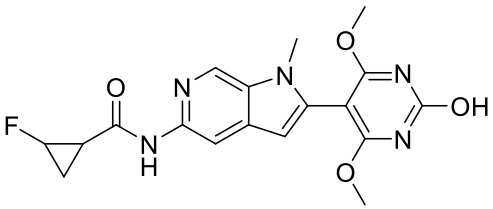
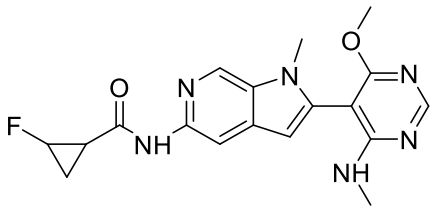
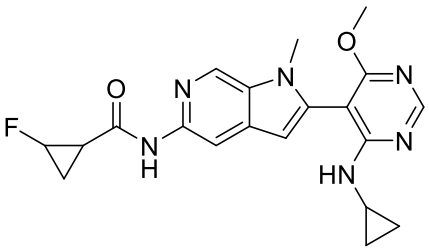
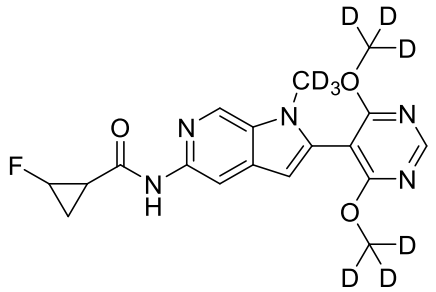
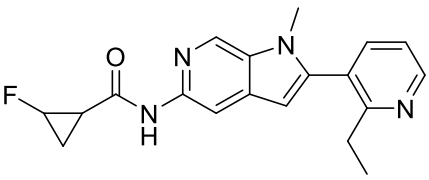
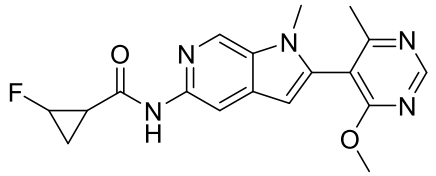
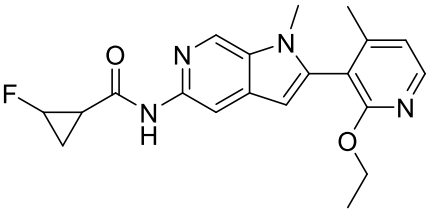
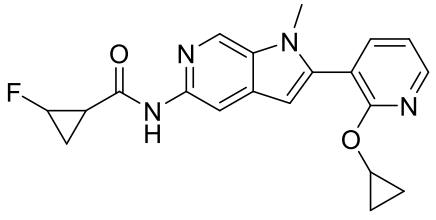
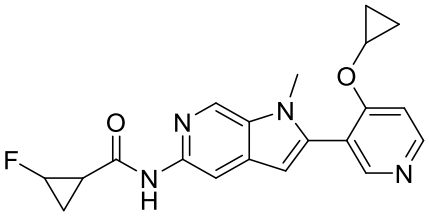
;

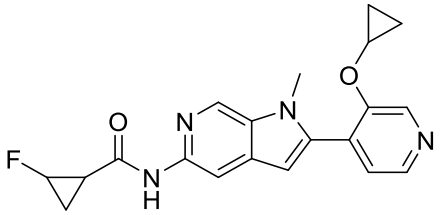
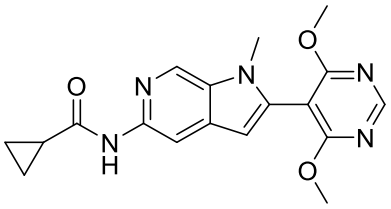
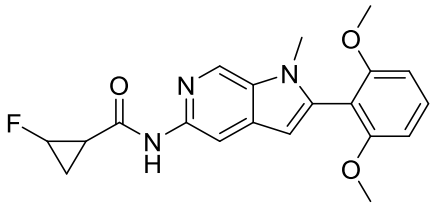
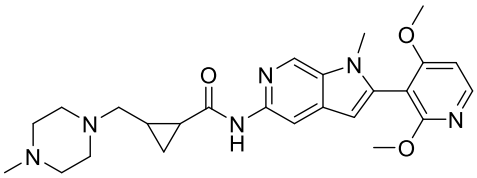
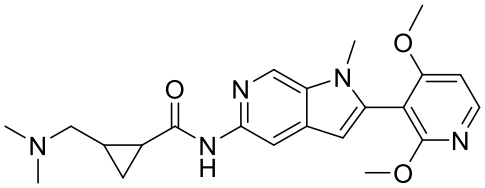
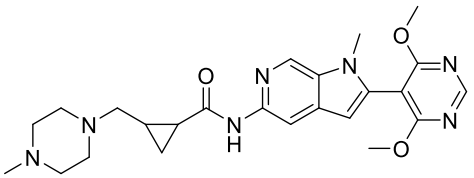
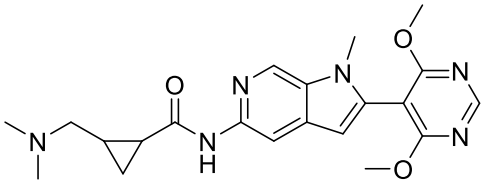
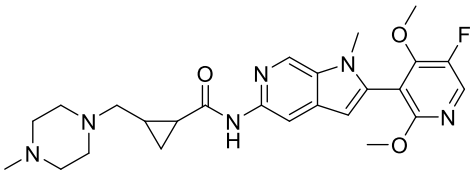
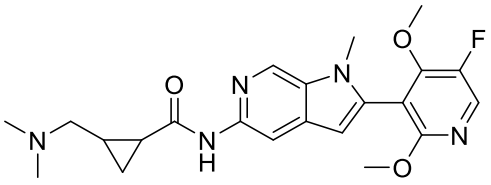
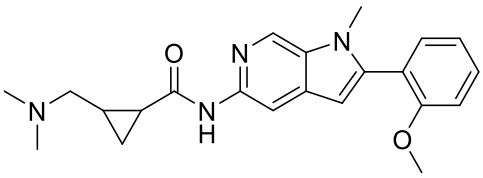
;

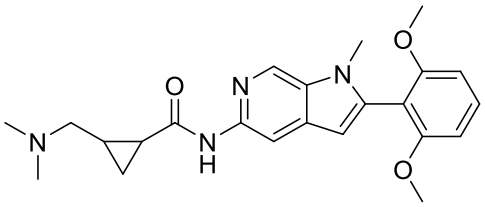

;

;

;

;

;

;

;

;

;

;

;

;

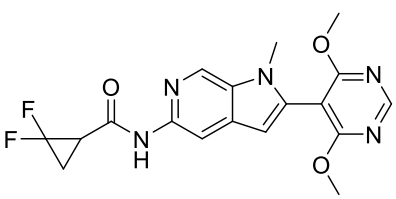
;

;


;

;

;

;

;

;

;

;

;

;

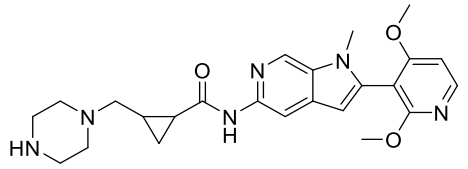
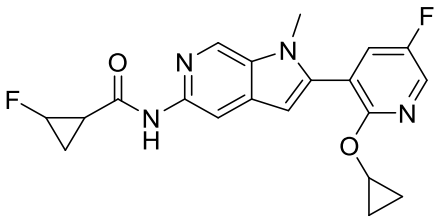

