NOVEL HDAC INHIBITORS AND THERAPEUTIC USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/285,558, filed on December 3, 2021, the entire disclosure of which is hereby incorporated by reference herein in its entirety for all purposes.

FIELD

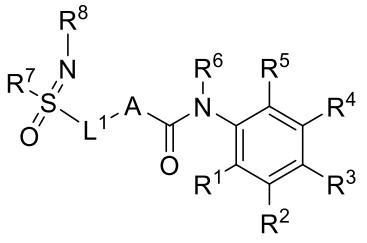
[0002] Provided herein are compounds, and compositions and methods thereof. In some embodiments, provided are compounds for inhibiting histone deacetylase (HDAC). In some embodiments, provided are methods for treatment of diseases or disorders, such as cancer.

BACKGROUND

[0003] Histone deacetylases (HDAC) are a class of epigenetic proteins implicated in a variety of diseases, including cancers, and inhibition of specific HDACs in certain patients may treat or otherwise ameliorate such diseases. There are four families of HDACs encompassing 18 HDAC isoforms. Jenke, R., et al. Anticancer Therapy with HDAC Inhibitors: Mechanism-Based Combination Strategies and Future Perspectives. Cancers 13: 634 (2021). Some HDAC inhibitors have been approved by the United States Food and Drug Administration (FDA), but currently approved HDAC therapies are not known to be specific to only a few HDAC isoforms, increasing the potential for adverse effects due to broad inhibitory properties. Thus, there is a need for selective HDAC inhibitors for treating diseases or disorders, such as cancers.

SUMMARY

[0003a] In a first aspect of the present disclosure, there is provided a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof,

wherein

A is phenyl or heteroaryl, wherein heteroaryl has 5, 6 or 9 ring atoms, 1 to 4 ring atoms selected from N, O, and S, and wherein A is substituted with 0-4 R^9 groups;

L^1 is -CR'_2-, -$CR'_2CR'_2$-, or a bond;

each R' is independently H or C_1-C_6 alkyl; or two R' together with the carbon or carbons to which they are attached form a 3-6-membered cycloalkyl ring;

each R^1, R^3 and R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halogen;

R^2 is phenyl or monocyclic heteroaryl, wherein heteroaryl has 5 or 6 ring atoms with 1 to 2 ring atoms selected from N, O, and S, and R^2 is substituted with 0-4 R^{10} groups;

R^5 is NH_2 or OH;

R^6 is H or C_1-C_6 alkyl;

R^7 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -$(CH_2)_{0-2}$-phenyl, -$(CH_2)_{0-2}$-C_3-C_7 cycloalkyl, -$(CH_2)_{0-2}$-heteroaryl or -$(CH_2)_{0-2}$-heterocyclyl, wherein each alkyl, heteroalkyl, phenyl, cycloalkyl, heteroaryl or heterocyclyl is substituted with 0-4 R^{11} groups;

R^8 is H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, phenyl, cycloalkyl, heterocyclyl, cyano, CO-R', or CO_2-R', wherein heterocyclyl has 4-11 ring atoms with 1 to 4 ring atoms selected from N, O, and S; each alkyl or heteroalkyl is substituted with 0-4 groups independently selected from halogen and OH, and each phenyl, cycloalkyl, or heterocyclyl is substituted with 0-4 R^{10} groups; or

R^7 and R^8 are taken together with the nitrogen and sulfur to which they are attached to form a 4-7 membered heterocycle with 0-2 additional ring heteroatoms selected from O, S, and N, and wherein the heterocycle is substituted with 0-4 R^{10} groups;

each R^9 is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_7 cycloalkyl, hydroxy, cyano, or halogen, wherein each alkyl or heteroalkyl is optionally substituted with 1-4 groups independently selected from halogen and OH;

each R^{10} and R^{11} is independently C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 heteroalkyl, phenyl, C_3-C_7 cycloalkyl, heterocyclyl, C_1-C_6 alkylene-phenyl, C_1-C_6 alkylene- C_3-C_7 cycloalkyl, C_1-C_6 alkylene- heterocyclyl, hydroxy, cyano, CO-R^C, NR^D_2, or halogen, wherein heterocyclyl has 4-11 ring atoms with 1 to 4 ring atoms selected from N, O, and S; each alkyl or heteroalkyl is optionally substituted with 1-4 groups independently selected from halogen and OH, and wherein each phenyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-4 R^E;

each R^C is independently H, OH, NR^{12}_2, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 heteroalkyl, wherein each alkyl or heteroalkyl is optionally substituted with 1-4 substituents independently selected from halogen and OH;

each R^D is independently H, C_1-C_6 alkyl, CO-C_1-C_6 alkyl; CO_2-C_1-C_6 alkyl; SO_w-C_1-C_6 alkyl; C_1-C_6 heteroalkyl, wherein each alkyl or heteroalkyl is optionally substituted with 1-4 substituents independently selected from halogen and OH; or

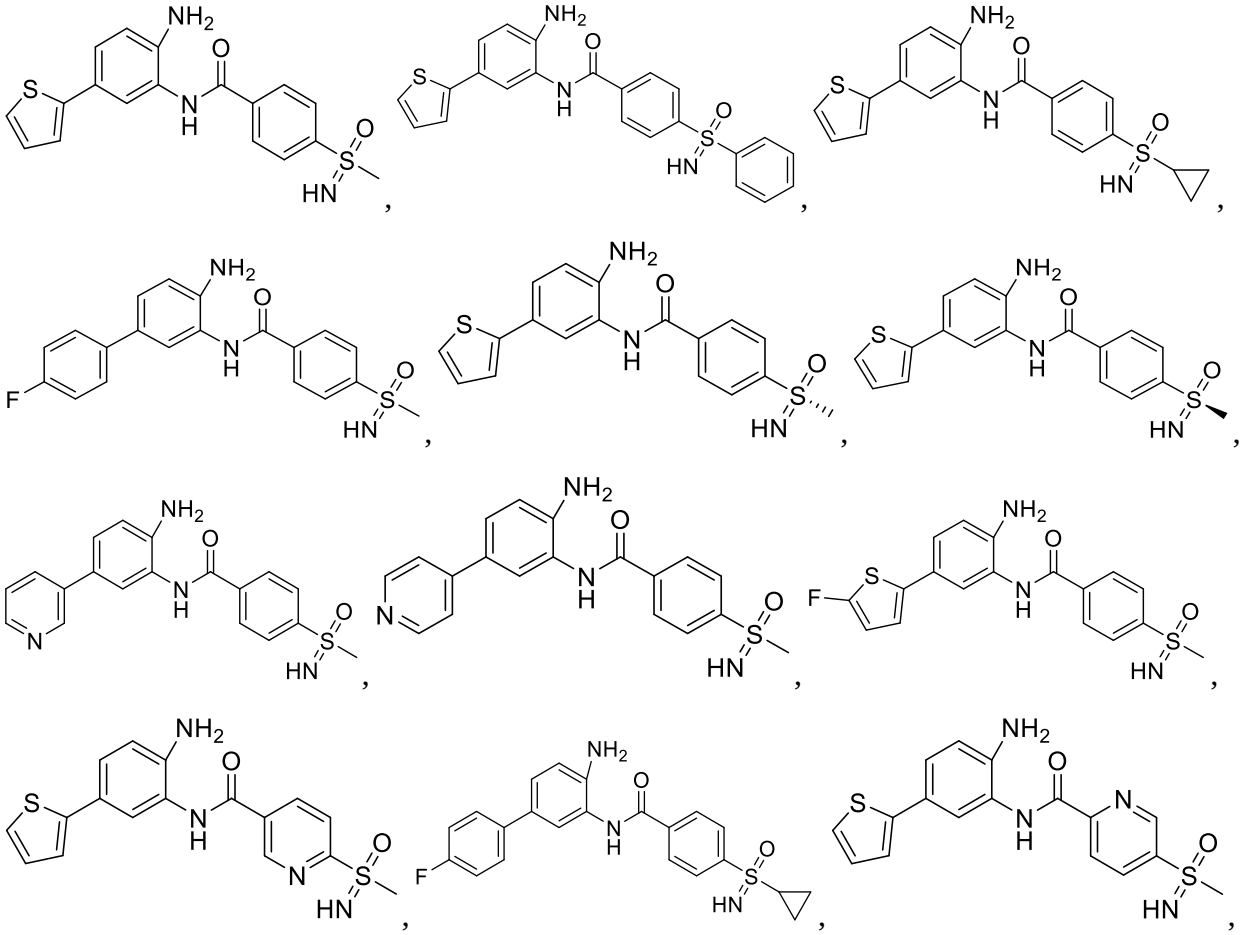
two R^D attached to the same nitrogen are taken together with the nitrogen to which they are attached to form a 3-7 membered heterocycle with 0-2 additional ring heteroatoms selected from O, S, and N, and wherein the heterocycle is optionally substituted with 1-4 substituents independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and OH;

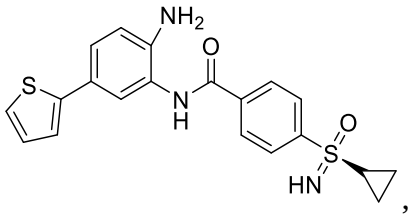
each R^E is independently H, halo, OH, O-C_1-C_6 alkyl, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl;

each R^{12} is independently H or C_1-C_6 alkyl; and

$_W$ is 0, 1, or 2.

[0003b] In another aspect of the present disclosure, there is provided a compound as disclosed herein or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

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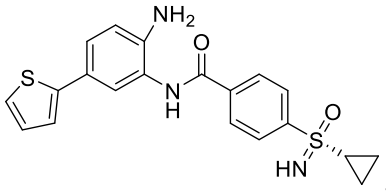
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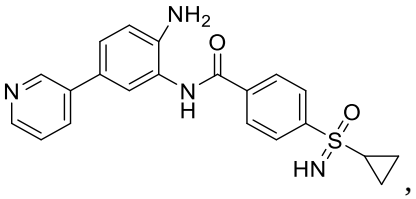
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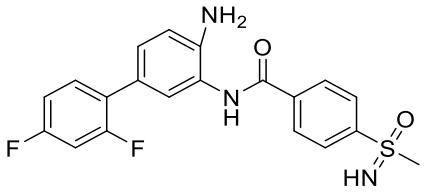
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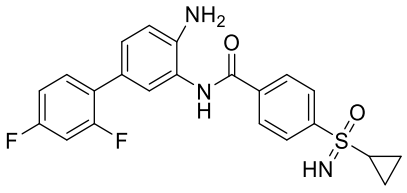
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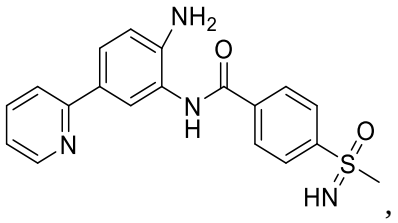
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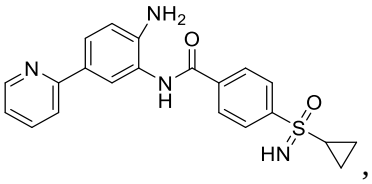
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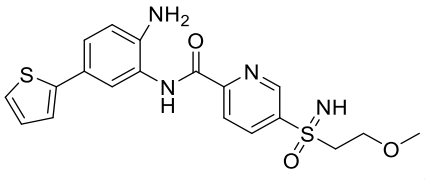
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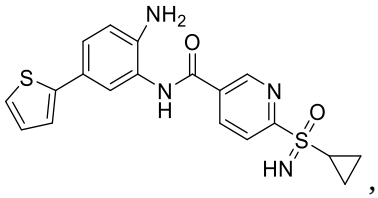
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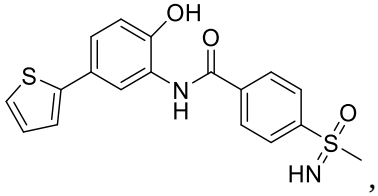
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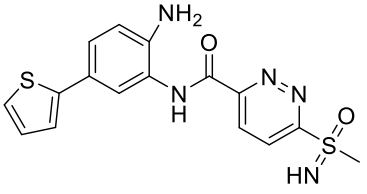
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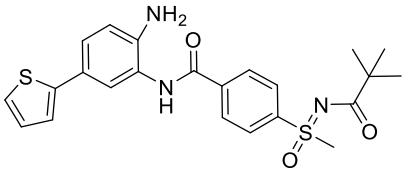
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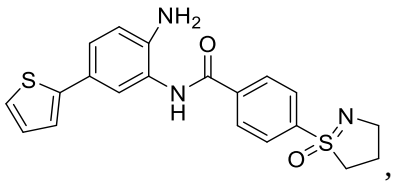
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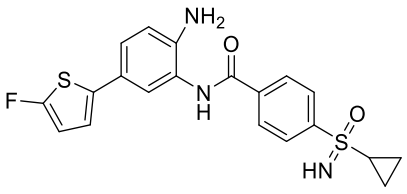
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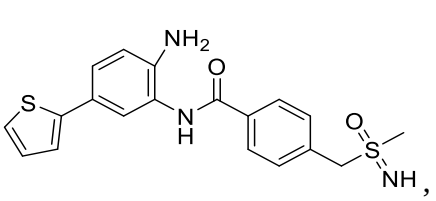
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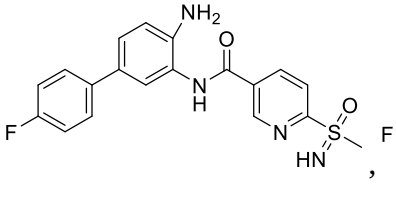
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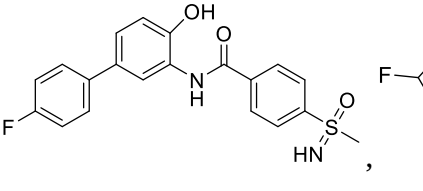
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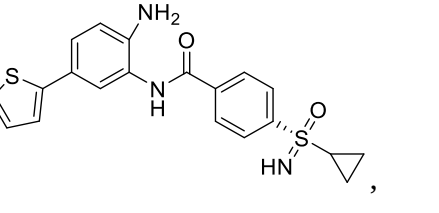
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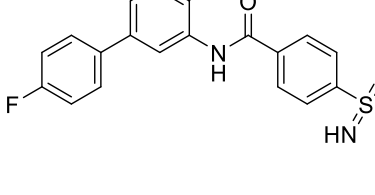
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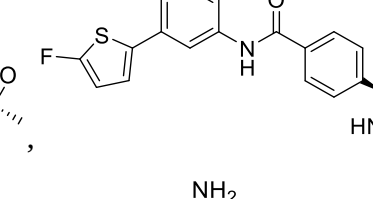
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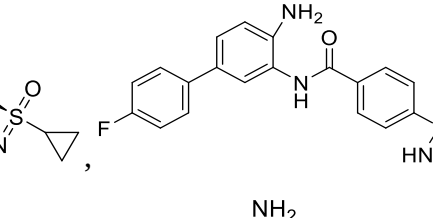
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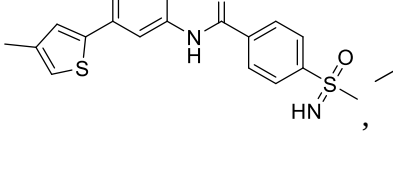
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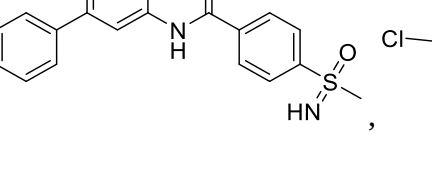
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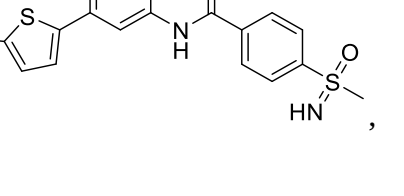
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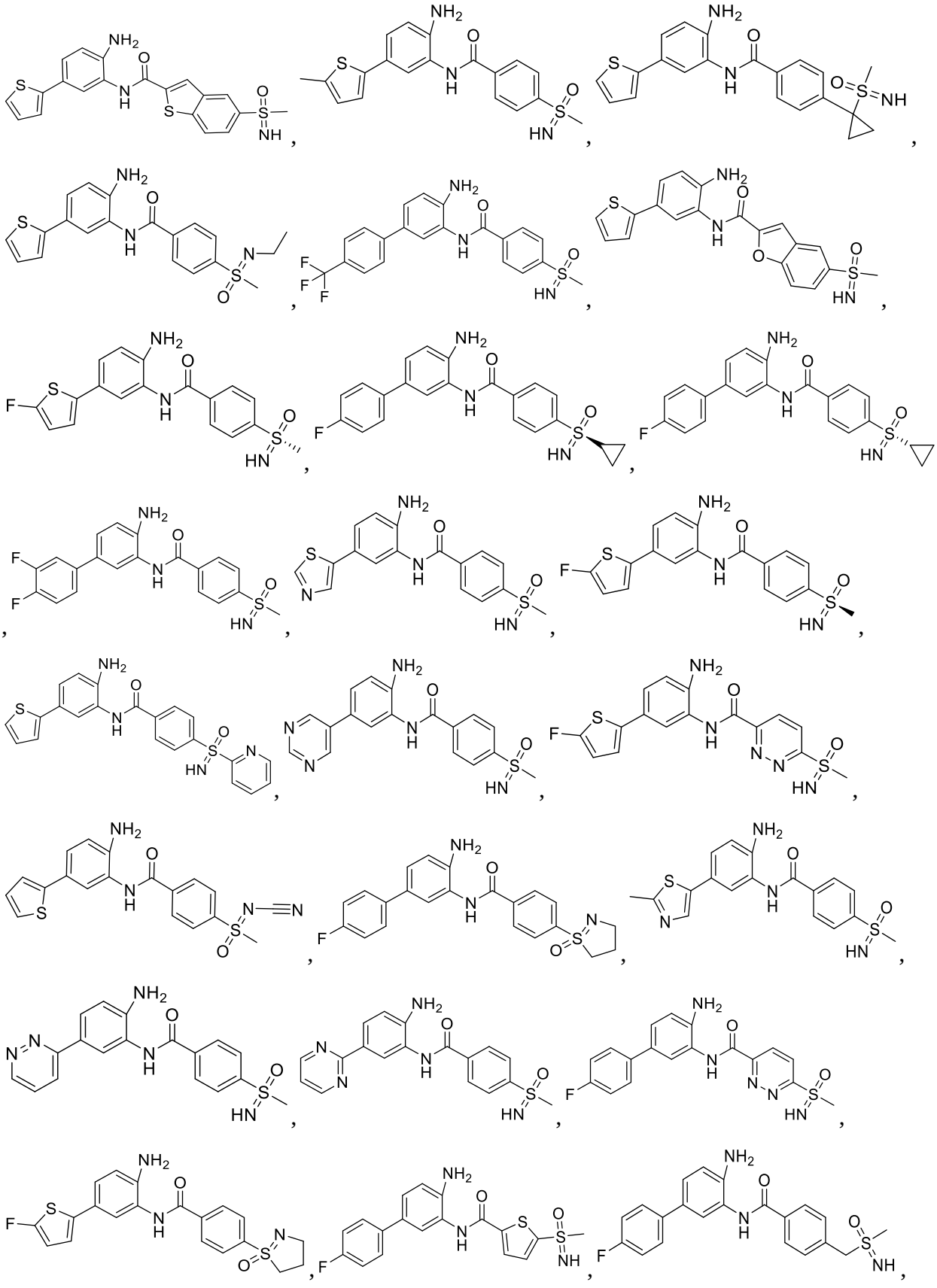

