Brief Description of the Figures

[0006] FIG. 1 depicts the Neurite outgrowth (% of control) for HDAC6 inhibitors.

[0007] FIG. 2 shows a western blot of acetylated α-tubulin (Ac-α-tub) and actin protein in primary DRG cells after 48 hours of treatment of HDAC6 inhibitors.

[0008] FIG. 3 shows the protective effect of HDAC6 inhibitors in ameliorating cisplatin induced neurite degeneration.

[0009] FIG. 4 shows the 50% paw withdrawal threshold (PWT) of the following groups: the Sham control (no cisplatin treatment, no testing drug treatment), the Vehicle control group (treated with cisplatin and drug vehicle only), COMPOUND 2 treatment group, ACY-1215 treatment group, and the pregabalin treatment group.

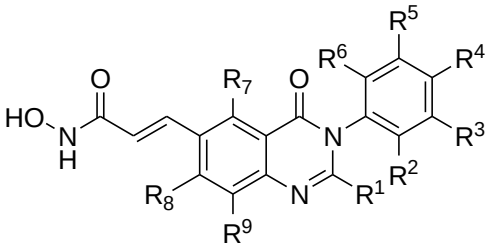
[00010] FIG. 5 depicts lung histology images for Compounds 34, 33, 2, and Nintedanib and the control.

[00011] FIG. 6 depicts the IL-6 concentration for HDAC6 inhibtors.

[00012] FIG. 7 shows the 50% paw withdrawl threshold (PWT) to a static mechanical stimulus, using Von Frey filaments and the up-and-down method.

Summary

[0012a] In one aspect of the present disclosure, there is provided a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen, (C_{1-2})alkyl, or fluoro(C_{1-2})alkyl;

R^2 is hydrogen, halogen, or (C_{1-3})alkyl;

R^3 is hydrogen, or (C_{1-3})alkyl;

R^4 is hydrogen, halogen, (C_{1-3})alkyl, or methoxy, $N(C_{1-3})(C_{1-3})$;

R^5 is hydrogen, (C_{1-3})alkyl, halogen, or trifluoromethyl;

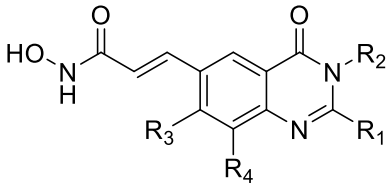
R^6 is hydrogen, (C_{1-3})alkyl, halogen;

R^7 is hydrogen or halogen;

R^8 is hydrogen, methyl, methoxy, or fluoro; and

R^9 is hydrogen or fluoro.

[0012b] In another aspect of the present disclosure, there is provided a compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt thereof, wherein

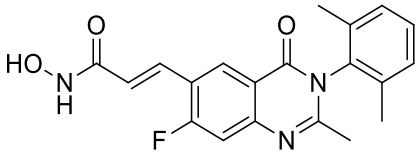
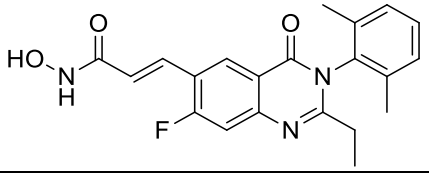
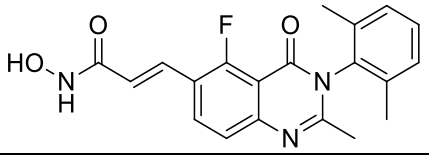
R^1 is methyl, ethyl, or fluoro(C1-2)alkyl;