;

;

;

;

;

;

;

;

;

;

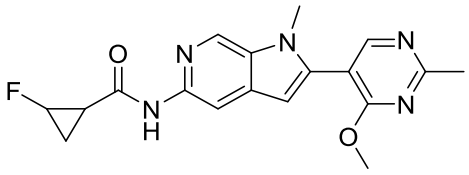
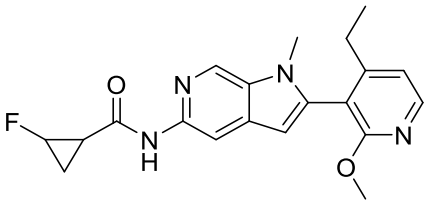
;

;

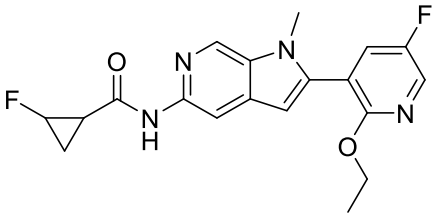
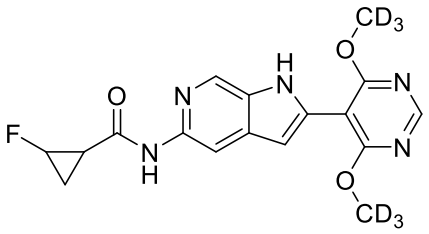
;

;

;

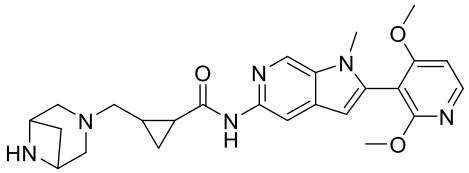
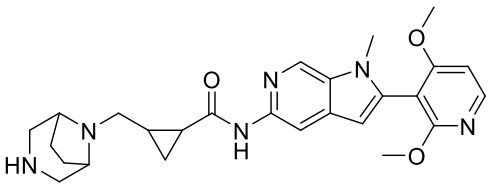
;


;

;


;

;

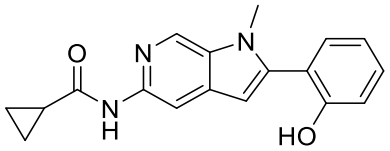
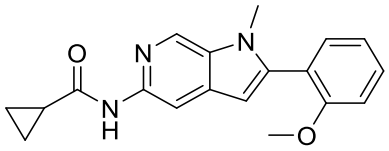

;

;

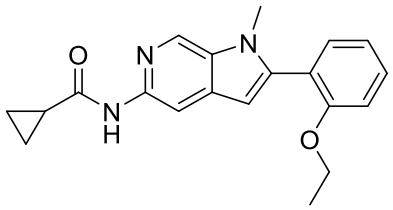
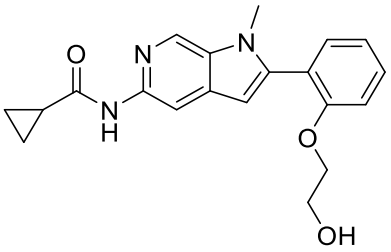
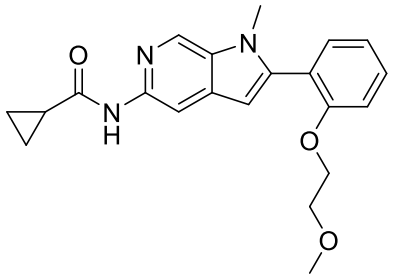
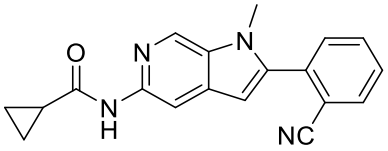
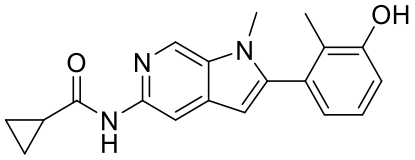
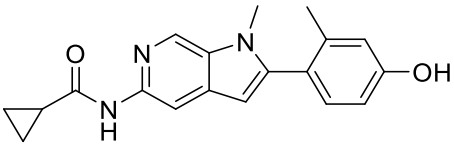
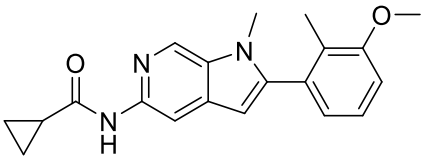
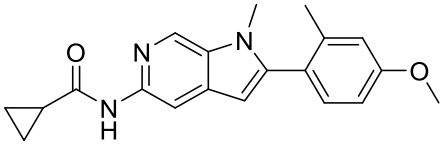
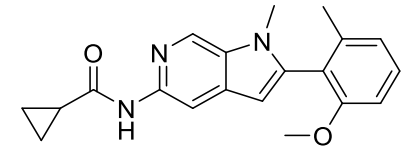
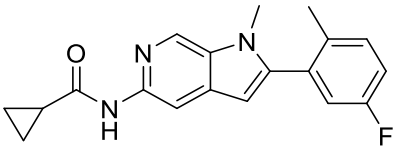
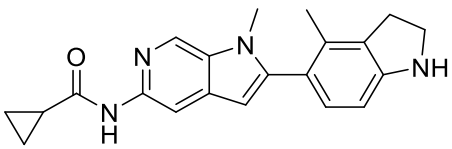
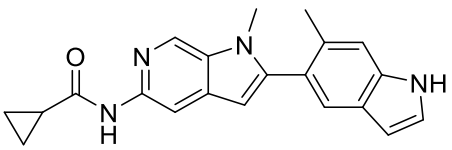
and