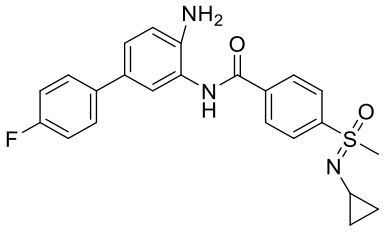
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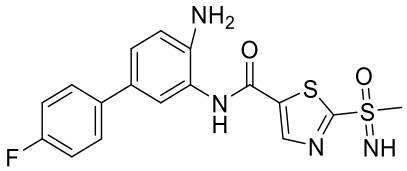
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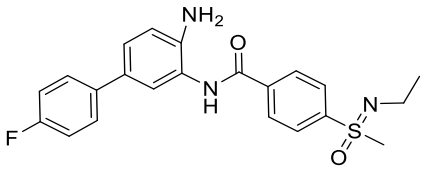
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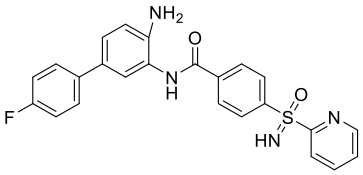
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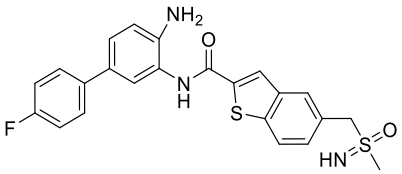
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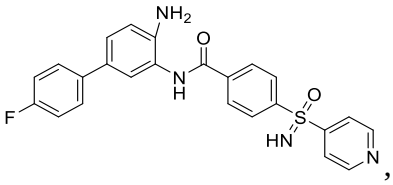
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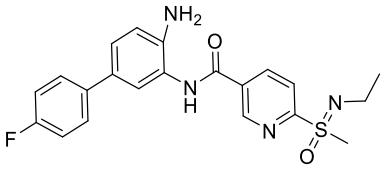
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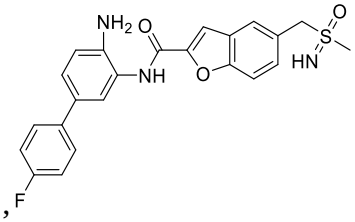
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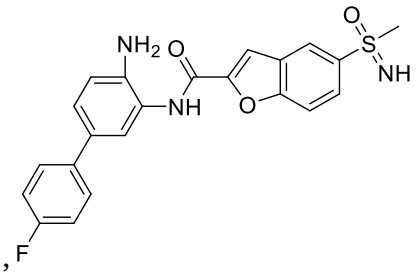
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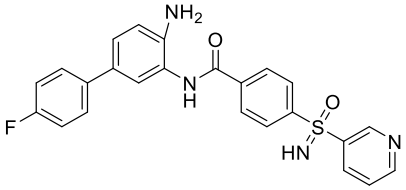
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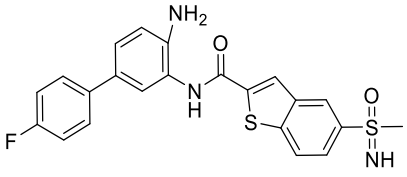
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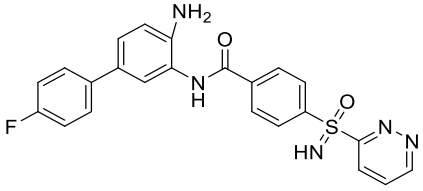
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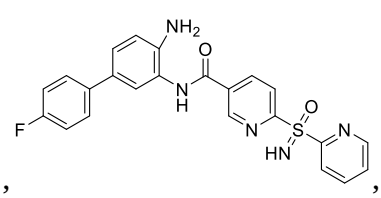
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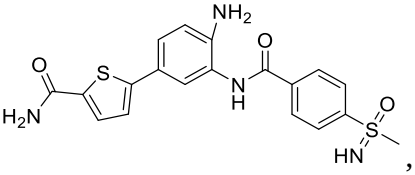
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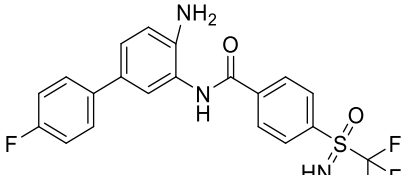
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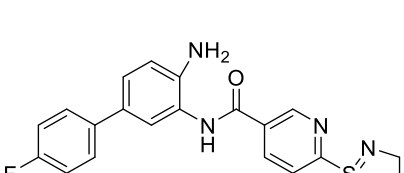
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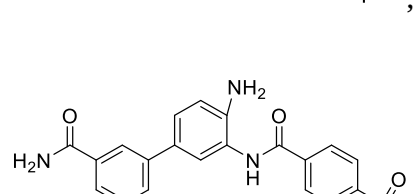
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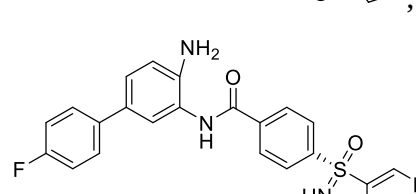
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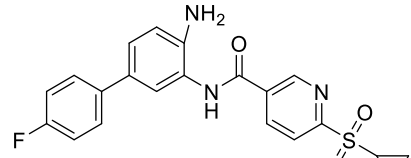
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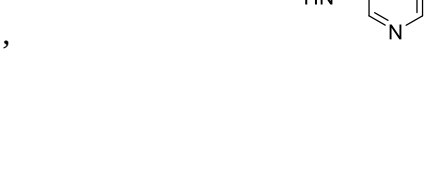
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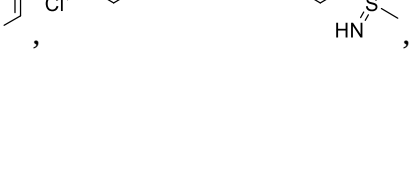
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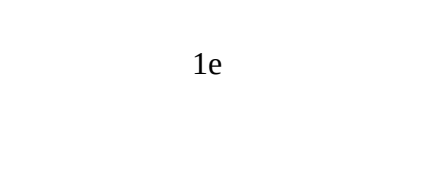
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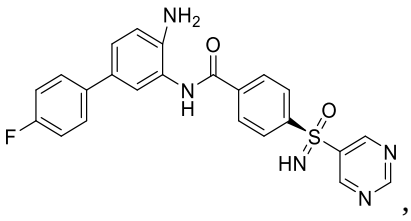
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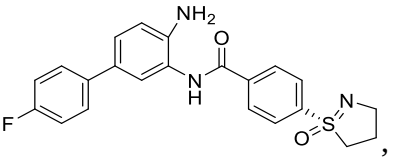
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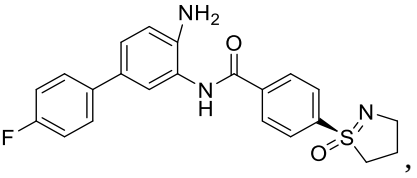
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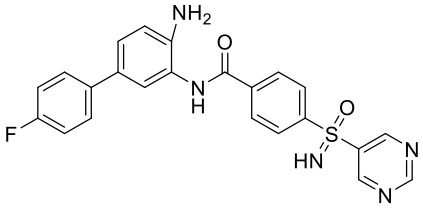
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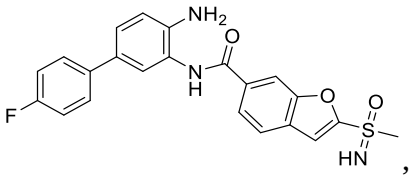
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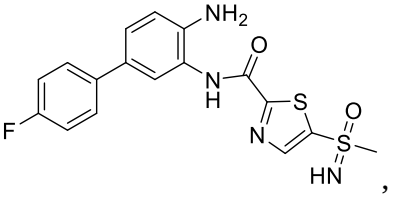
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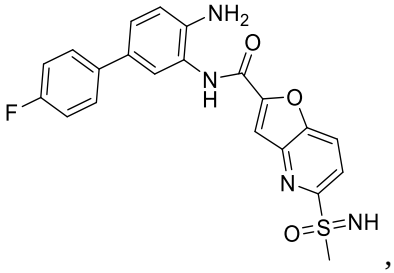
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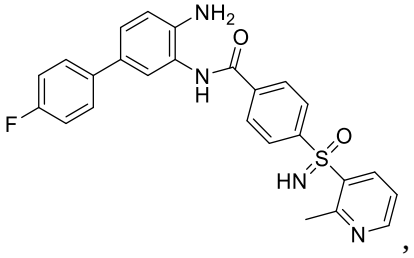
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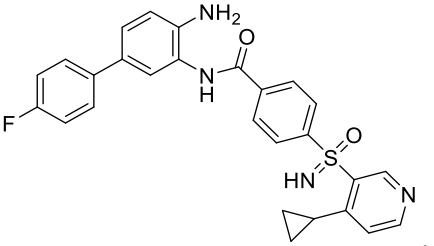
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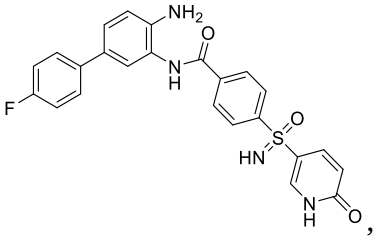
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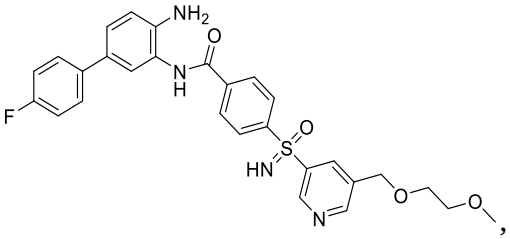
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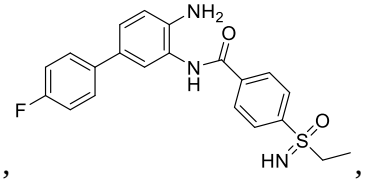
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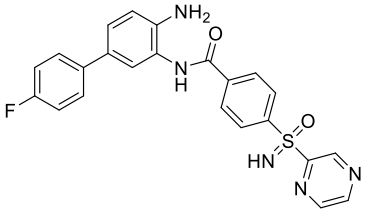
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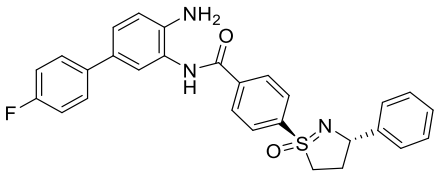
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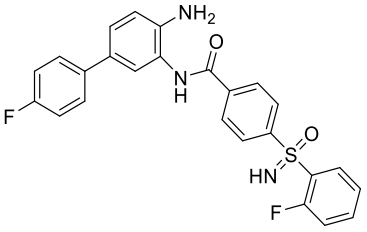
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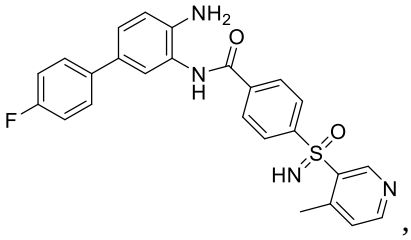
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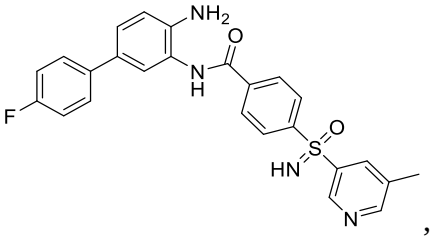
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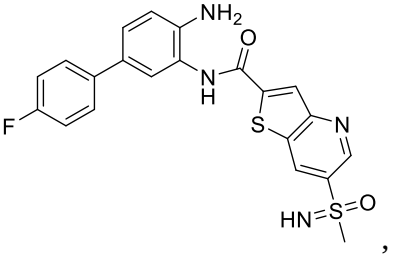
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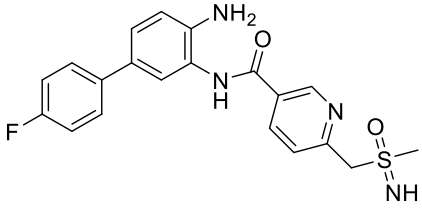
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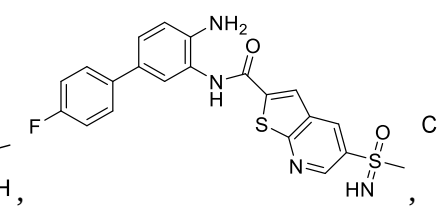
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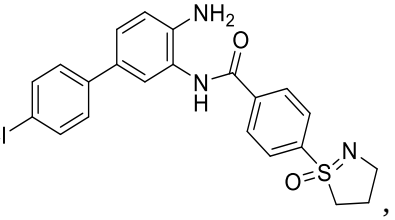
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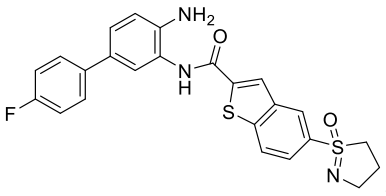
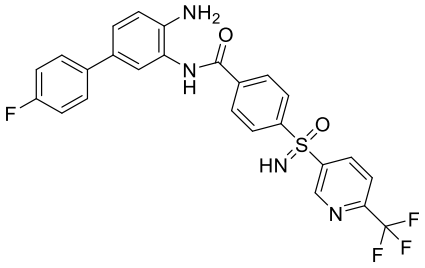
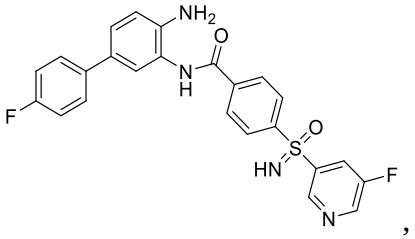
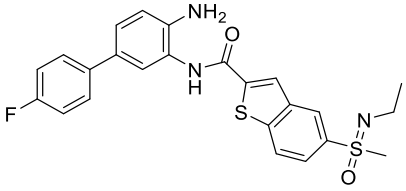
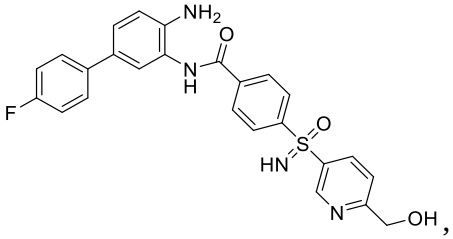
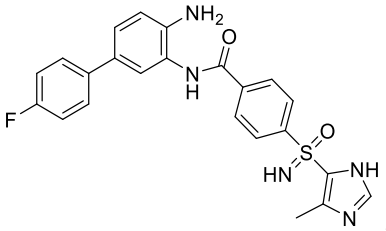
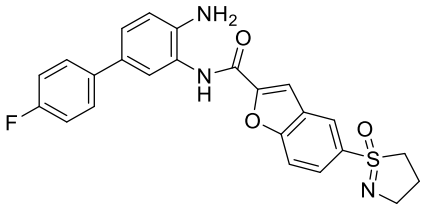
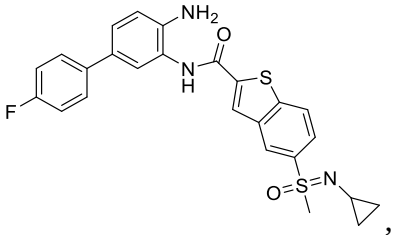
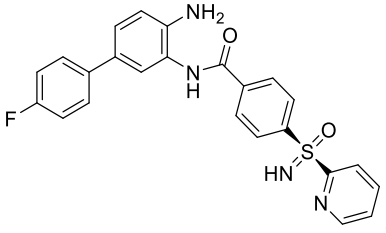