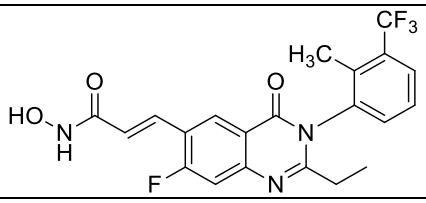
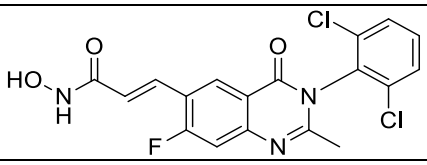
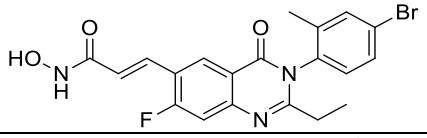
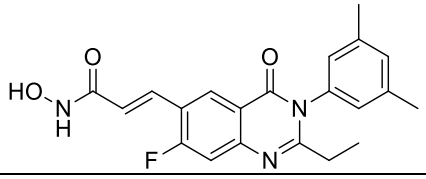
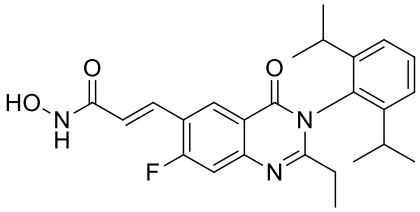
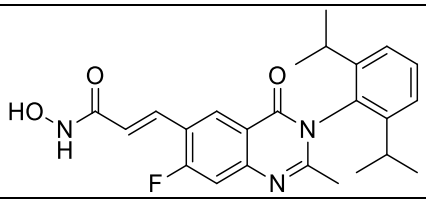
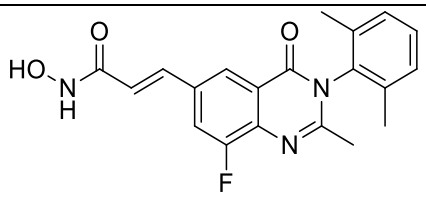
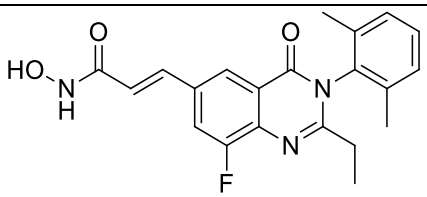
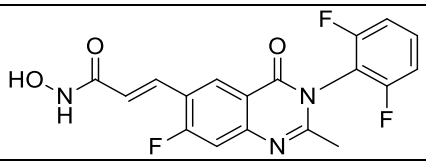
R^2 is phenyl or phenyl substituted with 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, methoxy, trifluoromethyl, and halogen;

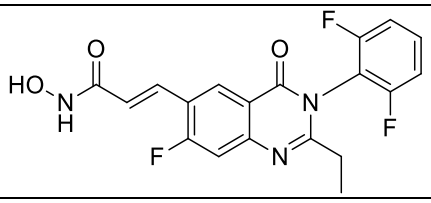
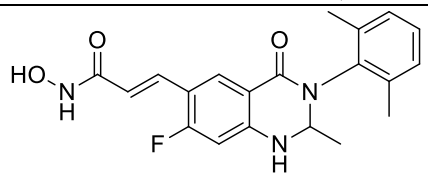
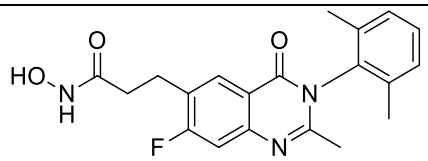
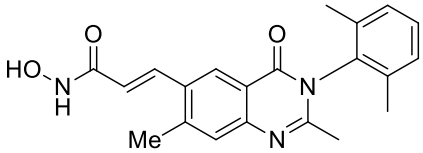
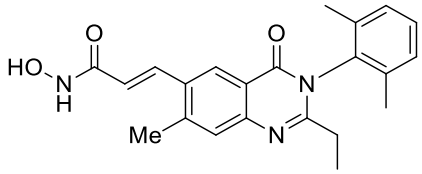
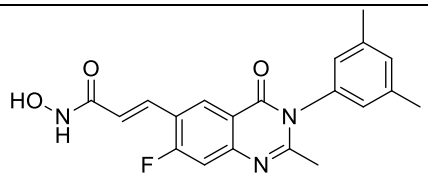
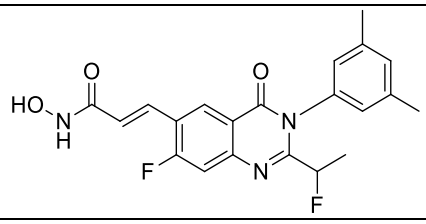
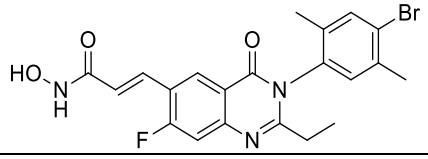
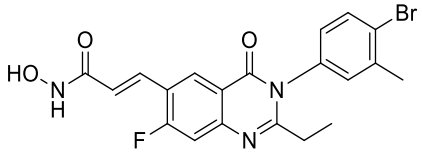
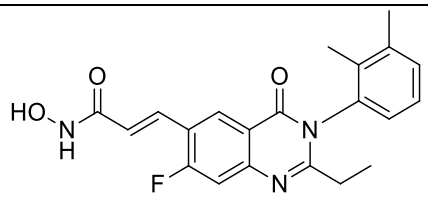
R^3 is hydrogen, methyl, methoxy, or fluoro; and