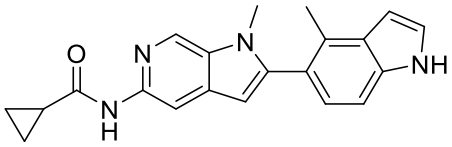
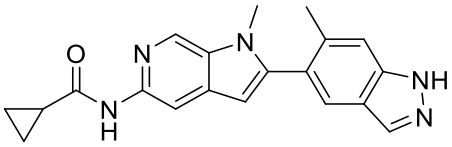
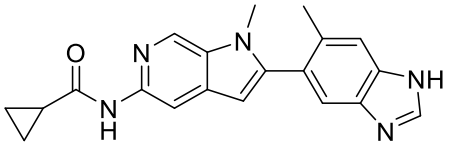
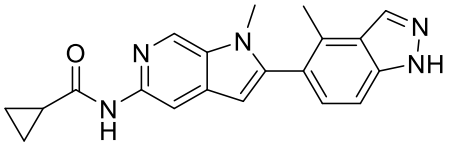
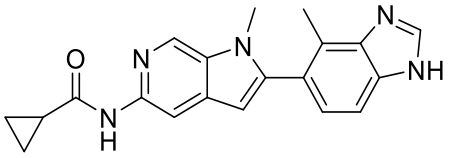
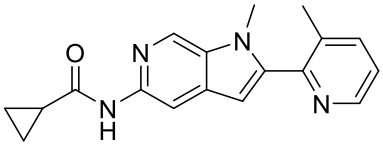
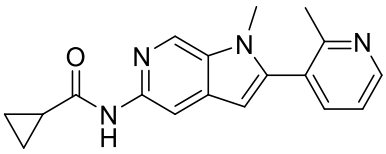
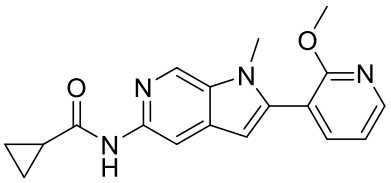
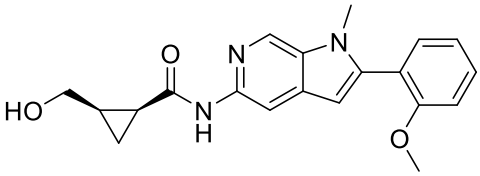
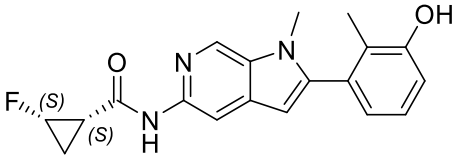
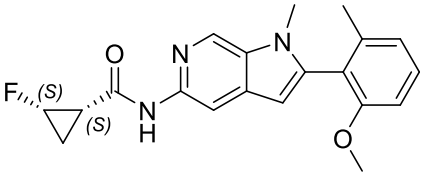
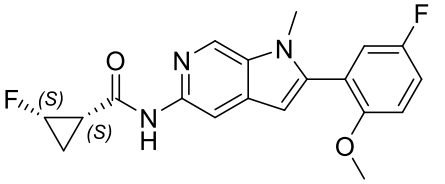
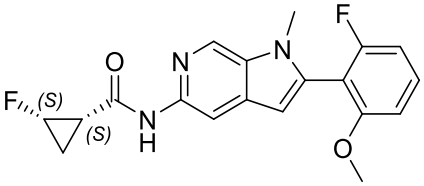
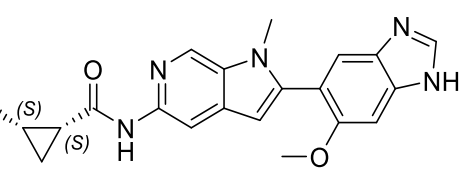

;

,

or a pharmaceutically acceptable salt thereof.

Claim 19. A compound selected from the group consisting of:

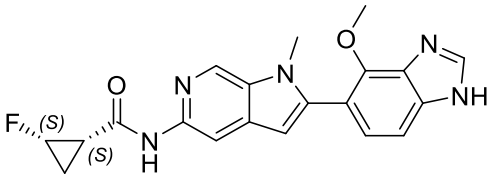
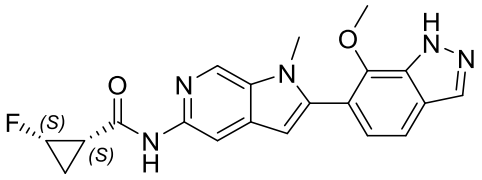
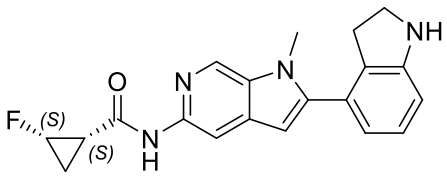
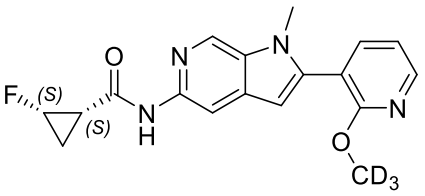
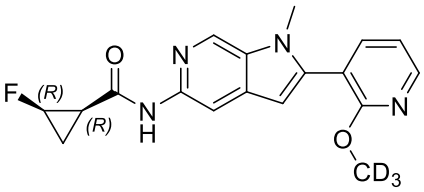
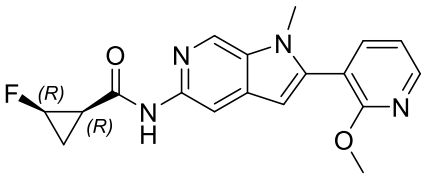
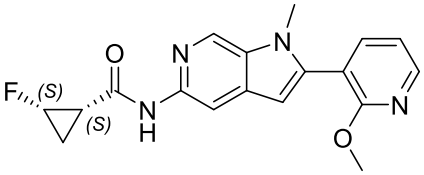
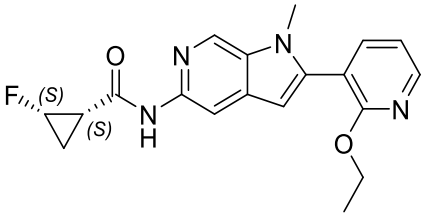
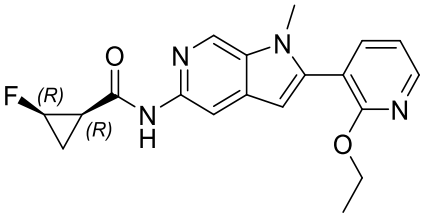
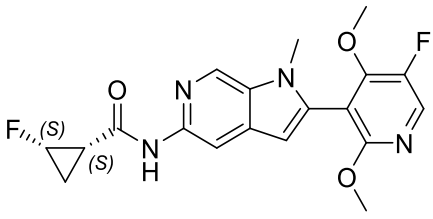
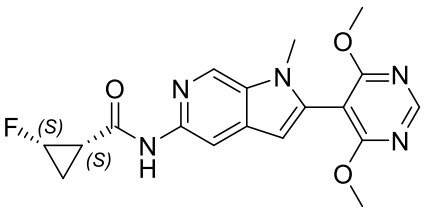

;

;


;

;

;

;

;

;

;

;

;

;

;

;

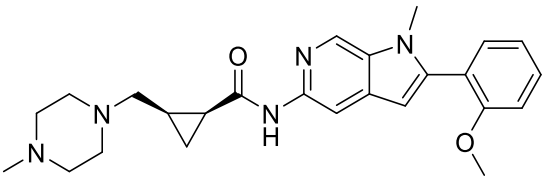

;

;

;

;

;

;

;

;

;

;

;

;

;

;