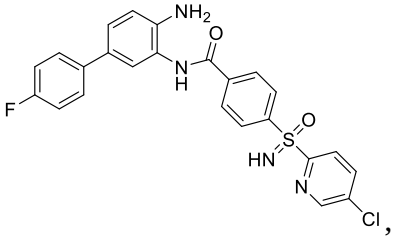
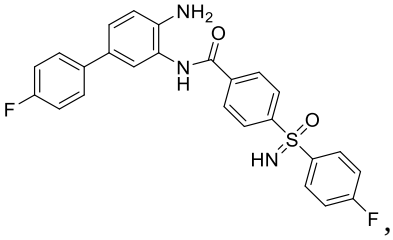
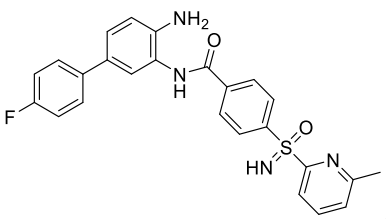
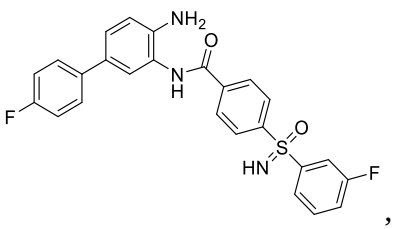
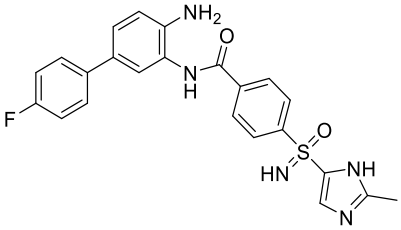
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
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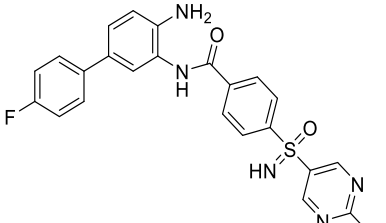
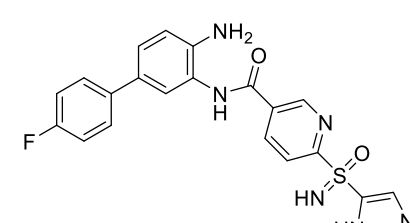
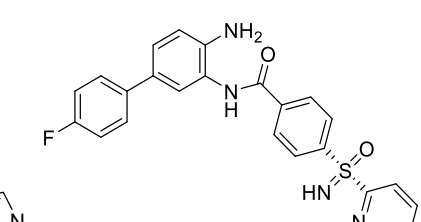
 ,
 ,
 ,
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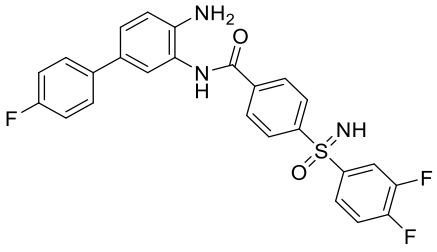
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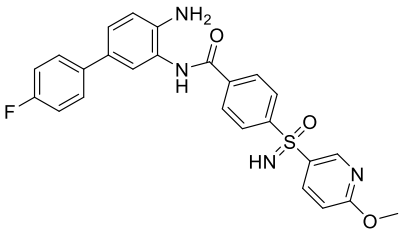
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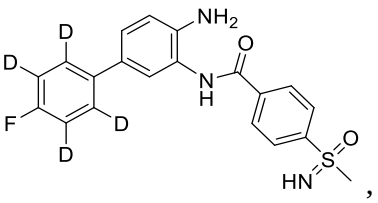
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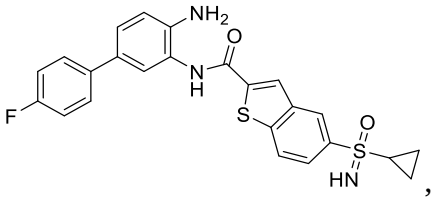
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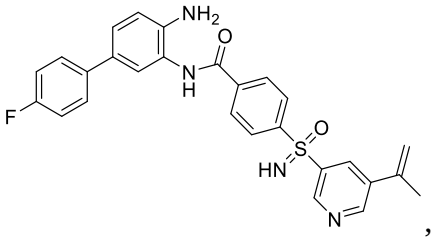
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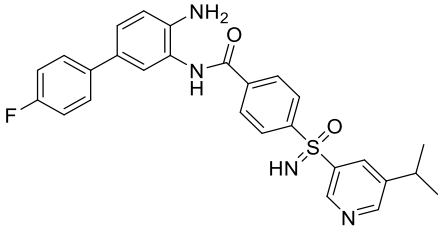
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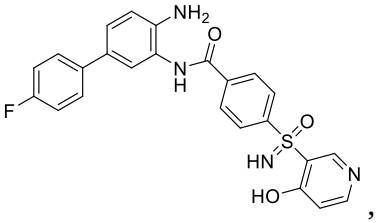
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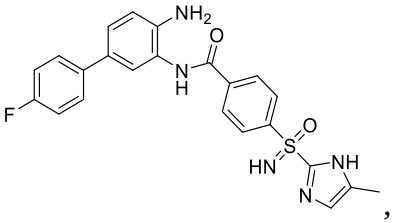
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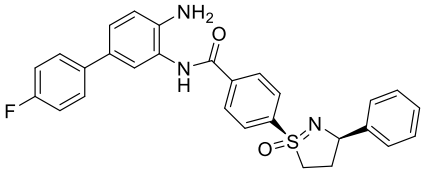
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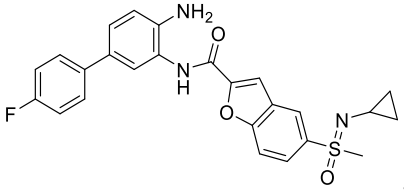
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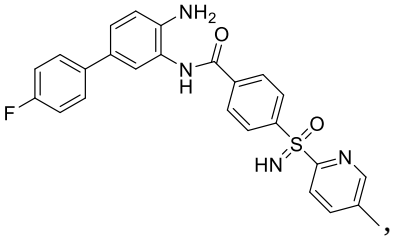
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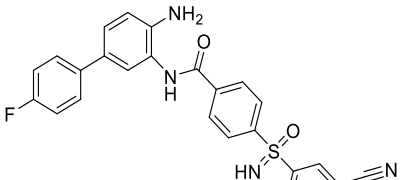
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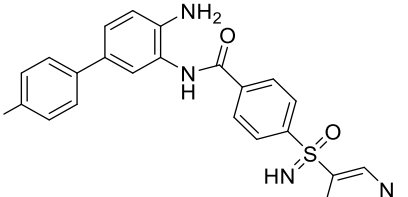
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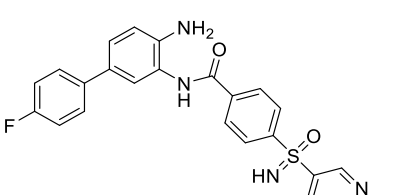
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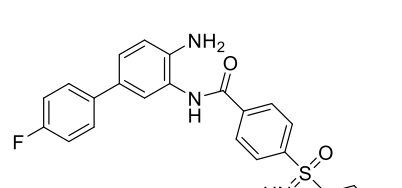
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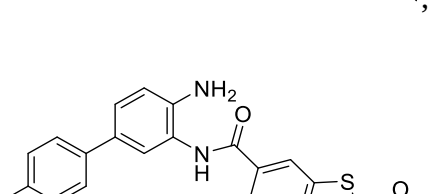
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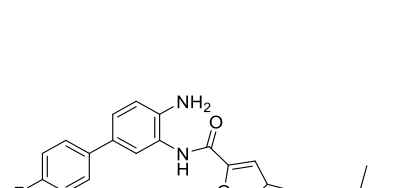
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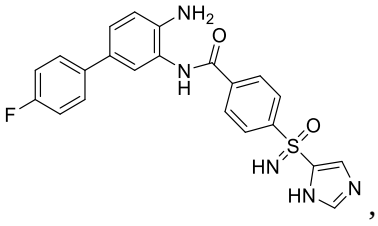
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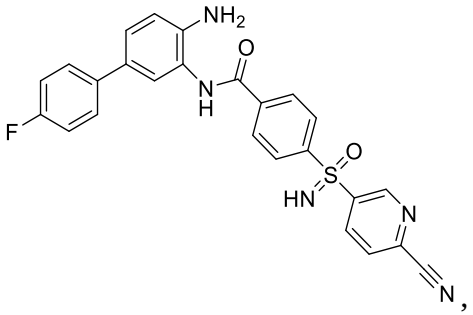
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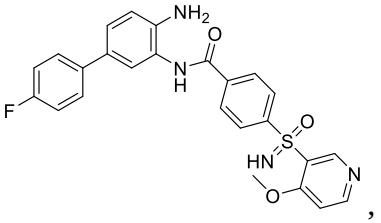
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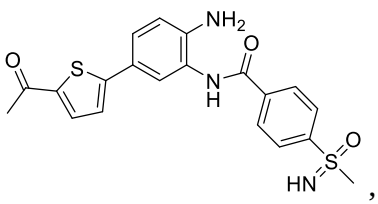
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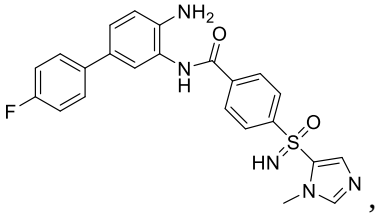
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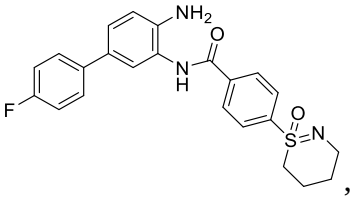
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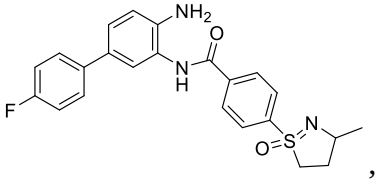
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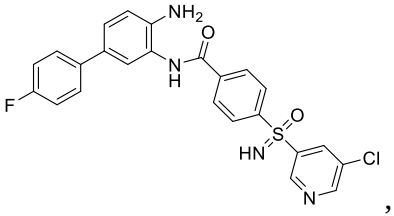
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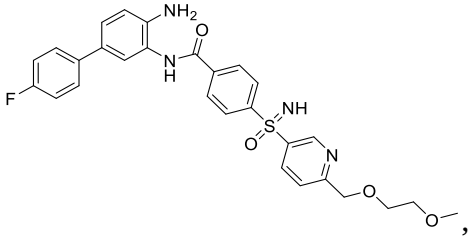
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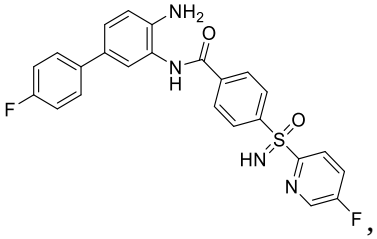
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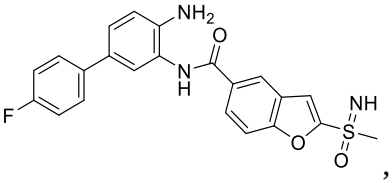
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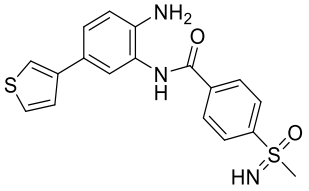
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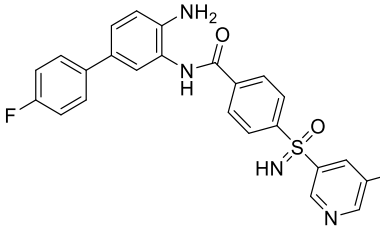
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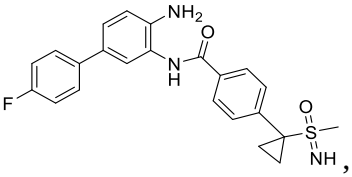
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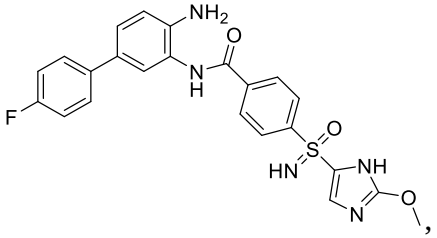
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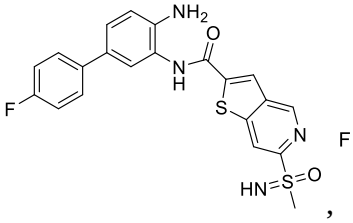
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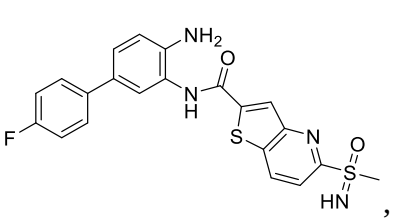
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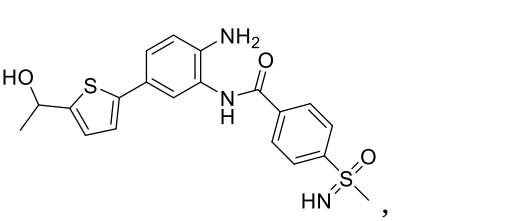
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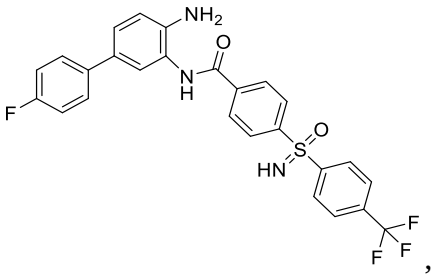
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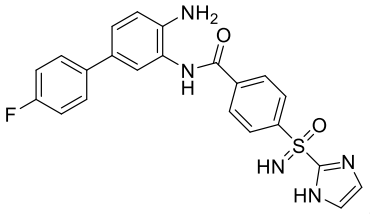
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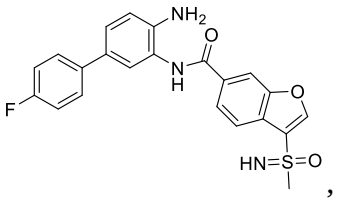
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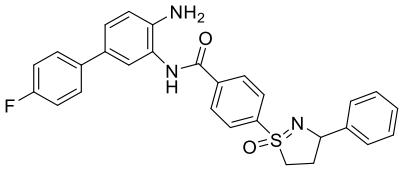
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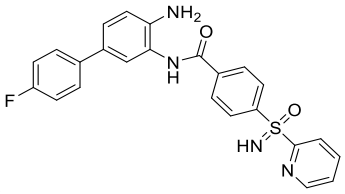
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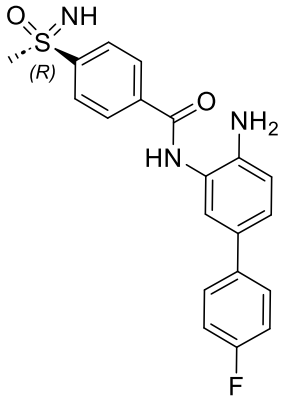
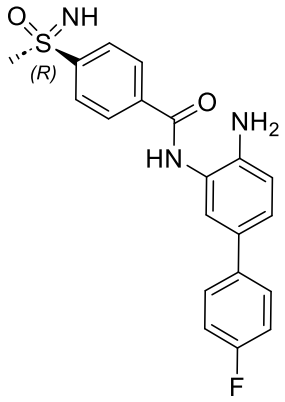
[0003c] In yet another aspect of the present disclosure, there is provided a compound of Formula