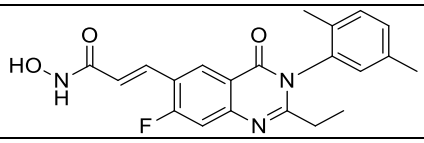
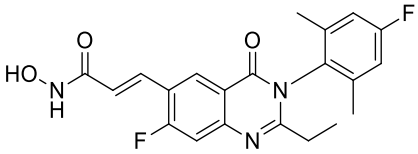
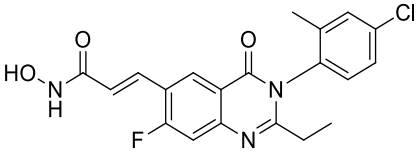
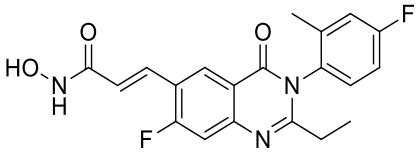
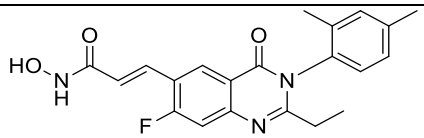
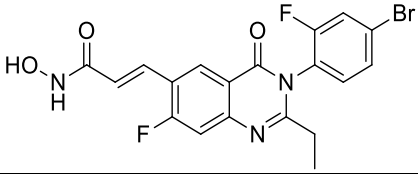
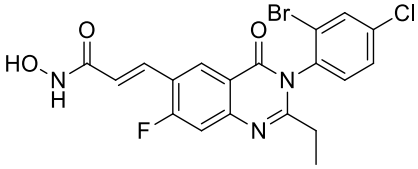
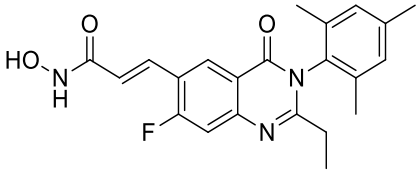
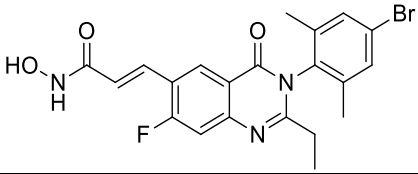
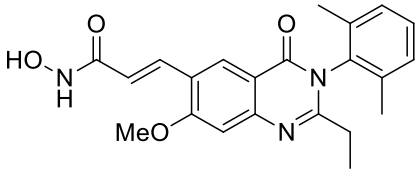
R^4 is hydrogen or fluoro.

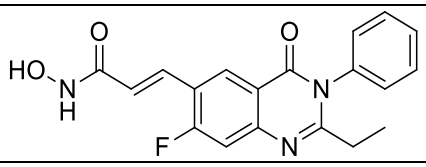
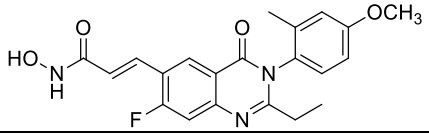
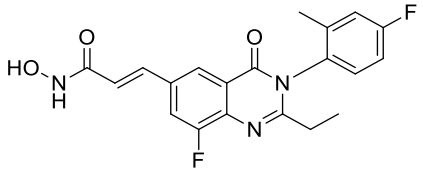
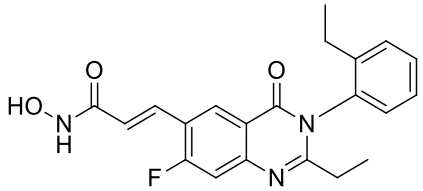
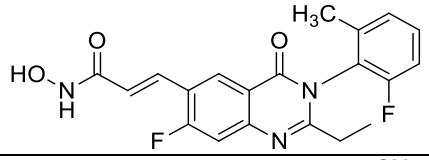
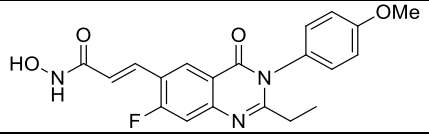
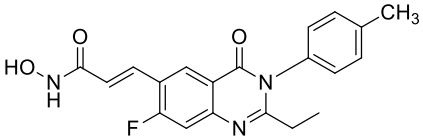
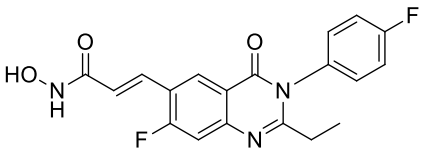
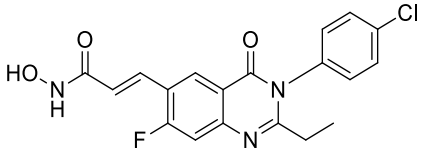
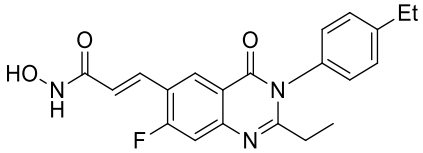
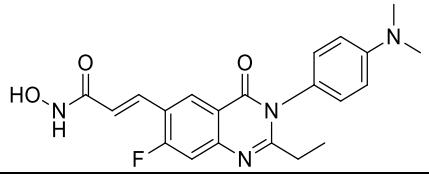
[0012c] In a further aspect of the present disclosure, there is provided a compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the following table:

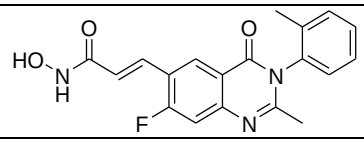
Compound No.	**Structure**
1	
2	
3	

4	
5	
6	
7	
8	
9	
10	
11	
12	

13	
14	
15	
16	
17	
18	
19	
20	
21	
22	

23	
24	
25	
26	
27	
28	
29	
30	
31	
32	

33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	

44	

.