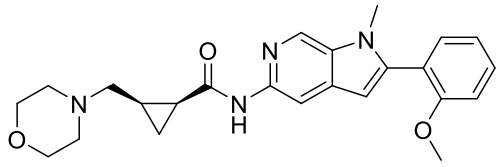
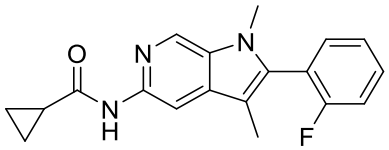
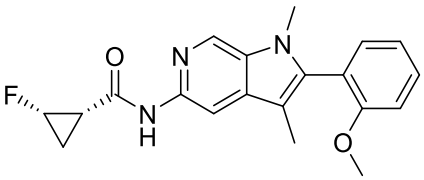
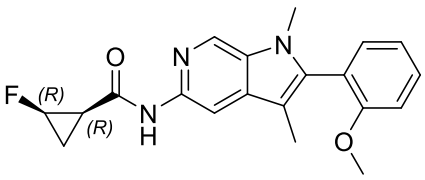
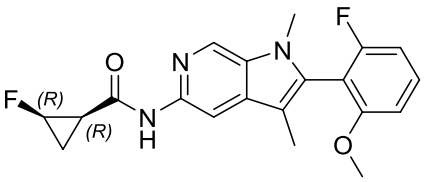
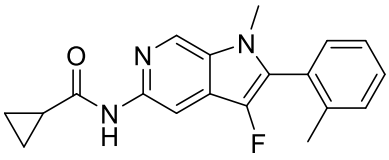
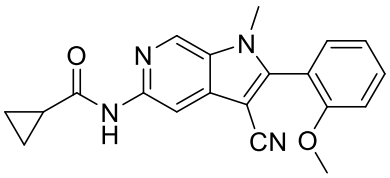
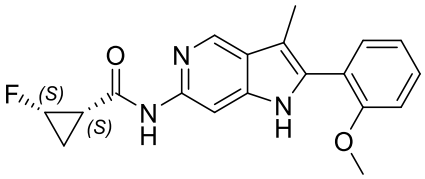
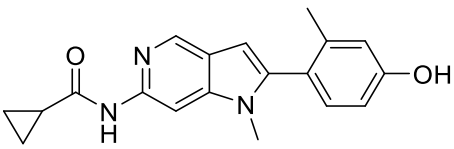
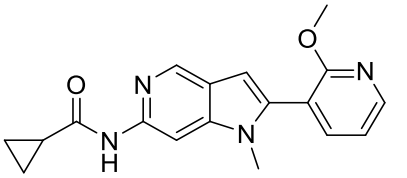
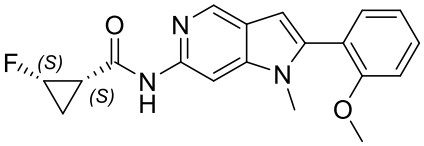
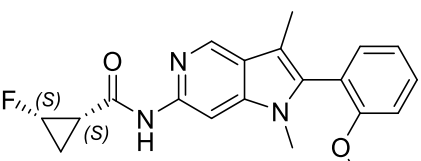
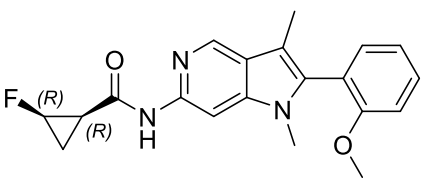
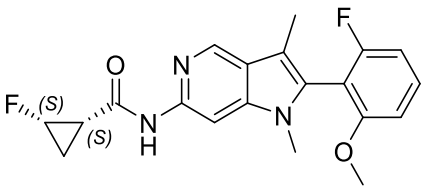
;

;


;

;

;

;

;

;

;

;

;

;

;

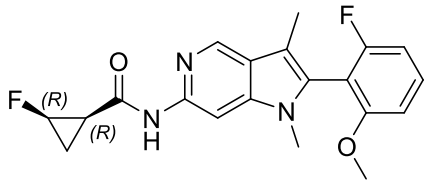
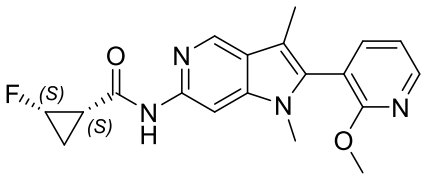
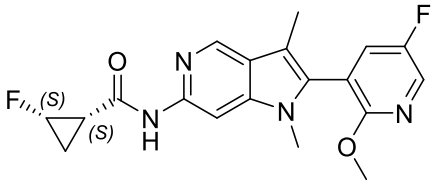
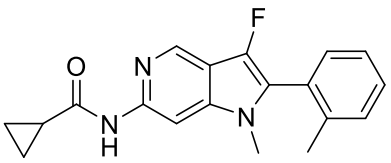
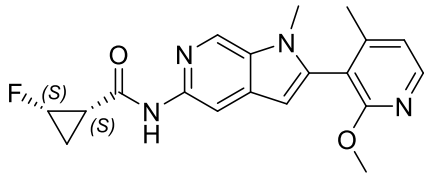
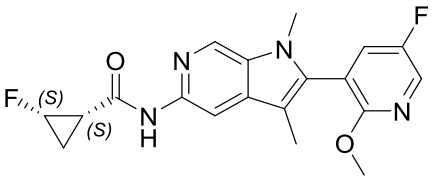
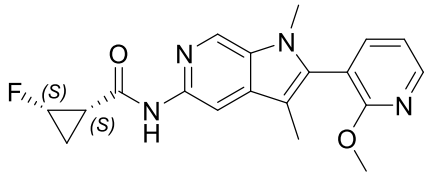
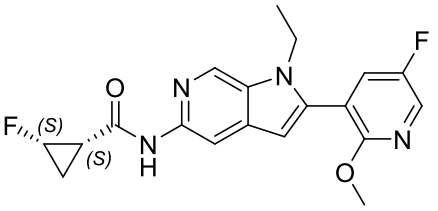
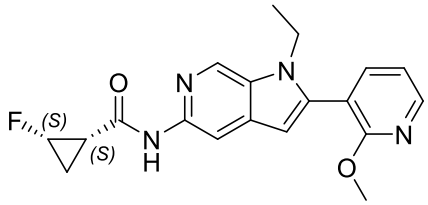
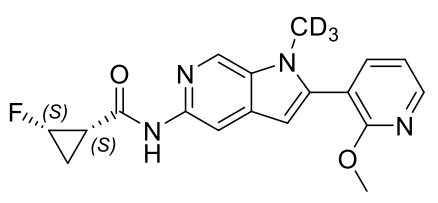
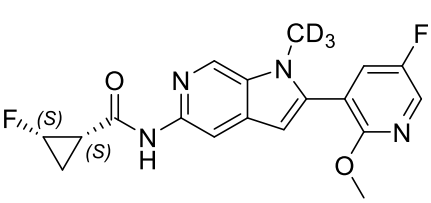
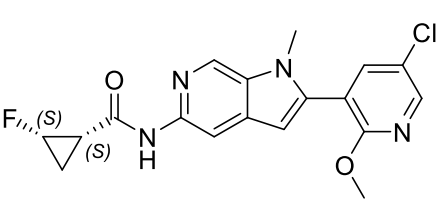
;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