or a pharmaceutically acceptable salt thereof.

[0003d] In a further aspect of the present disclosure, there is provided a compound of Formula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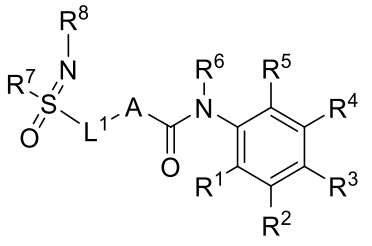
[0003e] In another aspect of the present disclosure, there is provided a composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0003f] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of a composition as disclosed herein, in the manufacture of a medicament for treating a cancer that can be treated by inhibition of a histone deacetylase (HDAC).

[0003g] In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition as disclosed herein, for use in therapy.

[0004] In one example, provided is a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof,

wherein

A is an optionally substituted aryl or heteroaryl;

L^1 is -CR'$_2$-, -CR'$_2$CR'$_2$-, or a bond;

each R' is independently H or C_1-C_6 alkyl; or two R' together with the carbon or carbons to which they are attached form a 3-6-membered cycloalkyl ring;

each R^1, R^3 and R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halogen;

R^2 is aryl or heteroaryl, each optionally substituted;

R^5 is NH_2 or OH;

R^6 is H or C_1-C_6 alkyl;

R^7 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -$(CH_2)_{0-2}$-phenyl, -$(CH_2)_{0-2}$-C_3-C_7 cycloalkyl, -$(CH_2)_{0-2}$-heteroaryl or -$(CH_2)_{0-2}$-heterocyclyl, wherein each alkyl, heteroalkyl, phenyl, cycloalkyl, heteroaryl or heterocyclyl is optionally substituted;

R^8 is H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, phenyl, cycloalkyl, heterocyclyl, cyano, CO-R', or CO_2-R', wherein each alkyl, heteroalkyl, phenyl, cycloalkyl, or heterocyclyl is optionally substituted; or

R^7 and R^8 are taken together with the nitrogen and sulfur to which they are attached to form a 4-7 membered heterocycle with 0-2 additional ring heteroatoms selected from O, S, and N, and wherein the heterocycle is optionally substituted.

[0005] In some examples, provided is a composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0006] In some examples, provided is a method of treating a disease or disorder that can be treated by inhibition of HDAC, the method comprising administering to a patient in need thereof a compound described herein or a composition described herein.

[0007] In some examples, provided is a use of a compound disclosed herein in the manufacture of a medicament for the treatment of a disease or disorder that can be treated by inhibition of a histone deacetylase (HDAC). In some examples, provided is a use of a compound disclosed herein in the manufacture of a medicament for the treatment of cancer.

[0008] In one example, provided is a use of a compound as described herein, or a pharmaceutically acceptable salt thereof, or a composition as described herein in treating a disease or disorder that can be treated by inhibition of a histone deacetylase (HDAC).

[0009] In one example, provided is a compound as described herein, or a pharmaceutically acceptable salt thereof, or a composition as described herein for use in a method of treating a disease or disorder that can be treated by inhibition of a histone deacetylase

(HDAC), the method comprising administering to a patient in need thereof a compound as described herein, or a pharmaceutically acceptable salt thereof, or a composition as described herein.

[0010] Still other objects and advantages of the disclosure will become apparent to those of skill in the art from the disclosure herein, which is simply illustrative and not restrictive. Thus, other examples will be recognized by the skilled artisan without departing from the spirit and scope of the disclosure.

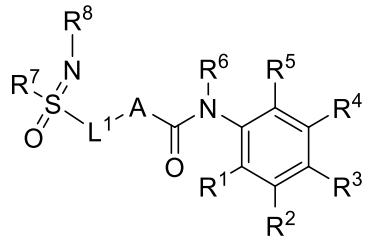
DETAILED DESCRIPTION

[0011] In some embodiments, provided herein are compounds (e.g., compounds of Formula (I), (Ia), (Ib), (Ic), (Id), (Ie), and (If), or compounds of Table 1, or pharmaceutically acceptable salts thereof) that are useful for treating diseases or disorders (e.g., cancer) associated with inhibition of HDAC.

Compounds

[0012] Provided herein are compounds of Formula (I). Unless the context requires otherwise, reference throughout this specification to "a compound of Formula (I)" or "compounds of Formula (I)" refers to all embodiments of Formula (I), including, for example, compounds of Formulas (Ia), (Ib), (Ic), (Id), (Ie), and (If), as well as the compounds of Table 1. In some embodiments, provided are compounds of Formula (I) or pharmaceutically acceptable salts thereof. In some embodiments, the compounds of Formula (I) are provided as pharmaceutically acceptable salts. In some embodiments, the compounds of Formula (I) are provided as the corresponding free base (*i.e.*, are not salts).

[0013] In some embodiments, provided herein is a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof,

wherein

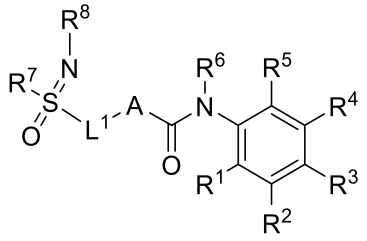
A is an optionally substituted aryl or heteroaryl;

L^1 is -CR'$_2$-, -CR'$_2$CR'$_2$-, or a bond;

CLAIMS

We claim:

1. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof,

wherein

A is phenyl or heteroaryl, wherein heteroaryl has 5, 6 or 9 ring atoms, 1 to 4 ring atoms selected from N, O, and S, and wherein A is substituted with 0-4 R^9 groups;

L^1 is -CR'_2-, -$CR'_2CR'_2$-, or a bond;

each R' is independently H or C_1-C_6 alkyl; or two R' together with the carbon or carbons to which they are attached form a 3-6-membered cycloalkyl ring;

each R^1, R^3 and R^4 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or halogen;

R^2 is phenyl or monocyclic heteroaryl, wherein heteroaryl has 5 or 6 ring atoms with 1 to 2 ring atoms selected from N, O, and S, and R^2 is substituted with 0-4 R^{10} groups;

R^5 is NH_2 or OH;

R^6 is H or C_1-C_6 alkyl;

R^7 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -$(CH_2)_{0-2}$-phenyl, -$(CH_2)_{0-2}$-C_3-C_7 cycloalkyl, -$(CH_2)_{0-2}$-heteroaryl or -$(CH_2)_{0-2}$-heterocyclyl, wherein each alkyl, heteroalkyl, phenyl, cycloalkyl, heteroaryl or heterocyclyl is substituted with 0-4 R^{11} groups;

R^8 is H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, phenyl, cycloalkyl, heterocyclyl, cyano, CO-R', or CO_2-R', wherein heterocyclyl has 4-11 ring atoms with 1 to 4 ring atoms selected from N, O, and S; each alkyl or heteroalkyl is substituted with 0-4 groups independently selected from halogen and OH, and each phenyl, cycloalkyl, or heterocyclyl is substituted with 0-4 R^{10} groups; or

R^7 and R^8 are taken together with the nitrogen and sulfur to which they are attached to form a 4-7 membered heterocycle with 0-2 additional ring heteroatoms selected from O, S, and N, and wherein the heterocycle is substituted with 0-4 R^{10} groups;

each R^9 is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_7 cycloalkyl, hydroxy, cyano, or halogen, wherein each alkyl or heteroalkyl is optionally substituted with 1-4 groups independently selected from halogen and OH;

each R^{10} and R^{11} is independently C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 heteroalkyl, phenyl, C_3-C_7 cycloalkyl, heterocyclyl, C_1-C_6 alkylene-phenyl, C_1-C_6 alkylene- C_3-C_7 cycloalkyl, C_1-C_6 alkylene- heterocyclyl, hydroxy, cyano, CO-R^C, $NR^D{}_2$, or halogen, wherein heterocyclyl has 4-11 ring atoms with 1 to 4 ring atoms selected from N, O, and S; each alkyl or heteroalkyl is optionally substituted with 1-4 groups independently selected from halogen and OH, and wherein each phenyl, cycloalkyl, or heterocyclyl is optionally substituted with 1-4 R^E;

each R^C is independently H, OH, $NR^{12}{}_2$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 heteroalkyl, wherein each alkyl or heteroalkyl is optionally substituted with 1-4 substituents independently selected from halogen and OH;

each R^D is independently H, C_1-C_6 alkyl, CO-C_1-C_6 alkyl; CO_2-C_1-C_6 alkyl; SO_w-C_1-C_6 alkyl; C_1-C_6 heteroalkyl, wherein each alkyl or heteroalkyl is optionally substituted with 1-4 substituents independently selected from halogen and OH; or

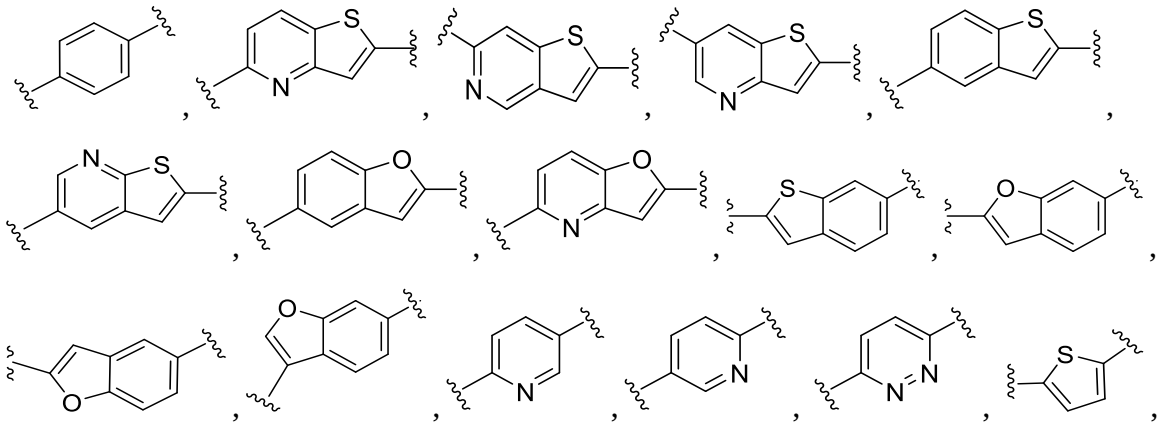
two R^D attached to the same nitrogen are taken together with the nitrogen to which they are attached to form a 3-7 membered heterocycle with 0-2 additional ring heteroatoms selected from O, S, and N, and wherein the heterocycle is optionally substituted with 1-4 substituents independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, and OH;

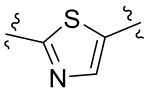
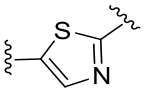
each R^E is independently H, halo, OH, O-C_1-C_6 alkyl, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl;

each R^{12} is independently H or C_1-C_6 alkyl; and

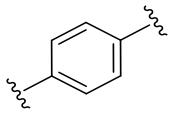
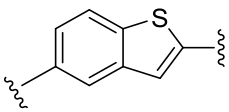
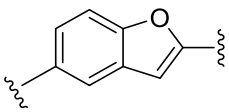
w is 0, 1, or 2.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is selected from:

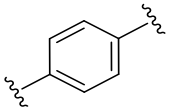


 and  , each substituted with 0-4 R^9 groups, wherein the left attachment point  represents the attachment point to L^1 and the right attachment point  represents the attachment point to the carbonyl.

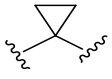
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is selected from:

 ,  and  , each substituted with 0-4 R^9 groups, wherein the left attachment point  represents the attachment point to L^1 and the right attachment point represents the attachment point to the carbonyl.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is

 substituted with 0-4 R^9 groups, wherein the left attachment point  represents the attachment point to L^1 and the right attachment point  represents the attachment point to the carbonyl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein A is not substituted with any R^9 groups.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein L^1 is selected from a bond, $–CH_2–$ and  .

7. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein L^1 is a bond.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^1 is H.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^3 is H.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^5 is NH_2.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^6 is H.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^2 is phenyl substituted with 0-4 R^{10} groups.

14. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^2 is a monocyclic heteroaryl substituted with 0-4 R^{10} groups.

15. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from phenyl, pyridine, pyrimidine, pyridazine, pyrazine, thiazole and thiophene, each substituted with 0-4 R^{10} groups.