[0012d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a therapeutically effective amount of the selective HDAC6 inhibitor (HDAC6i) disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or vehicle.

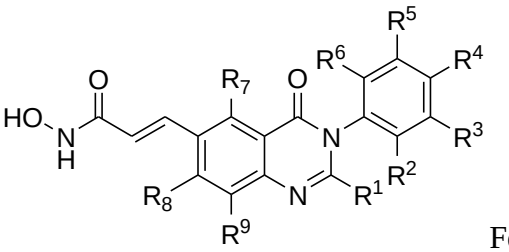
[0012e] In a further aspect of the present disclosure, there is provided a use of the compound disclosed herein or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for promoting neurite outgrowth, enhancing tubulin hyperacetylation of cells, or prevention or treatment of peripheral neuropathy, diabetes induced neuropathy, or fibrosis.

[0012f] In another aspect of the present disclosure, there is provided a use of the compound disclosed herein or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for decreasing expression of IL-1, TNF-α, IL-6 or Collagens.

[0012g] In a further aspect of the present disclosure, there is provided a use of the compound disclosed herein or the pharmaceutical composition of disclosed herein, in the manufacture of a medicament for treating or ameliorating cytokine-induced inflammatory conditions in a subject in need thereof, wherein said cytokine comprises IL-1, TNF-α, IL-6, M-CSF, VCAM-1, or MCP-1.

[0012h] In another aspect of the present disclosure, there is provided a compound disclosed herein or the pharmaceutical composition disclosed herein, for use in therapy.

[00013] In an example, provided herein is a compound of Formula (**I**):

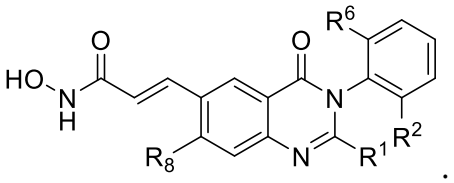


Formula (I)

or a pharmaceutically acceptable salt thereof, wherein R^1 is (C_{1-2})alkyl, or fluoro(C_{1-2})alkyl; R^2 is hydrogen, halogen, or (C_{1-3})alkyl; R^3 is hydrogen, or (C_{1-3})alkyl; R^4 is hydrogen, halogen, (C_{1-3})alkyl, or methoxy, R^5 is hydrogen, (C_{1-3})alkyl, halogen, or trifluoromethyl; R^6 is hydrogen, (C_{1-3})alkyl, halogen; R^7 is hydrogen or halogen; R^8 is hydrogen, methyl, methoxy, or fluoro; and R^9 is hydrogen or fluoro.

[00014] In some examples, R^1 is methyl. In other examples, R^1 is ethyl. In some examples R^2 is hydrogen, whereas in other examples R^2 is halogen. In certain examples R^2 is methyl. In other examples R^3 is hydrogen. In further examples R^6 is methyl.

[00015] In further examples, the compound is of Formula (IA)



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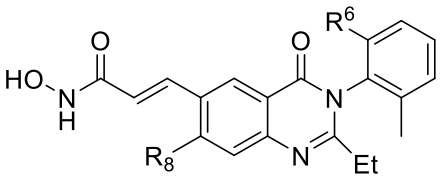
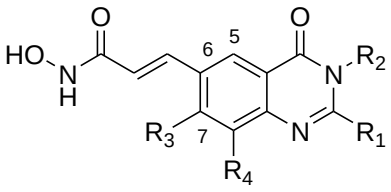
[00016] In other examples, the compound is of Formula (IB)



, wherein R^8 is fluoro.

[00017] In some examples, the compound is selected from Table 1.

[00018] In an example, provided herein is a compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl, ethyl, or fluoro(C_{1-2})alkyl; R^2 is phenyl or phenyl substituted with 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, methoxy, trifluoromethyl, and halogen; R^3 is hydrogen, methyl, methoxy, or fluoro; and R^4 is hydrogen or fluoro.

[00019] In one example, provided herein is a pharmaceutical compositions comprising a therapeutically effective amount of the selective HDAC6 inhibitor (HDAC6i) of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or vehicle.

[00020] In some examples, a method for the prevention or treatment of chemotherapy-induced peripheral neuropathy in a subject, wherein said subject is administered with effective amount of the selective HDAC6 inhibitor disclosed herein, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier or vehicle. In other examples, the said chemotherapy is platinum-based chemotherapy, alkaloid-based, or taxane-based chemotherapy.