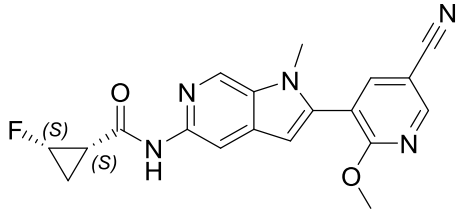
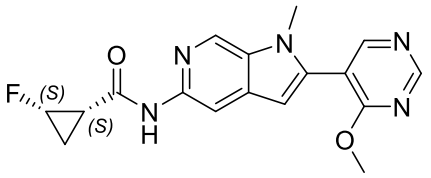
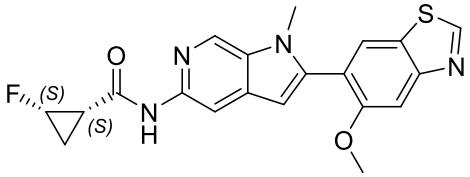
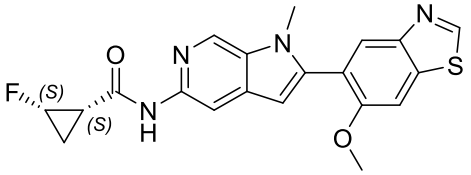
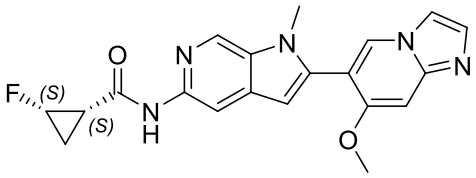
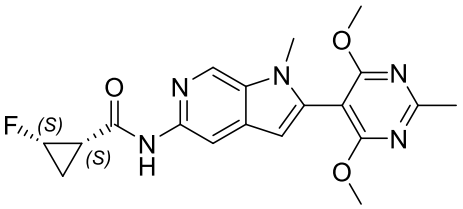
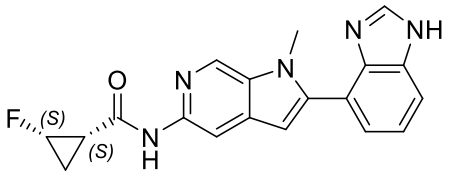
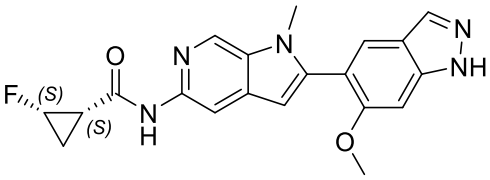
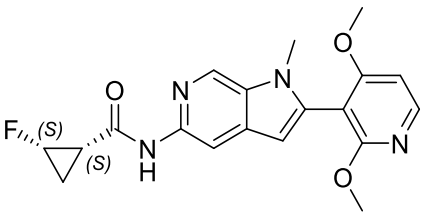
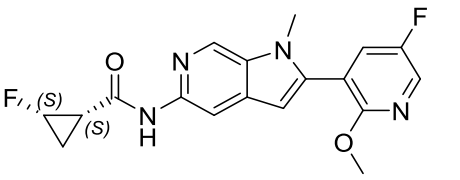
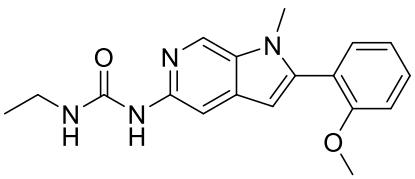
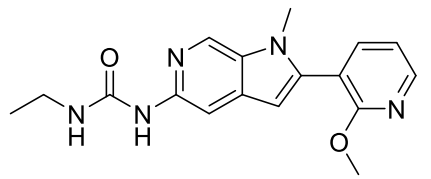
;

;


;

;

;

;

;

;

;

;

;

;

;

;

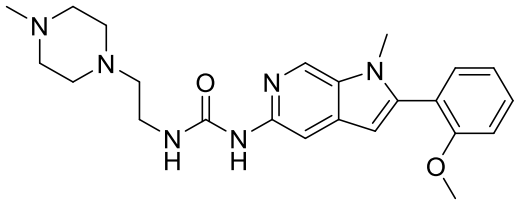
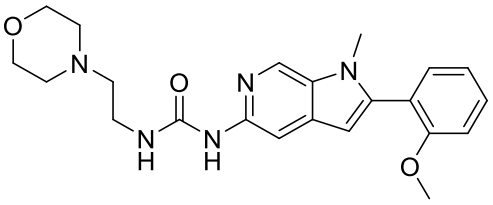
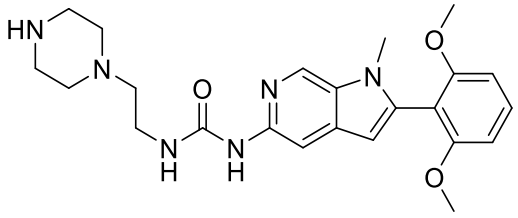
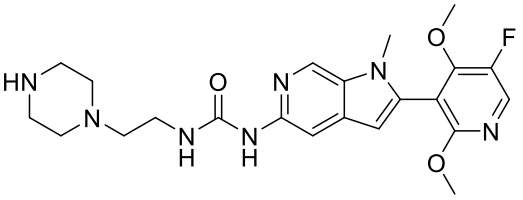
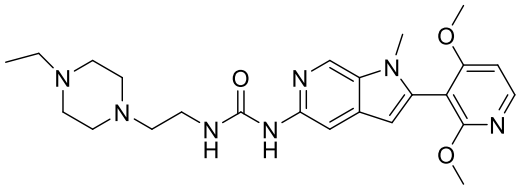
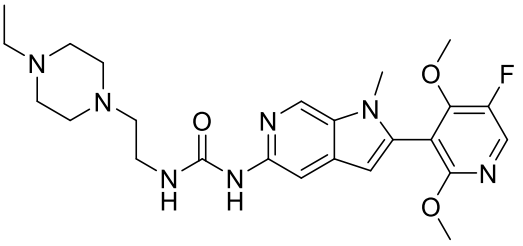
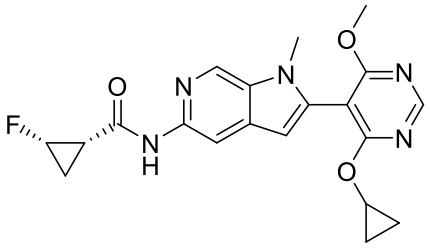
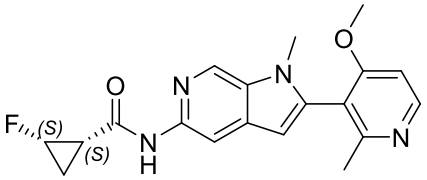
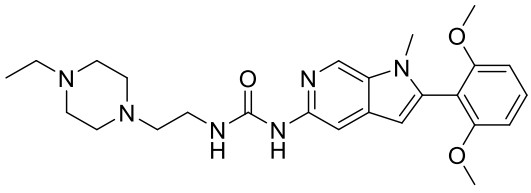
;

;