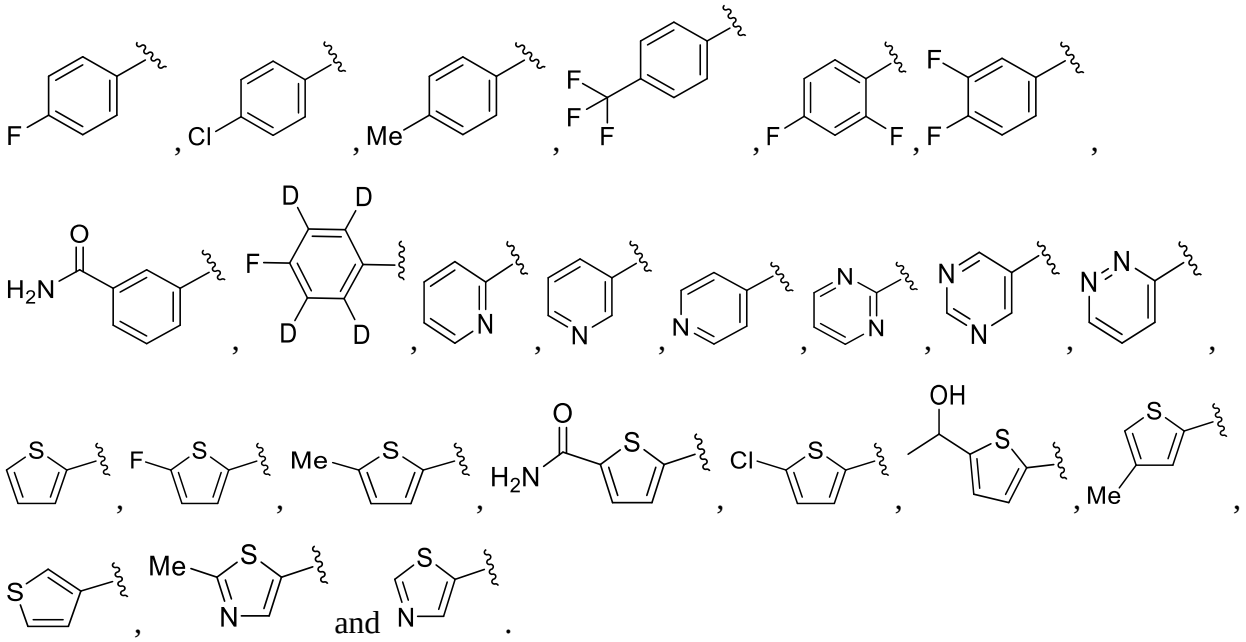
16. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from phenyl and thiophene, each substituted with 0-4 R^{10} groups.

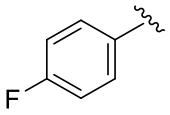
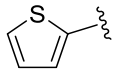
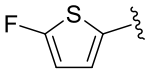
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein each R^{10} is independently selected from halogen, C_1-C_6 alkyl, and CO-R^C, wherein R^C is -NH_2 and wherein the alkyl is unsubstituted or substituted with 1-4 groups independently selected from halogen and OH.

18. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein each R^{10} is independently selected from –F, –Cl, – Me, CF_3, $–CONH_2$ and – $CH(OH)CH_3$.

19. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein each R^{10} is independently selected from –F, and – Me.

20. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from the group consisting of:



21. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from the group consisting of:  ,  and  .

22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_7 cycloalkyl, phenyl, or a monocyclic heteroaryl, wherein the heteroaryl has 5 or 6 ring atoms with 1 to 2 ring atoms being N; wherein each alkyl, heteroalkyl, phenyl, cycloalkyl and heteroaryl is substituted with 0-4 R^{11} groups; or

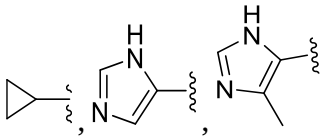
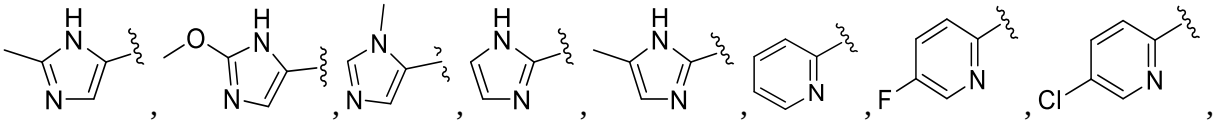
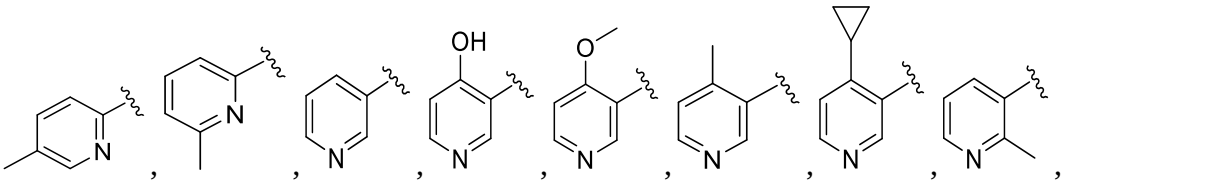
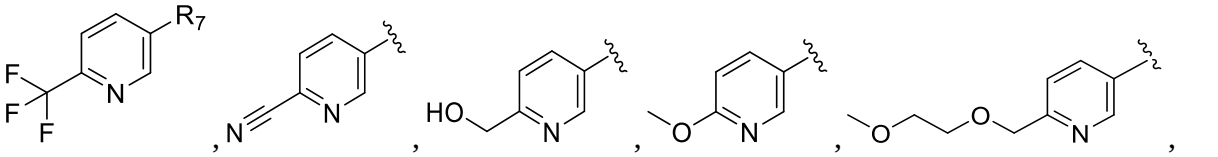
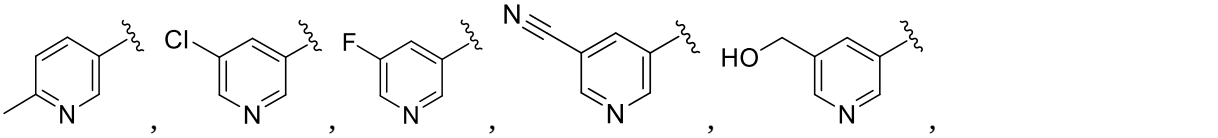
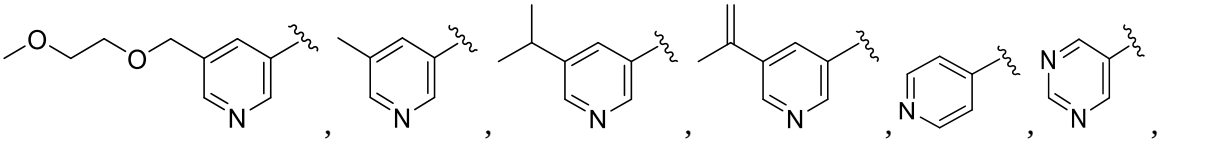
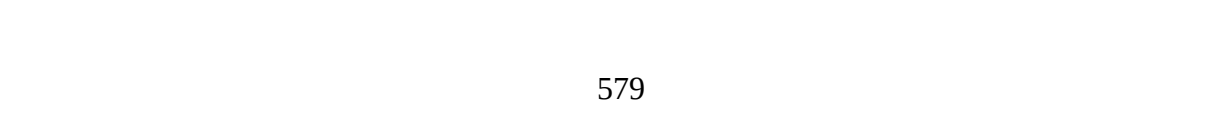
R^7 and R^8 are taken together with the nitrogen and sulfur to which they are attached to form a 4-7 membered heterocycle with 0 additional ring heteroatoms, wherein the heterocycle is substituted with 0-4 R^{10} groups.

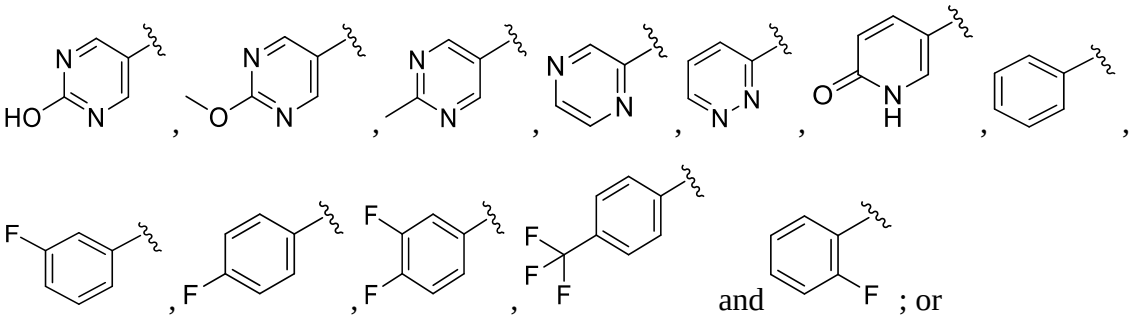
23. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from –Me, –Et, —CF_3, CH_2CH_2OMe, phenyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl and pyridinon-yl; each of which is substituted with 0-4 R^{11} groups; or

R^7 and R^8 are taken together with the nitrogen and sulfur to which they are attached to form a 5 or 6 membered heterocycle with 0 additional ring heteroatoms, wherein the heterocycle is substituted with or 1 instances of methyl or phenyl.

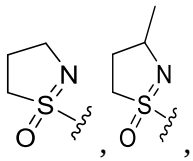
24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein each R^{11} is independently selected from –F, –Cl, –Me, –^{i}Pr, –$C(=CH_2)CH_3$, –CF_3, –CN, –OH, –OMe, –$CH_2OCH_2CH_2OMe$ and –CH_2OH.

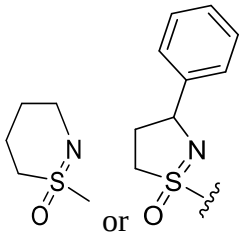
25. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof,

wherein R^7 is selected from –Me, –Et, –CF_3, –CH_2CH_2OMe,  ,  ,  ,  ,  ,  , 



and ; or

R_7 and R_8 are taken together with the atoms to which they are attached to form:  ,

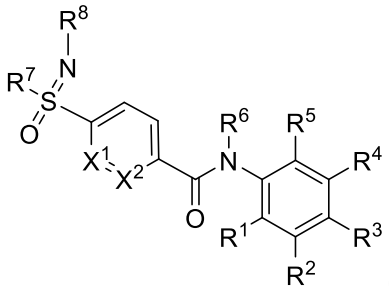
 or .

26. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein R^7 is –Me.

27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein R^8 is H, Me, Et, CN, cyclopropyl, CO-t-butyl, or -CO_2-t-butyl.

28. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, wherein R^8 is H.

29. The compound of any one of claims 1-28 of Formula (Ia)

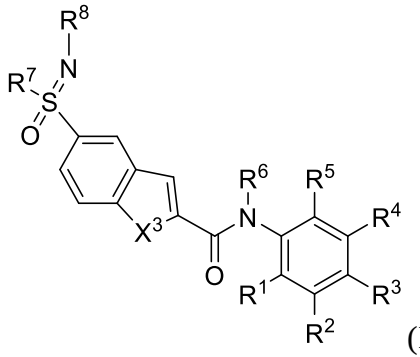
 (Ia),

or a pharmaceutically acceptable salt thereof,

wherein:

X^1 is N or CH; X^2 is N or CH.

30. The compound of any one of claims 1-28 of Formula (Ic)

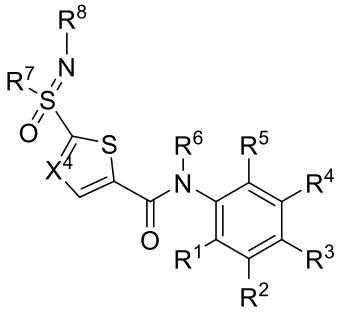


(Ic),

or a pharmaceutically acceptable salt thereof,

wherein X^3 is O or S.

31. The compound of any one of claims 1-28 of Formula (Ie)

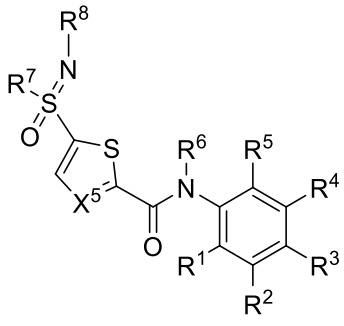


(Ie),

or a pharmaceutically acceptable salt thereof,

wherein X^4 is N or CH.

32. The compound of any one of claims 1-28 of Formula (Ig)

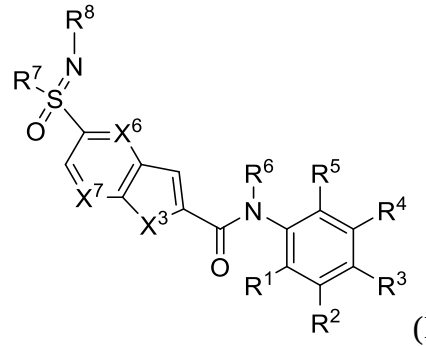


(Ig),

or a pharmaceutically acceptable salt thereof,

wherein X^5 is N or CH.

33. The compound of any one of claims 1-28 of Formula (Ii)


(Ii),

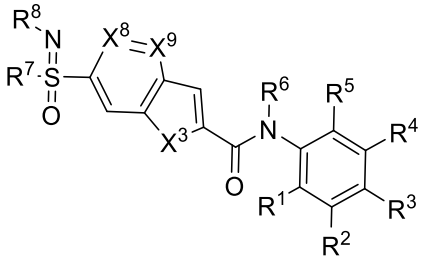
or a pharmaceutically acceptable salt thereof,

wherein X^3 is O or S;

X^6 is N or CH; and

X^7 is N or CH.

34. The compound of any one of claims 1-28 of Formula (Ik)


(Ik),

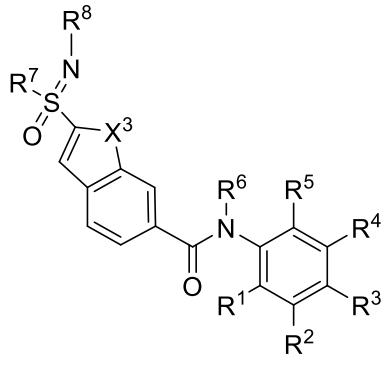
or a pharmaceutically acceptable salt thereof,

wherein X^3 is O or S;

X^8 is N or CH; and

X^9 is N or CH.

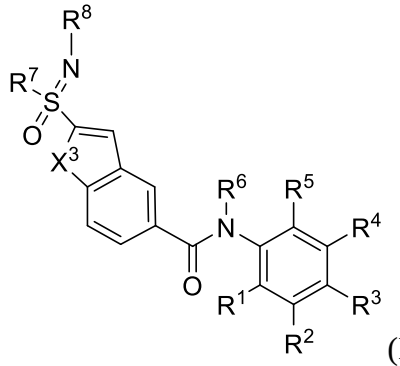
35. The compound of any one of claims 1-28 of Formula (In)


(In),

or a pharmaceutically acceptable salt thereof,

wherein X^3 is O or S.

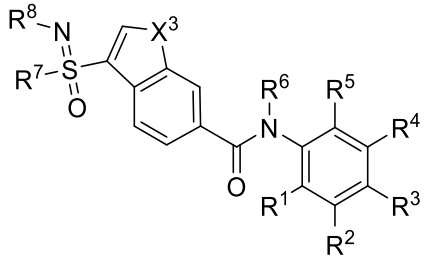
36. The compound of any one of claims 1-28 of Formula (Ip)



(Ip),

or a pharmaceutically acceptable salt thereof,
wherein X^3 is O or S.

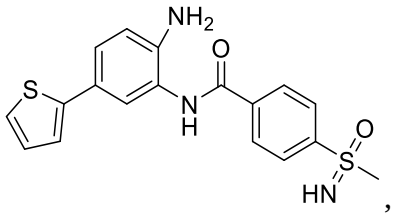
37. The compound of any one of claims 1-28 of Formula (Ir)



(Ir),

or a pharmaceutically acceptable salt thereof,
wherein X^3 is O or S.