[00021] In some examples, a method for enhancing tubulin hyperacetylation of cells in a subject, wherein said subject is treated is effective amount of the selective HDAC6 inhibitor disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or vehicle.

[00022] In other examples, a method for the prevention or treatment of fibrosis of a subject, wherein said subject is administered with effective amount of the selective HDAC6 inhibitor disclosed herein, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier or vehicle. In further examples, said fibrosis is pulmonary fibrosis, hepatic fibrosis, or renal fibrosis, wherein said pulmonary fibrosis is associated with increased expression of IL-6 in said subject. In other examples, said pulmonary fibrosis is idiopathic pulmonary fibrosis or virus-induced fibrosis.

[00023] In some examples, a method of decreasing expression of IL-6 in a subject in need, wherein said subject is administered with effective amount of the selective HDAC6 inhibitor disclosed herein, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier or vehicle.

[00024] In further examples, a method of treating or ameliorating cytokine-induced inflammatory conditions in a subject in need, wherein said cytokine comprises IL-6, M-CSF, VCAM-1, MCP-1 tPA, MMP-1, MMP9, collagen 1 and collagen III, and said subject is administered with effective amount of the selective HDAC6 inhibitor disclosed herein, or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier or vehicle. In other examples, said conditions are selected from a group consisting of pulmonary fibrosis, coronavirus-induced pulmonary inflammation, liver fibrosis, and renal fibrosis.

[00025] In some examples, use of the selective HDAC6 inhibitor disclosed herein in the manufacture of a medicament for the prevention or treatment of chemotherapy-induced peripheral neuropathy in a subject in need thereof.

[00026] In other examples, use of the selective HDAC6 inhibitor disclosed herein in the manufacture of a medicament for the prevention or treatment of fibrosis in a subject in need thereof

[00027] In further examples, use of the selective HDAC6 inhibitor disclosed herein in the manufacture of a medicament for the treatment of pulmonary fibrosis, cornonavirus-induced pulmonary inflammation, liver fibrosis, and renal fibrosis.

[00028] In some examples, a method for the prevention or treatment of diabetes induced neuropathy in a subject, wherein said subject is administered with effective amount of the selective HDAC6 inhibitor of disclosed herein or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier or vehicle.

Detailed Description of Certain Embodiments of the Invention

[00029] As generally described herein, the present invention provides compounds designed, for example, to act as histone deacetylases (HDACs) inhibitors, e.g. inhibitors of HDAC6. In certain embodiments, such compounds are envisioned to be useful as therapeutic agents for treating diabetic induced neuropathy, for example diabetic peripheral neuropathy. In other embodiments, such compounds are envisioned to be useful as therapeutic agents for treating chemotherapy-induced neuropathy, e.g. chemotherapy-induced peripheral neuropathy.

Definitions

Chemical definitions

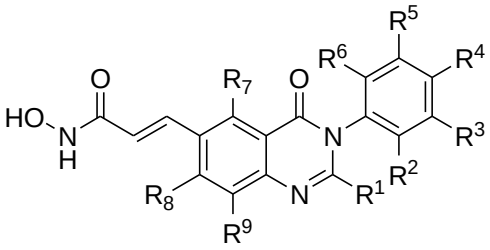
[00030] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[00031] Isomers, *e.g.*, stereoisomers, can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre

CLAIMS

What is claimed:

1. A compound of Formula (**I**):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is hydrogen, (C_{1-2})alkyl, or fluoro(C_{1-2})alkyl;

R^2 is hydrogen, halogen, or (C_{1-3})alkyl;

R^3 is hydrogen, or (C_{1-3})alkyl;

R^4 is hydrogen, halogen, (C_{1-3})alkyl, or methoxy, N(C_{1-3})(C_{1-3});

R^5 is hydrogen, (C_{1-3})alkyl, halogen, or trifluoromethyl;

R^6 is hydrogen, (C_{1-3})alkyl, halogen;

R^7 is hydrogen or halogen;

R^8 is hydrogen, methyl, methoxy, or fluoro; and

R^9 is hydrogen or fluoro.

2. The compound of claim 1, wherein R^1 is methyl or ethyl.

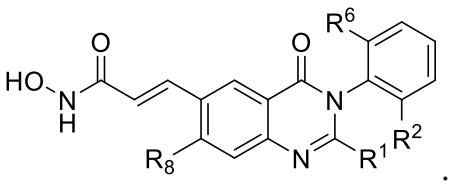
3. The compound of claim 1, wherein R^2 is hydrogen, halogen, methyl, or isopropyl.

4. The compound of claim 1, wherein R^3 is hydrogen.

5. The compound of claim 1, wherein R^6 is methyl or isopropyl.

6. The compound of claim 1, wherein R^4 is dimethylamino.

7. The compound of claim 1, wherein the compound is of Formula (IA)

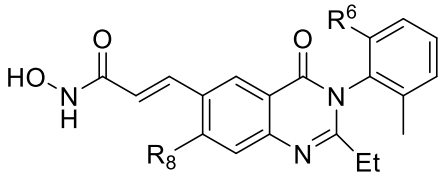


.