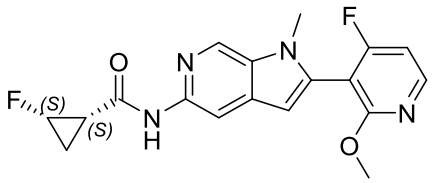
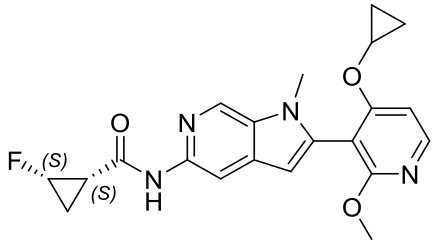
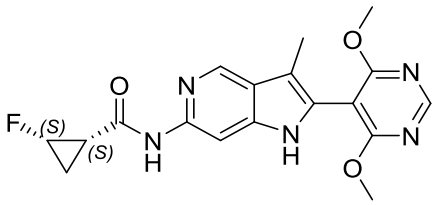
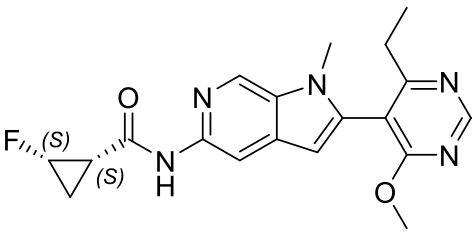
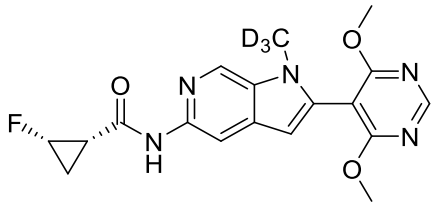
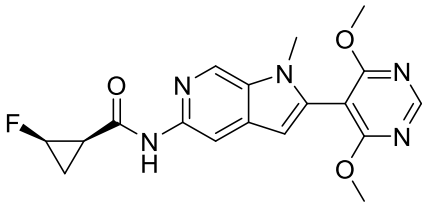
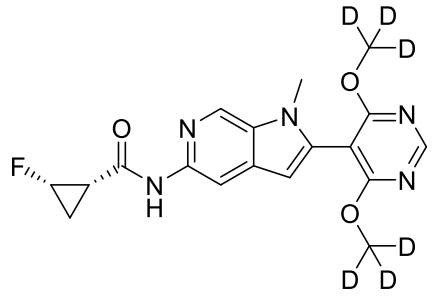
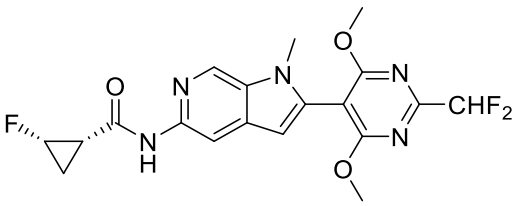
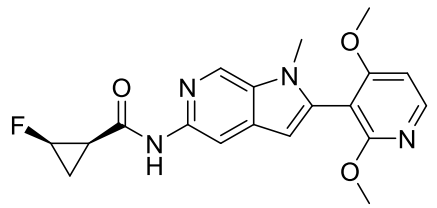
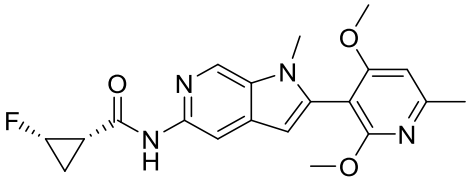

;

;

;

;

;

;

;

;

;

;

;

;

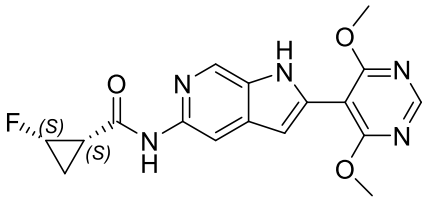
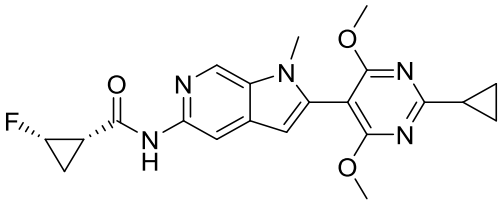
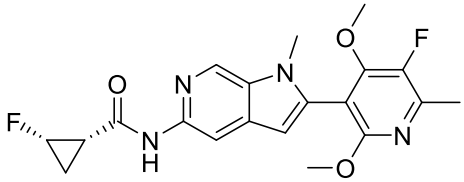
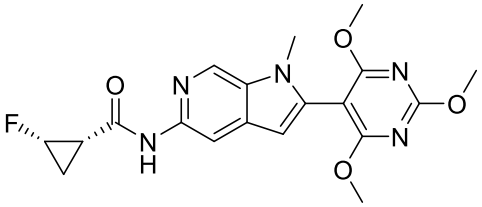
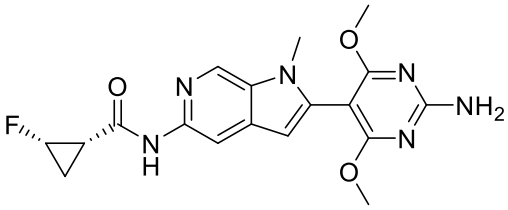
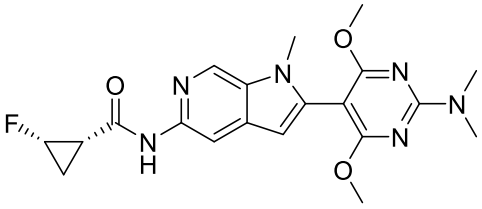
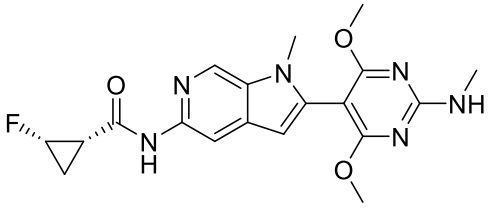
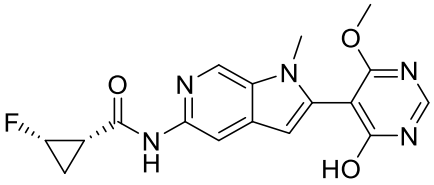
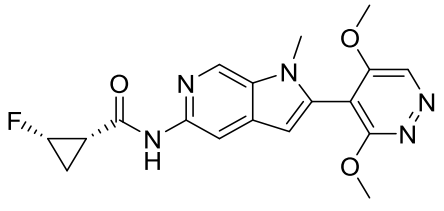
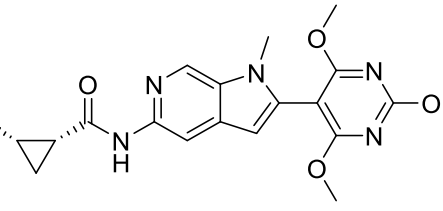
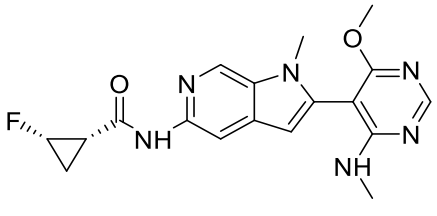
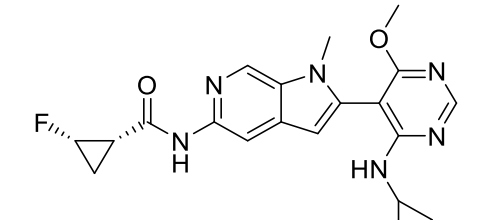
;

;


;

;

;

;

;

,

;

;

;