38. A compound of any one of claims 1-37 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from: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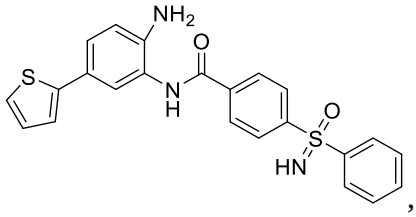
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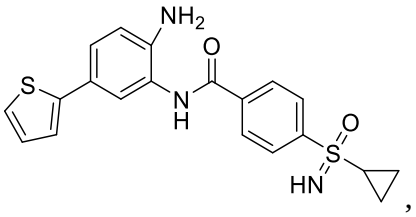
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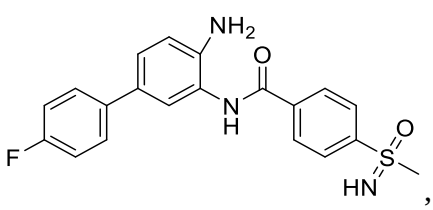
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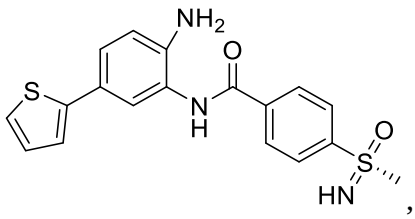
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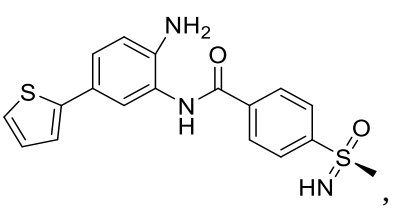
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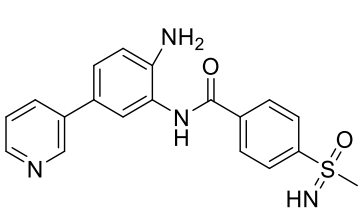
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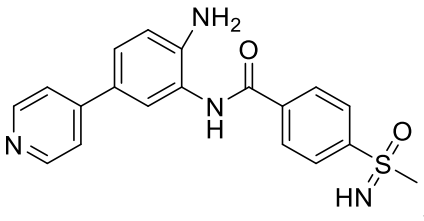
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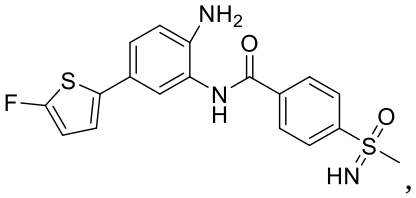
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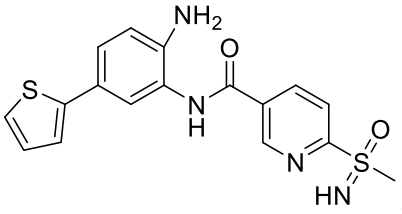
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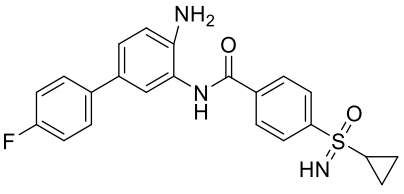
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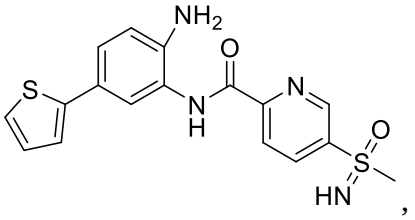
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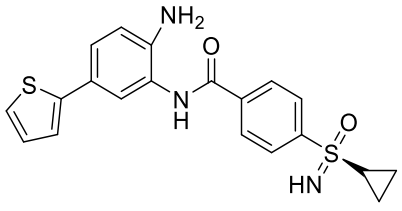
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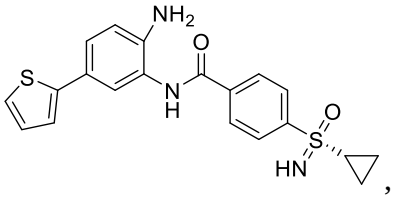
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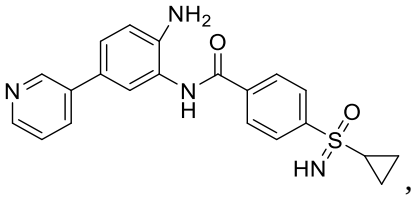
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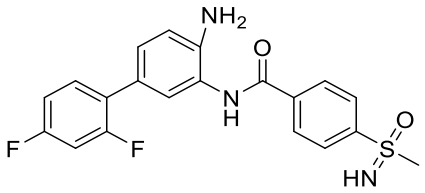
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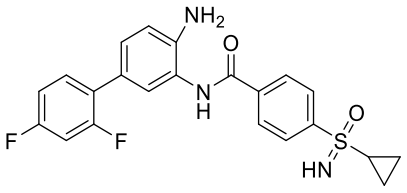
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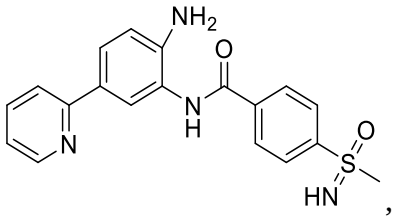
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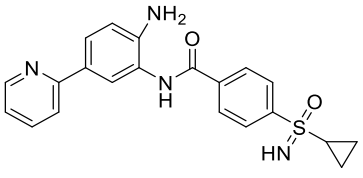
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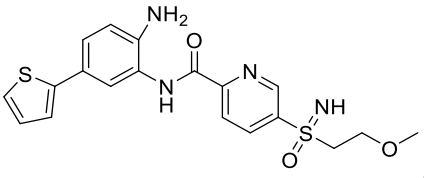
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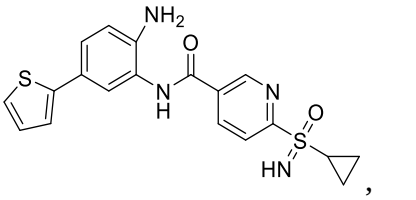
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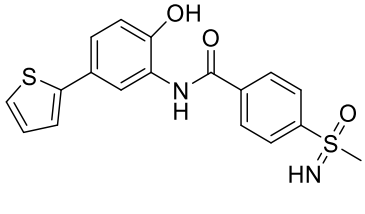
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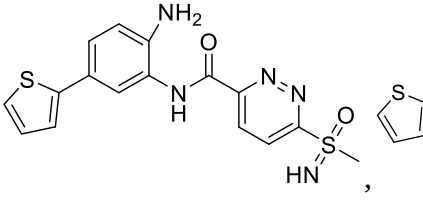
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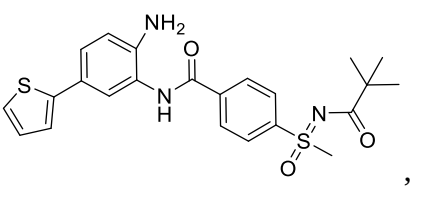
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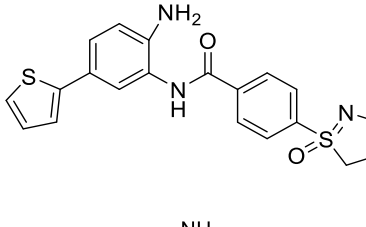
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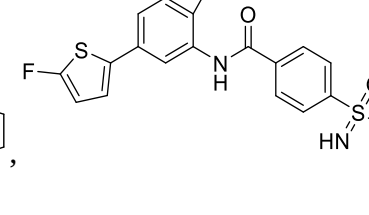
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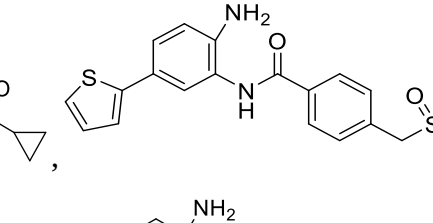
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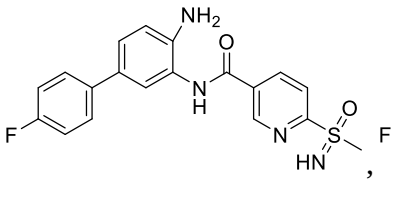
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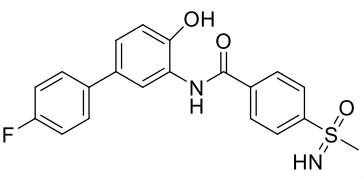
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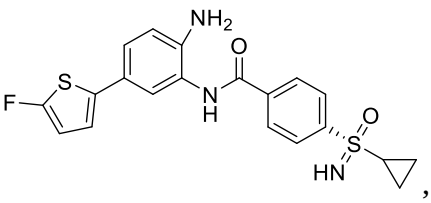
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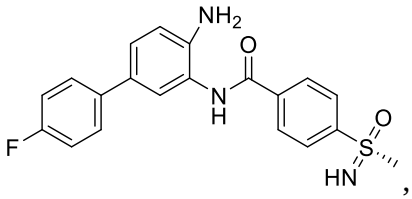
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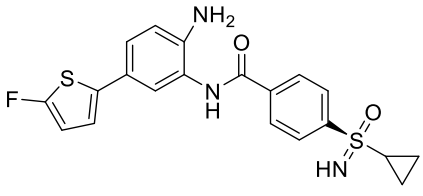
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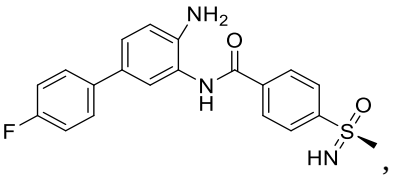
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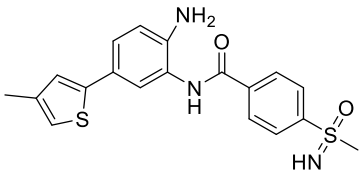
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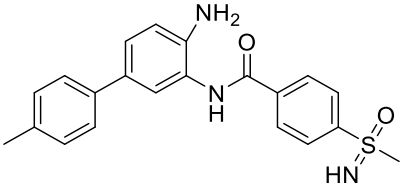
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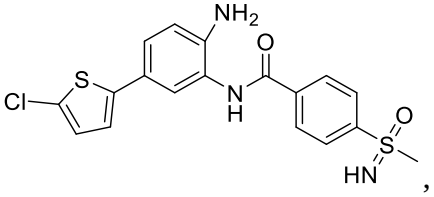
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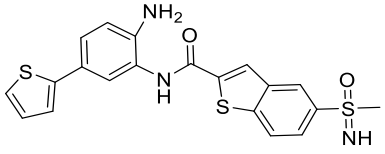
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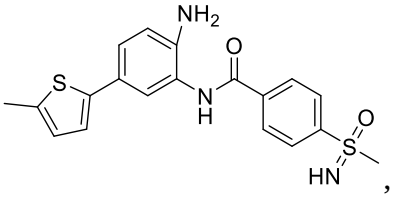
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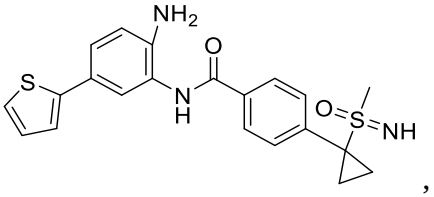
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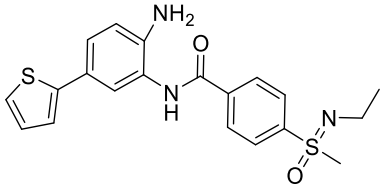
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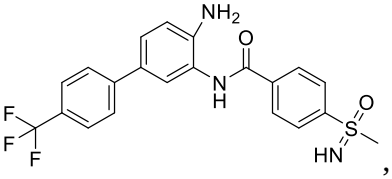
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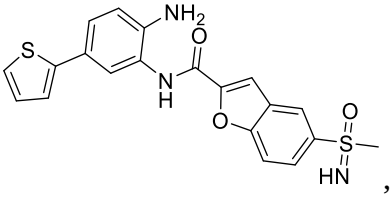
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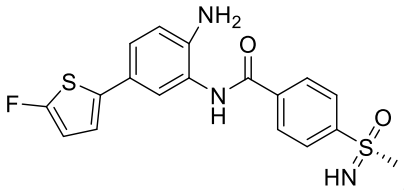
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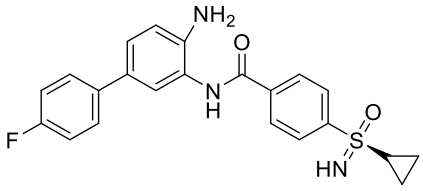
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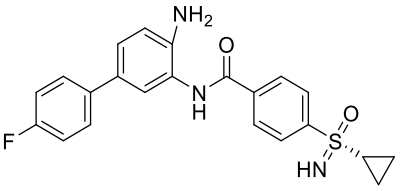
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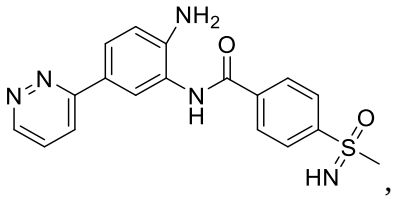
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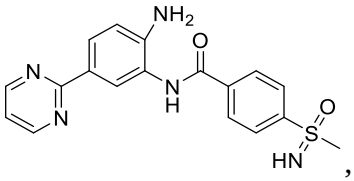
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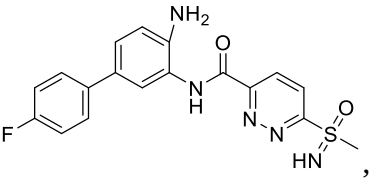
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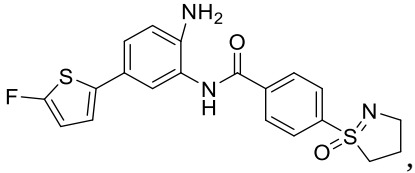
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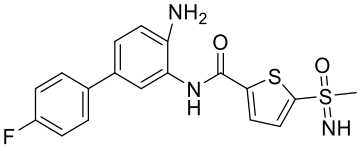
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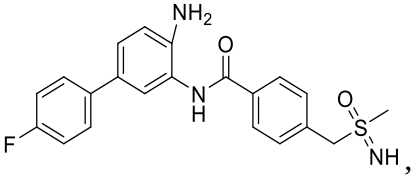
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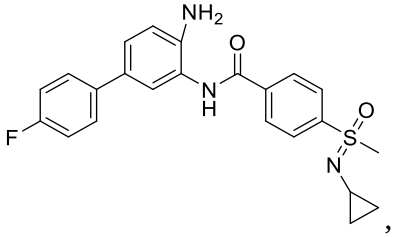
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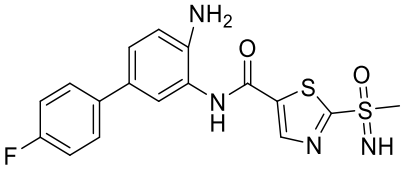
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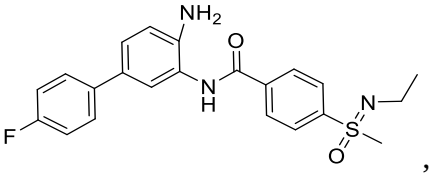
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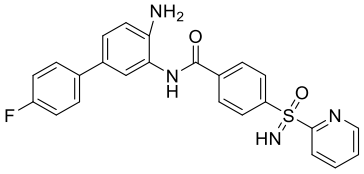
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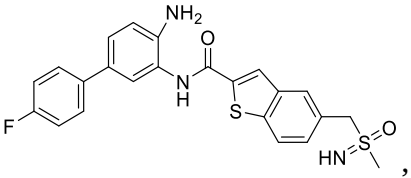
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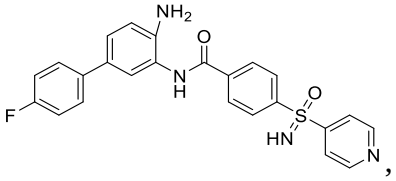
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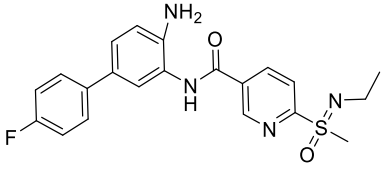
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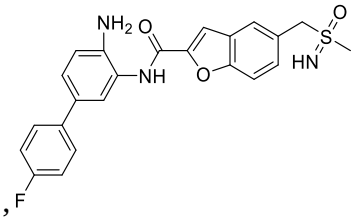
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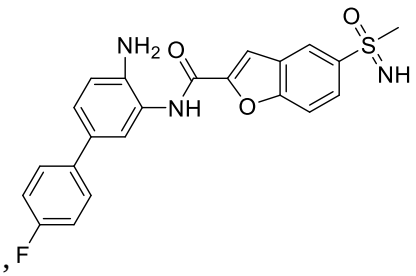
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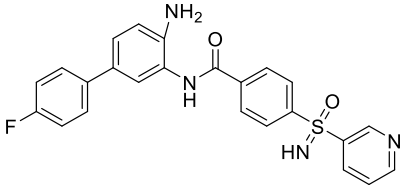
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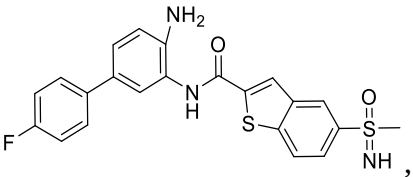
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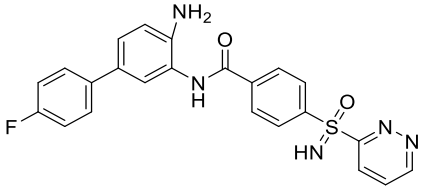
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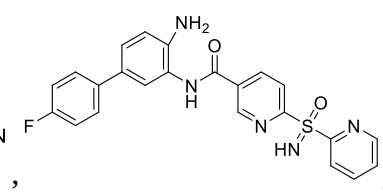
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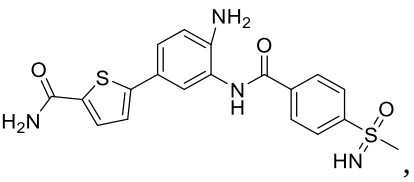
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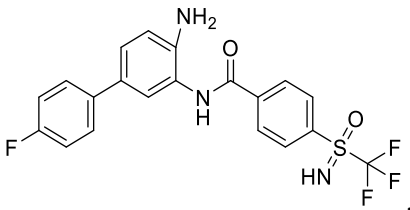
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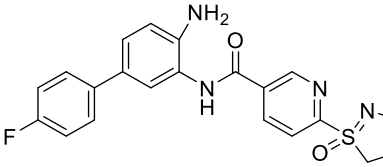
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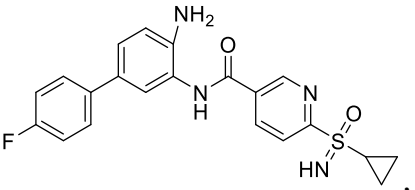
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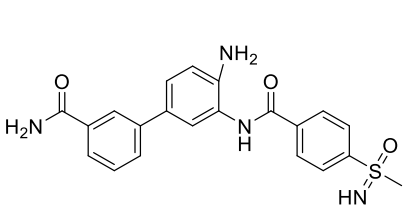
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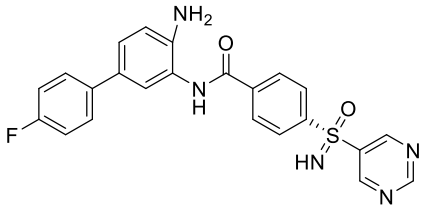
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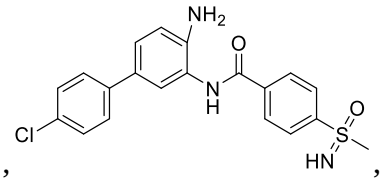
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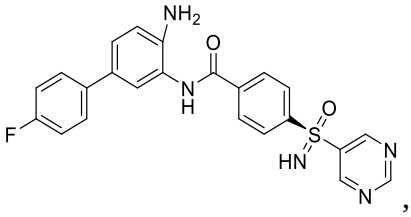
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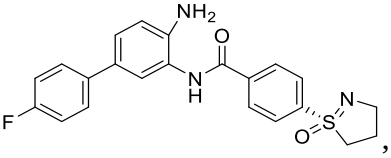
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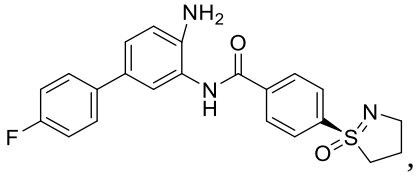
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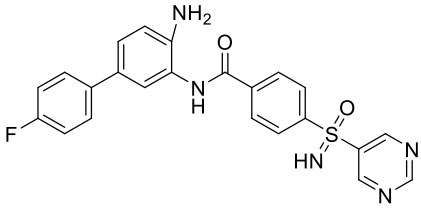
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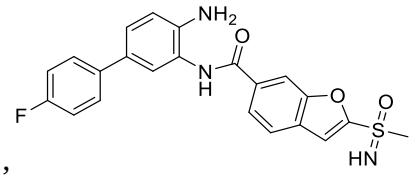