8. The compound of claim 7, wherein (i) R^2 and R^6 are each methyl; or (ii) R^2 and R^6 are each hydrogen.

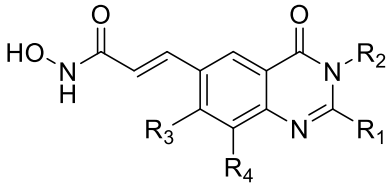
9. The compound of claim 8, wherein (i) R^1 is ethyl; or (ii) R^8 is fluoro.

10. The compound of claim 1, wherein the compound is of Formula (IB)



, wherein R^8 is fluoro.

11. A compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is methyl, ethyl, or fluoro(C1-2)alkyl;

R^2 is phenyl or phenyl substituted with 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, methoxy, trifluoromethyl, and halogen;

R^3 is hydrogen, methyl, methoxy, or fluoro; and

R^4 is hydrogen or fluoro.

12. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the following table:

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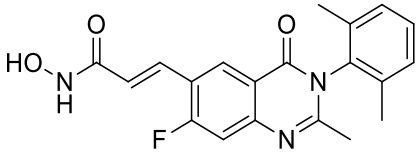
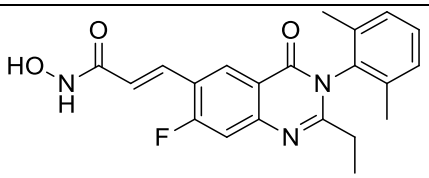
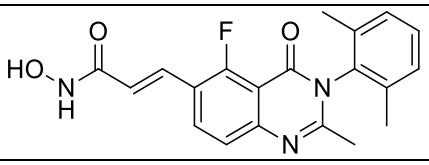
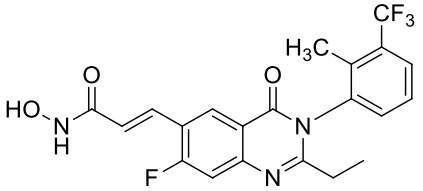
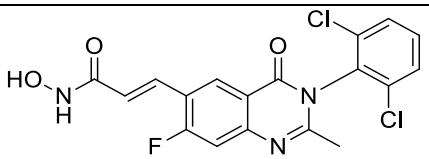
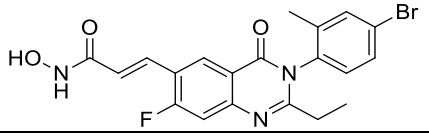
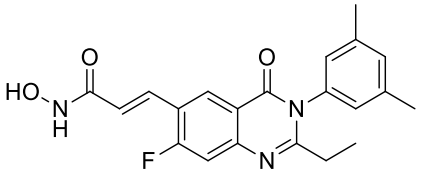
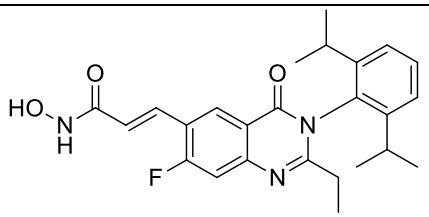
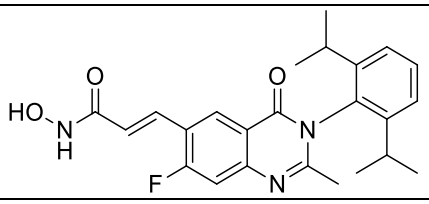
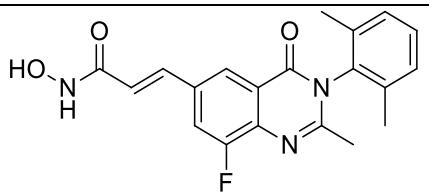
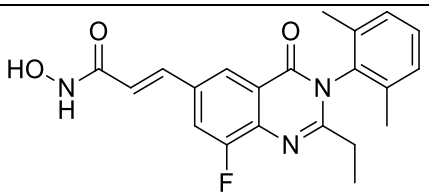
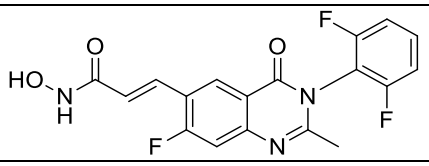
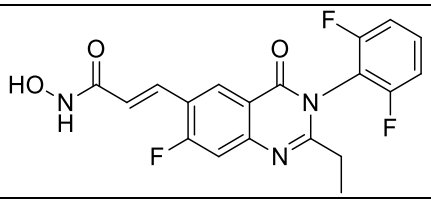