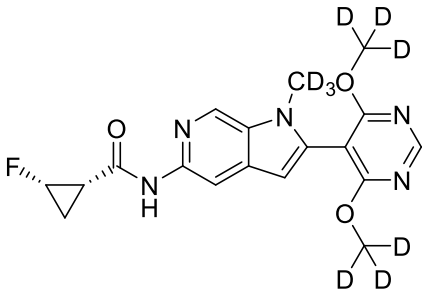
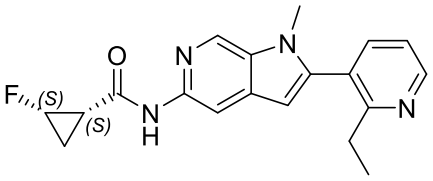
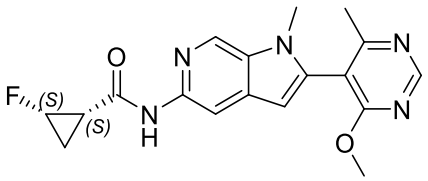
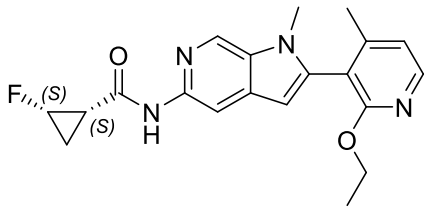
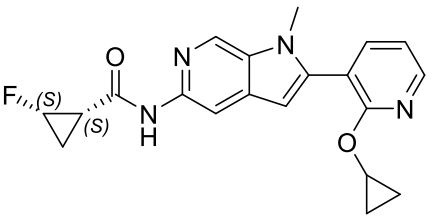
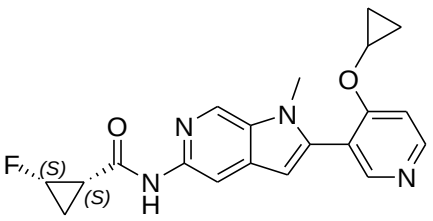
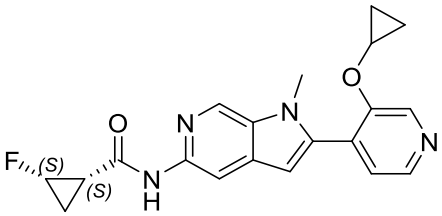
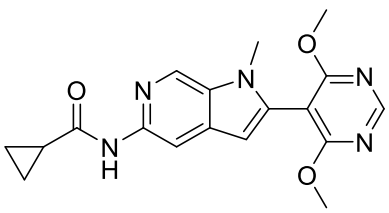
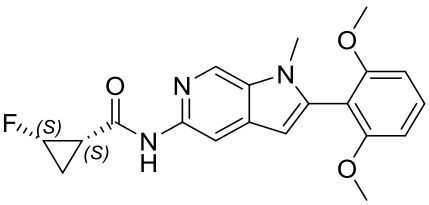
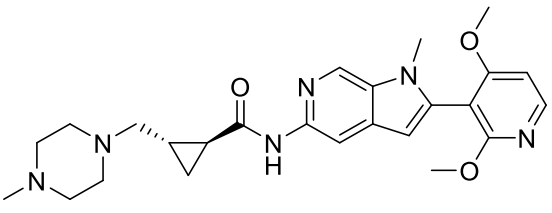
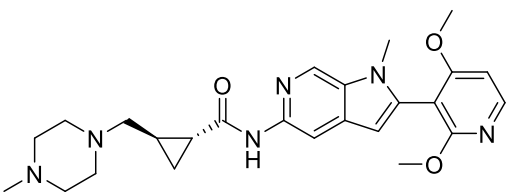
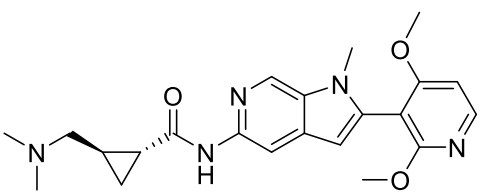
;

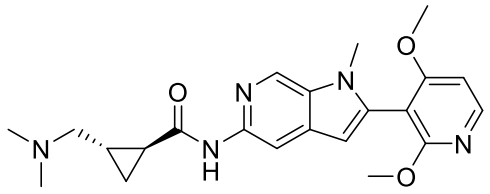
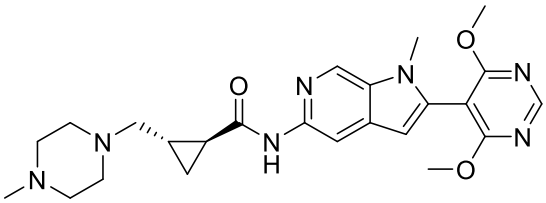
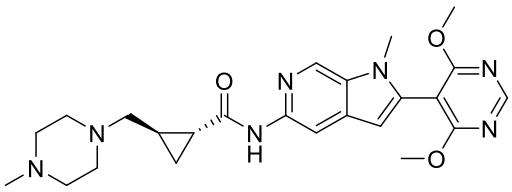
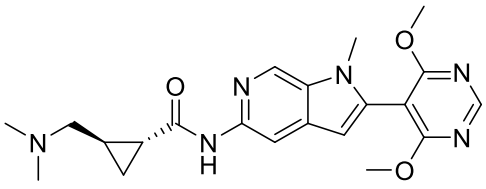
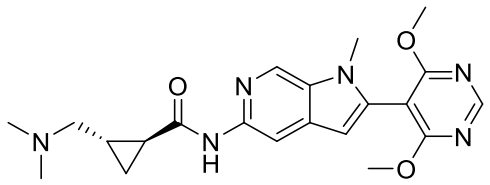
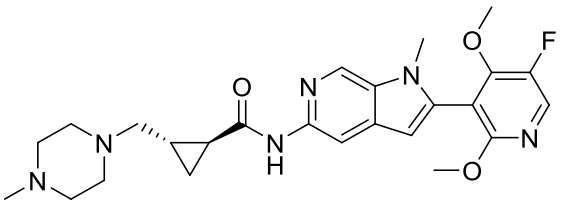
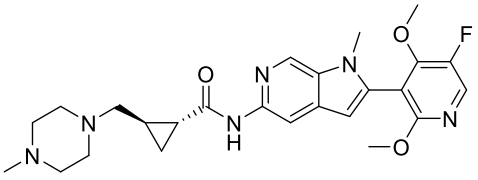
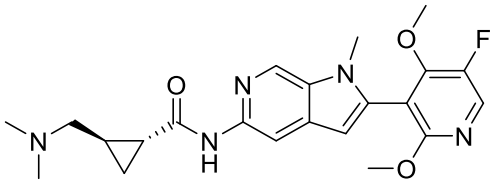
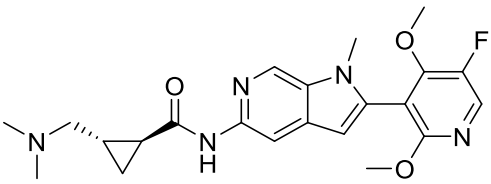
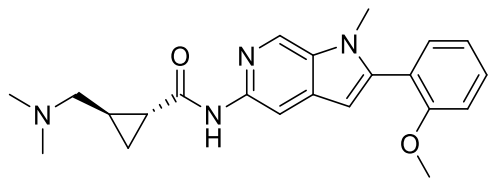

;

;

;

;

;

;

;

;

;

;

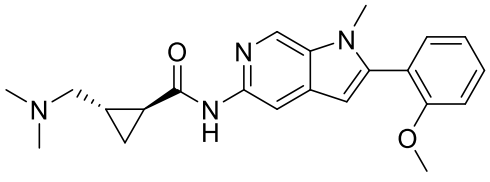
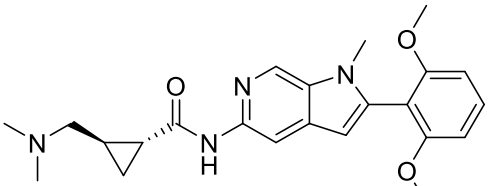

;

;

;

;

;

;

;

;

;

;

;

;

;