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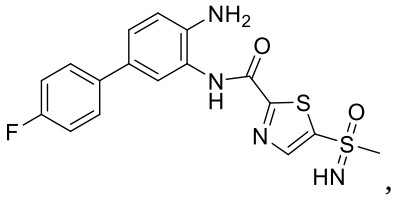
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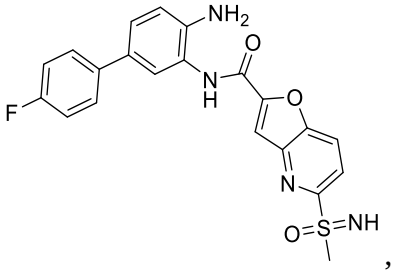
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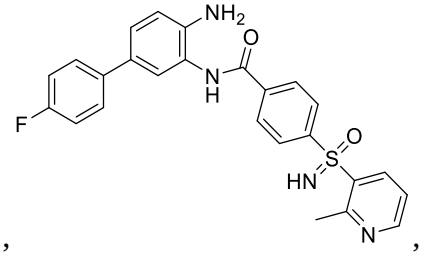
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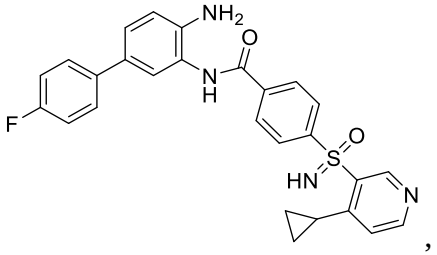
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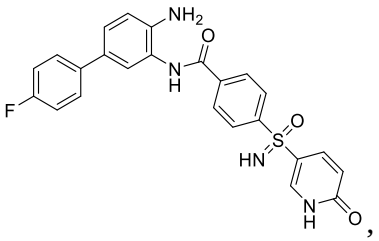
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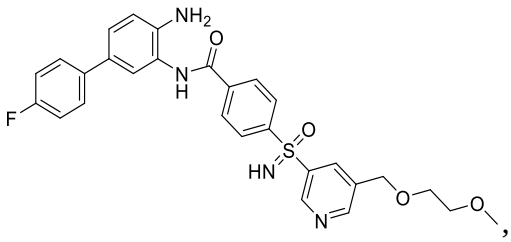
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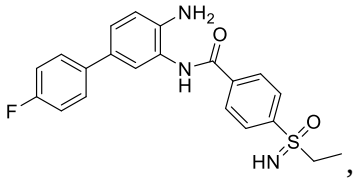
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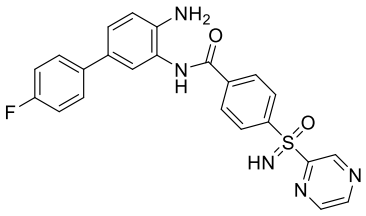
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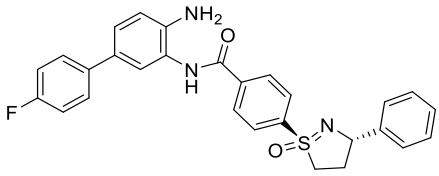
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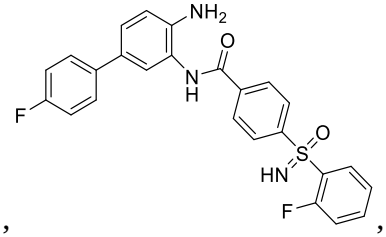
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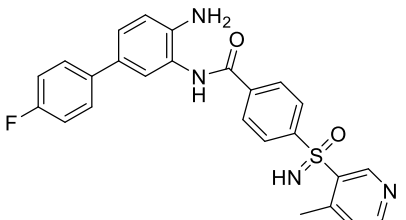
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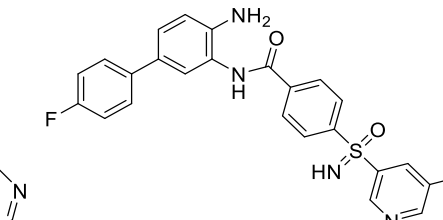
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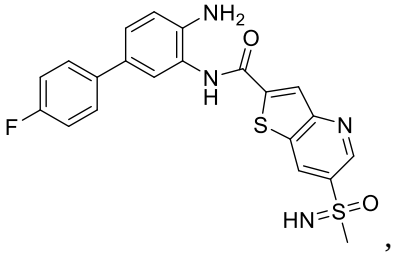
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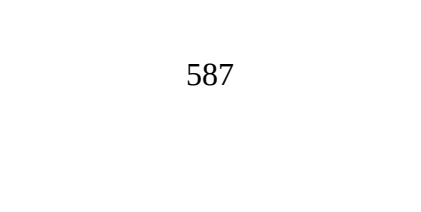
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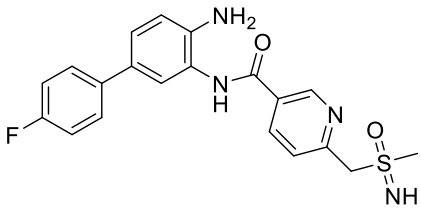
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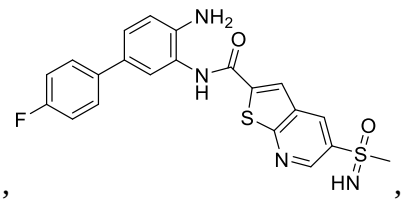
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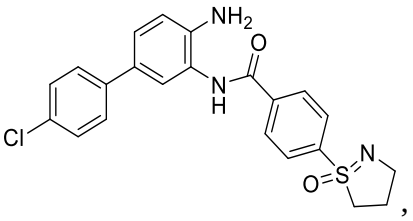
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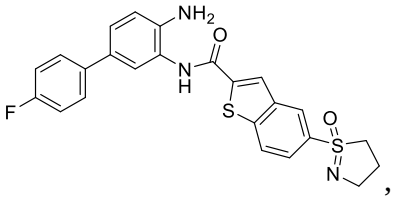
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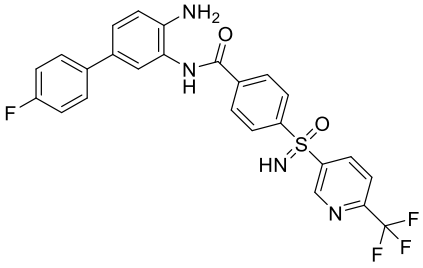
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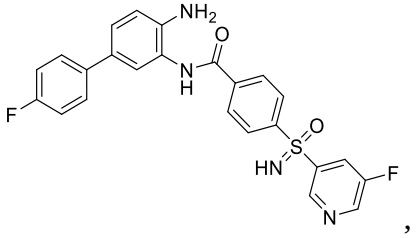
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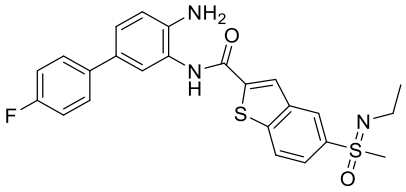
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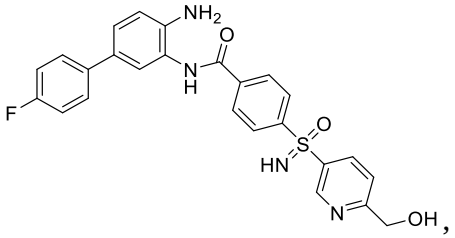
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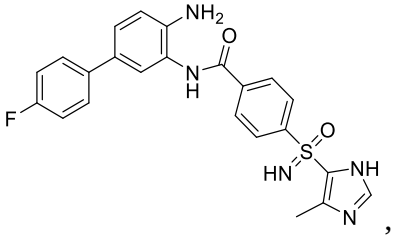
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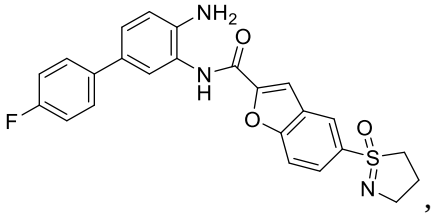
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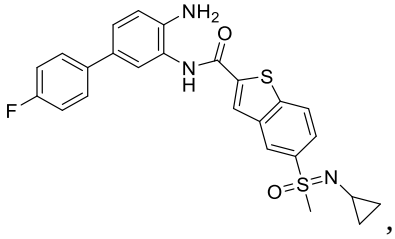
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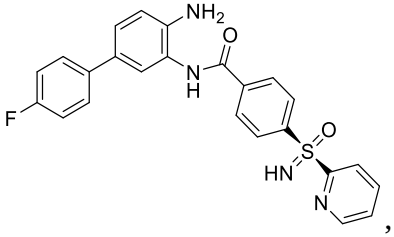
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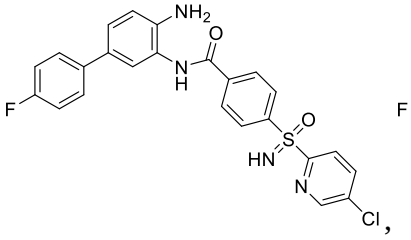
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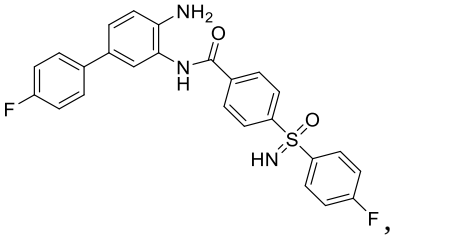
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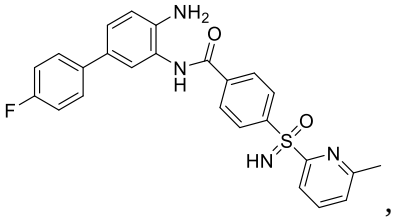
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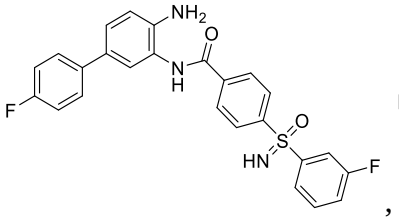
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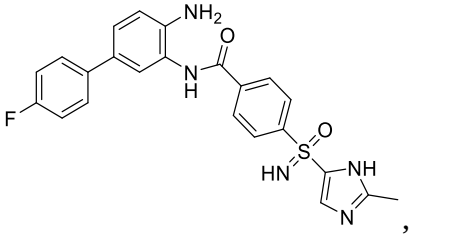
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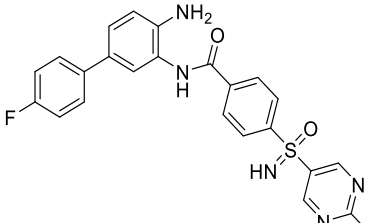
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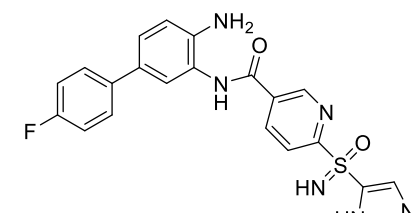
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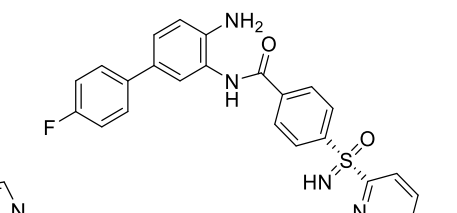
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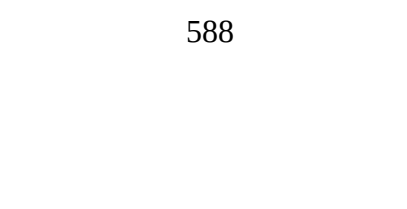
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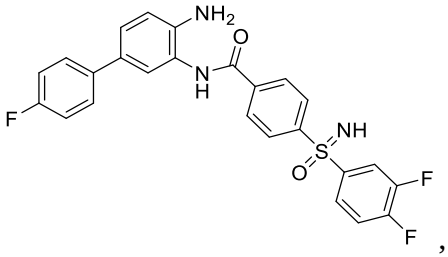
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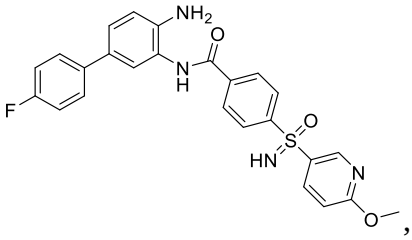
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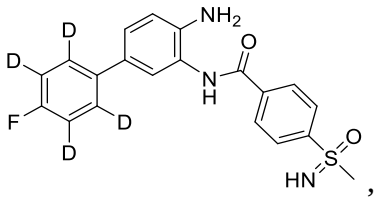
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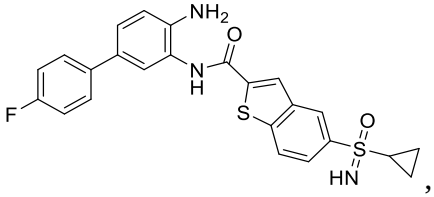
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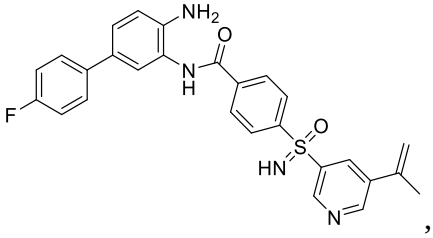
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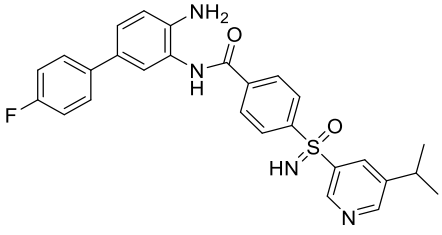
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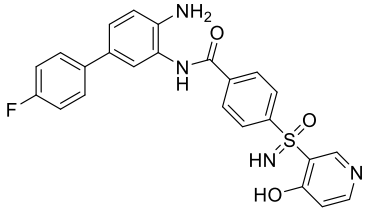
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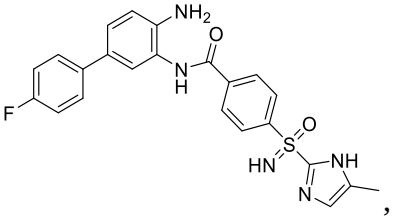
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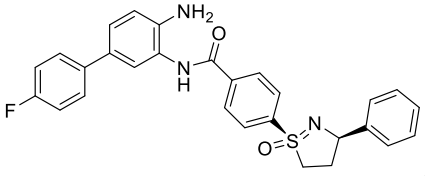
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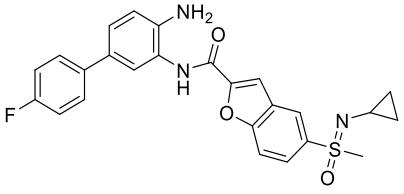
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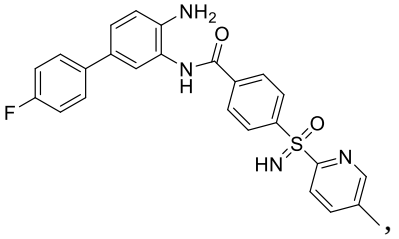
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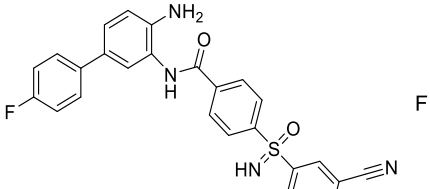
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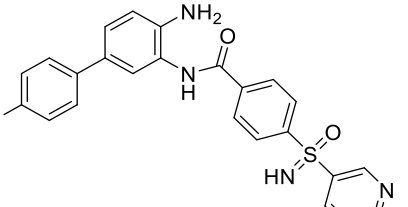
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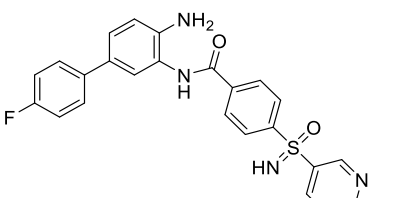
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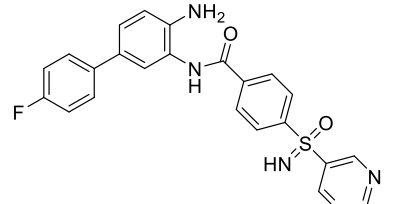
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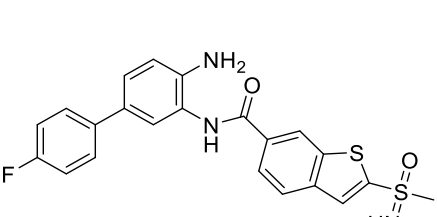
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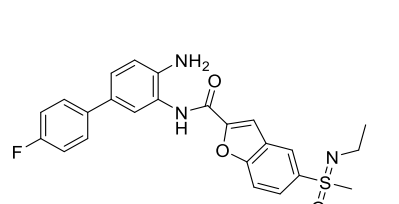
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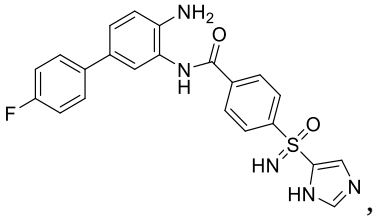
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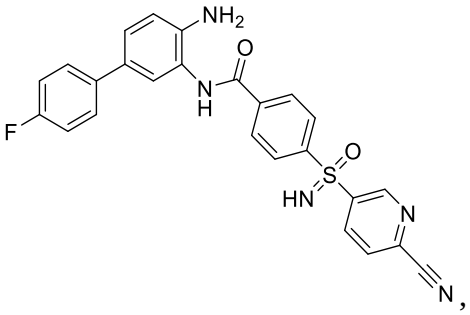
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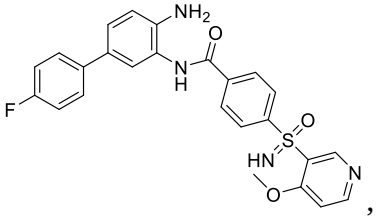
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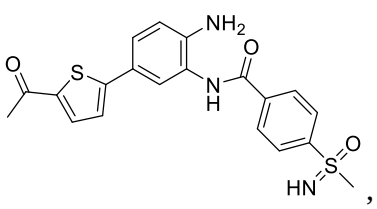
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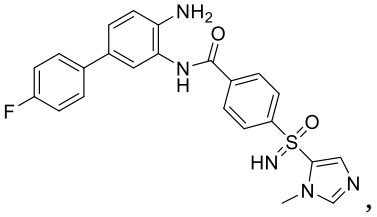
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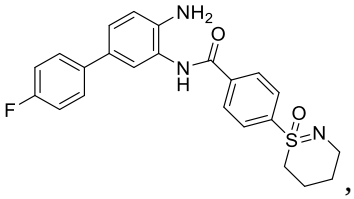
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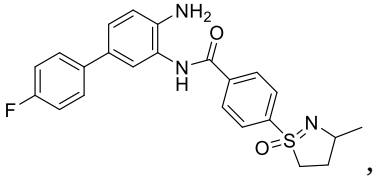
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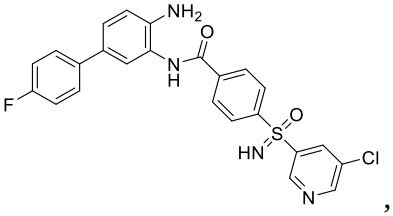
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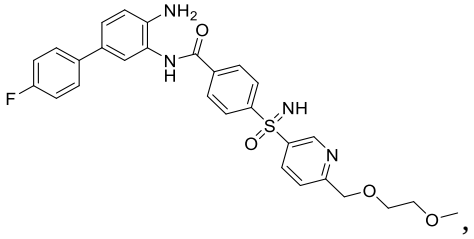
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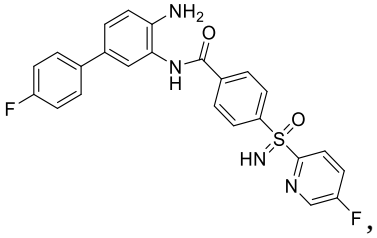
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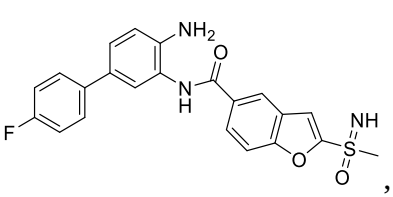
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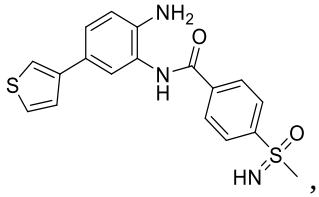
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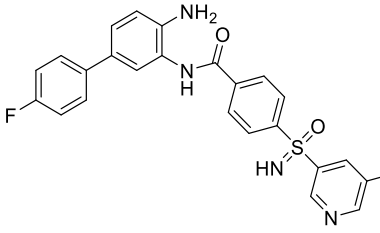
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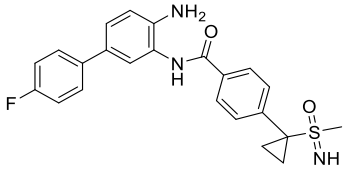
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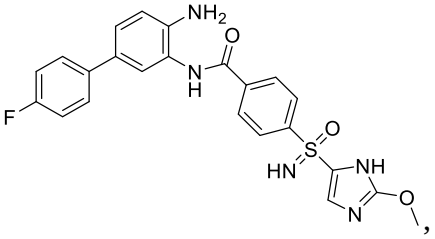
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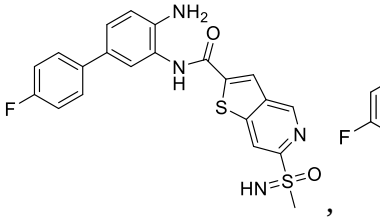
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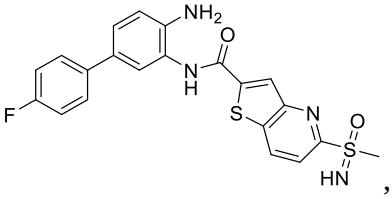
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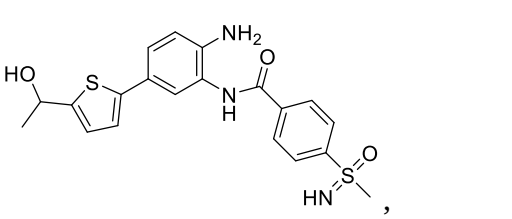
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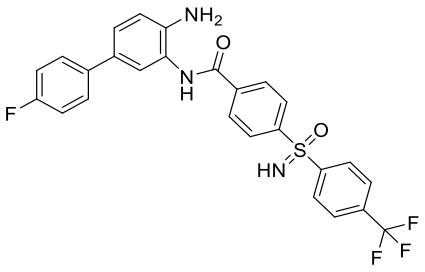
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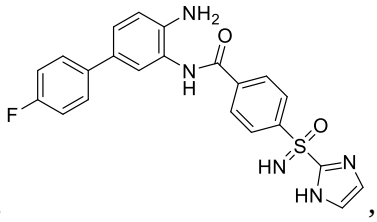
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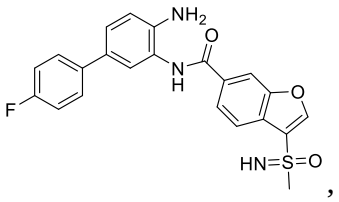
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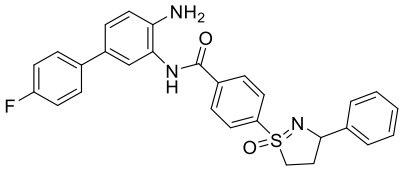
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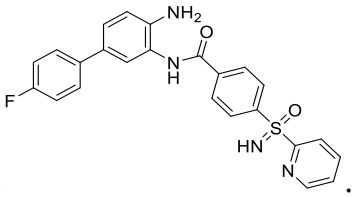
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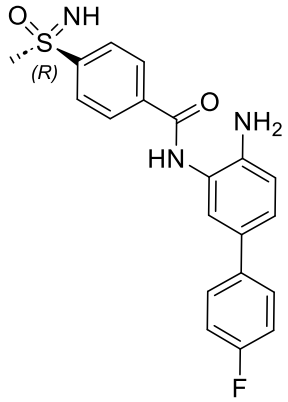
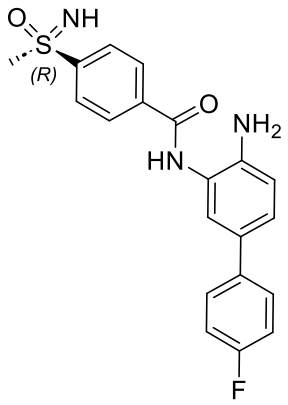
39. A compound of Formula