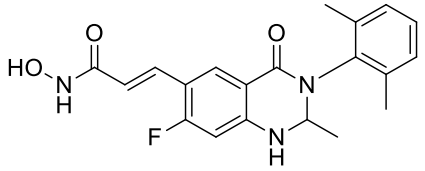
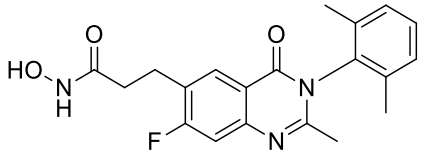
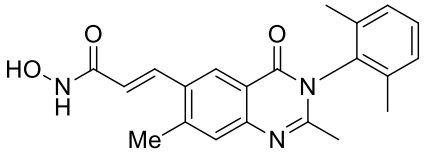
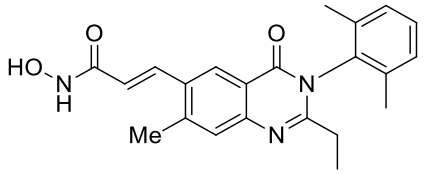
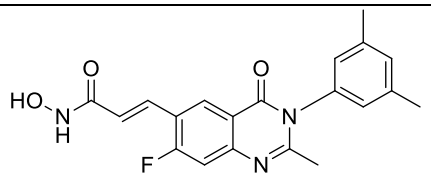
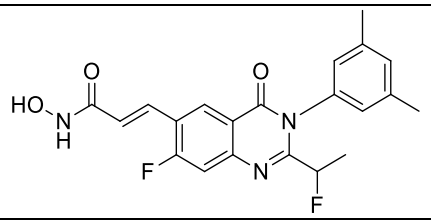
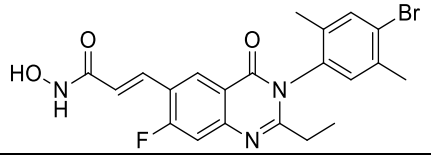
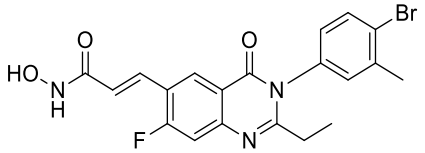
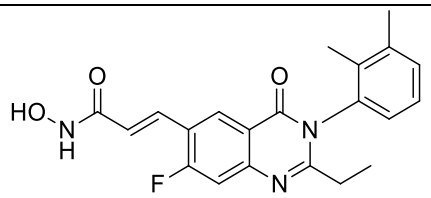
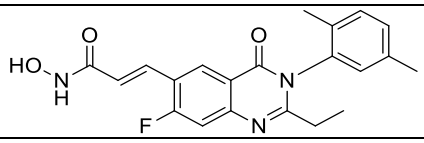
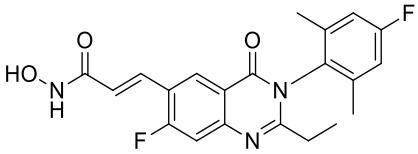
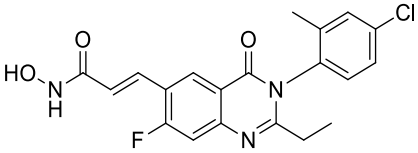
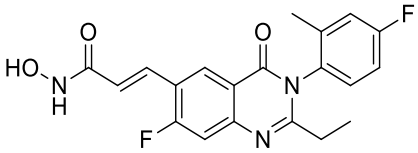
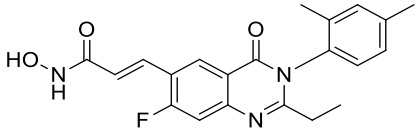
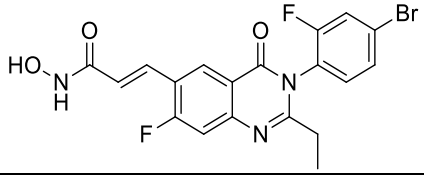
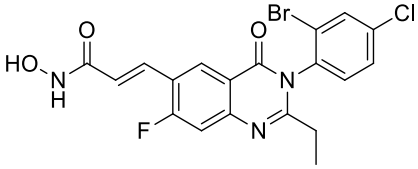
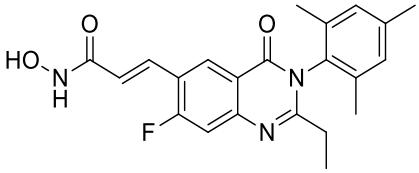
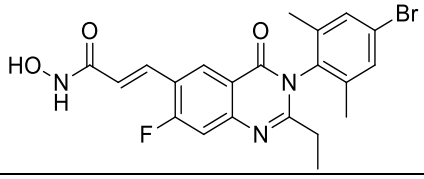
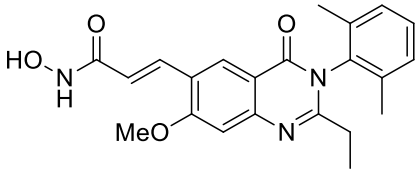
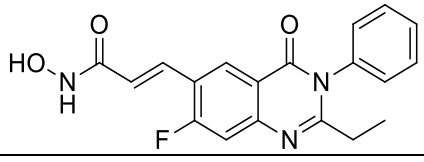
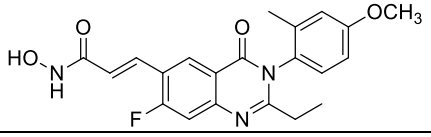
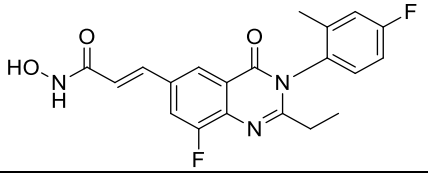
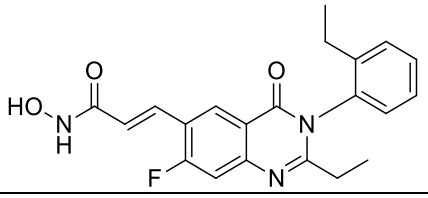
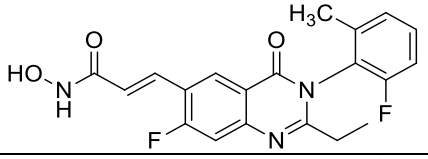
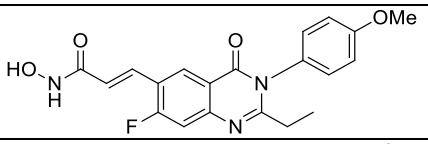
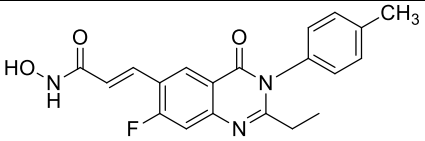
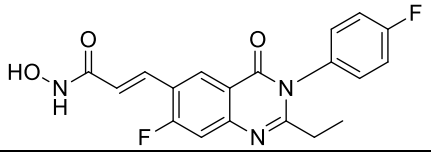
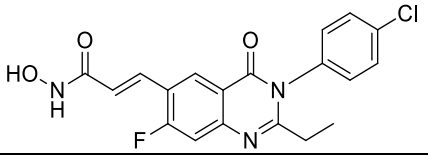
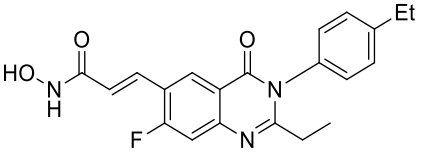
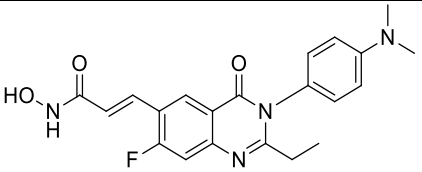
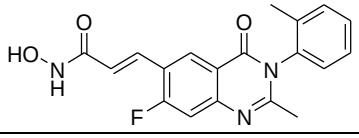
1	
2	