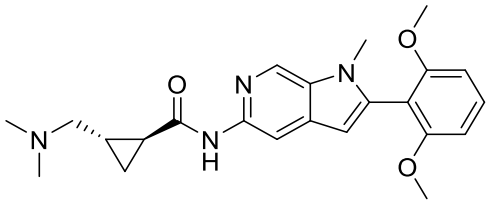
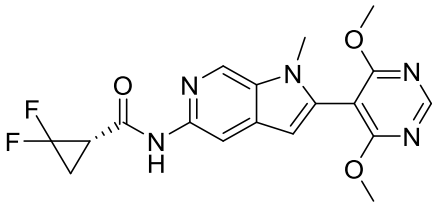
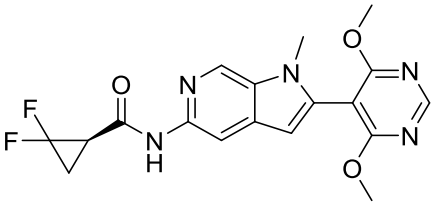
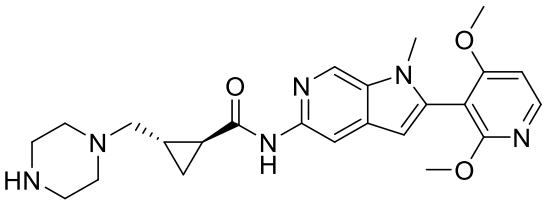
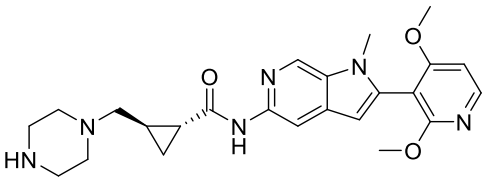
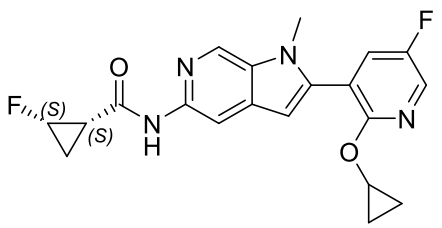
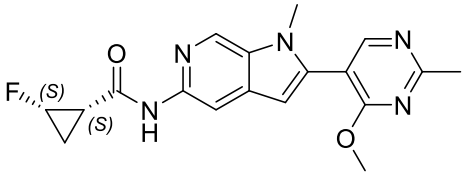
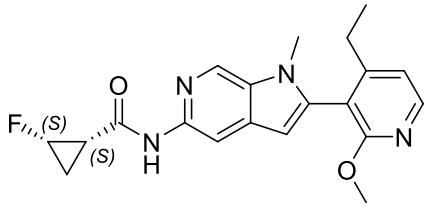
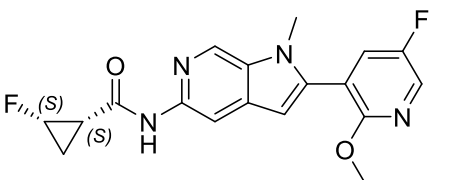
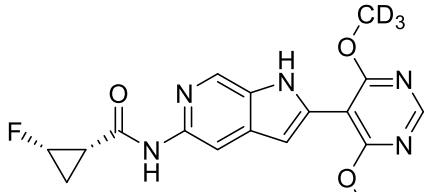
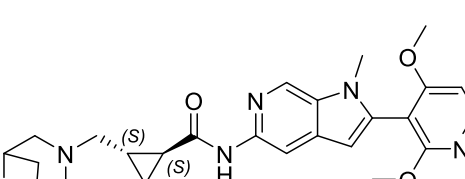
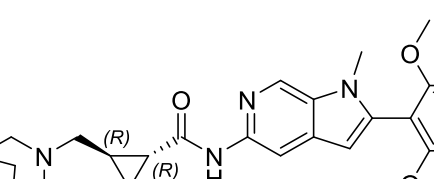
;


;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

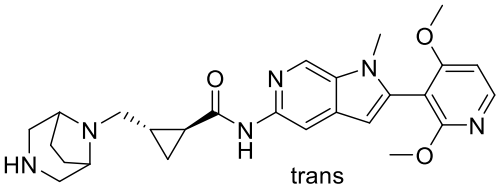
;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

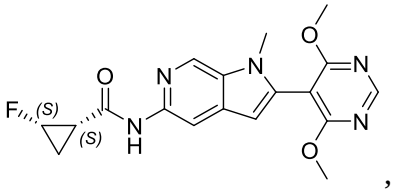
;

and 

,

or a pharmaceutically acceptable salt thereof.

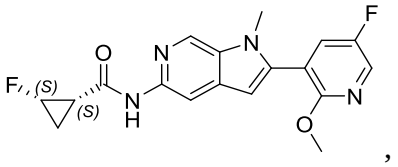
Claim 20. A compound having the structure



,

or a pharmaceutically acceptable salt thereof.

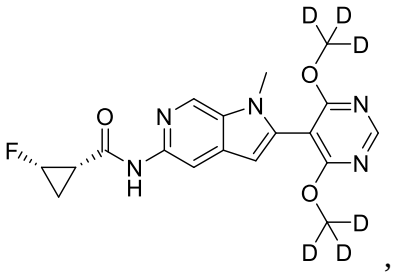
Claim 21. A compound having the structure



,

or a pharmaceutically acceptable salt thereof.

Claim 22. A compound having the structure



,

or a pharmaceutically acceptable salt thereof.

Claim 23. A pharmaceutical composition comprising the compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

Claim 24. Use of a compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 23, in the manufacture of a medicament for inhibiting Bcr-Abl enzymatic activity in a cell.

Claim 25. Use of a compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 23, in the manufacture of a medicament for treating chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or a mixed phenotype acute leukemia, in a human in need thereof.

Claim 26. The use of claim 25, wherein the leukemia is refractory leukemia.

Claim 27. The use of claim 26, wherein the refractory leukemia is associated with a mutation in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitutions selected from the group consisting of M244V, L248V, G250E, G250A, Q252H, Q252R, Y253F, Y253H, E255K, E255V, D276G, F311L, T315N, T315A, F317V, F317L, M343T, M351T, E355G, F359A, F359V, V379I, F382L, L387M, H396P, H396R, S417Y, E459K, F486S, and T315I.

Claim 28. The use of claim 27, wherein the refractory leukeumia is associated with a mutation in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitution T315I.

Claim 29. The use of claim 26, wherein the human having refractory leukemia has one or more mutations in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitutions selected from the group consisting of M244V, L248V, G250E, G250A, Q252H, Q252R, Y253F, Y253H, E255K, E255V, D276G, F311L, T315N, T315A, F317V, F317L, M343T, M351T, E355G, F359A, F359V, V379I, F382L, L387M, H396P, H396R, S417Y, E459K, F486S, and T315I.

Claim 30. The use of claim 29, wherein the human having refractory leukemia has a mutation in the Bcr-Abl tyrosine kinase gene resulting in specific amino acid substitution T315I.

Claim 31. The use of any one of claims 24 to 30, wherein the compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition is to be administered, and wherein one or more pharmaceutical agents including including anti-

microtubular therapies, topoisomerase inhibitors, alkylating agents, nucleotide synthesis inhibitors, DNA synthesis inhibtiors, protein synthesis inhibitors, developmental signaling pathway inhibitors, pro-apoptotic agents, Abl myristoyl-pocket binding inhibitors, MEK1/2 inhibitors, AKT inhibitors, PI3K inhibitors and/or radiation are to be further administered.

Claim 32. A compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 23, for use in therapy.