or a pharmaceutically acceptable salt thereof.

40. A compound of Formula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41. A composition comprising a compound of any one of claims 1-40, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

42. Use of a compound of any one of claims 1-40, or a pharmaceutically acceptable salt thereof, or of a composition of claim 41, in the manufacture of a medicament for treating a cancer that can be treated by inhibition of a histone deacetylase (HDAC).

43. The use of claim 42, wherein the cancer is selected from the group consisting of glioblastoma, malignant peripheral nerve sheath tumors (MPNST), esophageal cancer (*e.g.*, esophageal squamous cell carcinoma or esophageal adenocarcinoma), bladder cancer (*e.g.*, bladder urothelial carcinoma), pancreatic cancer (*e.g.*, pancreatic adenocarcinoma), mesothelioma, melanoma, non-small cell lung cancer (NSCLC; *e.g.*, lung squamous or lung adenocarcinoma), astrocytoma, undifferentiated pleiomorphic sarcoma, diffuse large B-cell lymphoma (DLBCL), leukemia, head and neck cancer, stomach adenocarcinoma, myxofibrosarcoma, cholangiosarcoma, and cancer of the brain, stomach, kidney, breast, endometrium, urinary tract, liver, soft tissue, pleura and large intestine or sarcoma.

44. The use of claim 43, wherein the cancer is selected from the group consisting of a melanoma, bladder cancer, colorectal cancer, head and neck cancer, esophageal cancer, liver cancer, lung cancer, pancreas cancer, and stomach cancer.

45. The use of claim 43, wherein the cancer is carcinoma of unknown primary (CUP), colorectal cancer, cervical cancer or non-small cell lung cancer (NSCLC).

46. The use of any one of claims 42-45, wherein the medicament is to be administered to a patient in need thereof, and wherein at least one additional therapeutic agent is to be further administered to the patient.

47. The use of claim 46, wherein the at least one additional therapeutic agent is chemotherapy or radiation.

48. The use of claim 46, wherein the at least one additional therapeutic agent is an immunotherapeutic agent.

49. The use of claim 48, wherein the immunotherapeutic agent is an anti-PD-1 antibody.

50. The use of claim 48, wherein the immunotherapeutic agent is an anti-PD-L1 antibody or an anti-PD-L1 small molecule.

51. A compound of any one of claims 1-40, or a pharmaceutically acceptable salt thereof, or a composition of claim 41, for use in therapy.