3	
4	
5	
6	
7	
8	
9	
10	
11	
12	

13	
14	
15	
16	
17	
18	
19	
20	
21	
22	

23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	

34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	

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13. A pharmaceutical composition comprising a therapeutically effective amount of the selective HDAC6 inhibitor (HDAC6i) of claim 1 to 12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or vehicle.

14. Use of the compound of any one of claims 1 to 12 or the pharmaceutical composition of claim 13, in the manufacture of a medicament for promoting neurite outgrowth, enhancing tubulin hyperacetylation of cells, or prevention or treatment of peripheral neuropathy, diabetes induced neuropathy, or fibrosis.

15. The use according to claim 14, wherein said peripheral neuropathy is chemotherapy-induced peripheral neuropathy, diabetic neuropathy, post-herpes zoster pain, or postherpetic neuralgia from shingles; said chemotherapy is platinum-based chemotherapy, alkaloid-based, or taxane-based chemotherapy; and/or said fibrosis is pulmonary fibrosis, hepatic fibrosis, or renal fibrosis.

16. The use according to claim 15, wherein said pulmonary fibrosis is associated with increased expression of IL-1, TNF-α, IL-6 or Collagens.

17. The use according to claim 15, wherein said pulmonary fibrosis is idiopathic pulmonary fibrosis or virus-induced fibrosis.

18. Use of the compound of any one of claims 1 to 12 or the pharmaceutical composition of claim 13, in the manufacture of a medicament for decreasing expression of IL-1, TNF-α, IL-6 or Collagens.

19. Use of the compound of any one of claims 1 to 12 or the pharmaceutical composition of claim 13, in the manufacture of a medicament for treating or ameliorating cytokine-induced inflammatory conditions in a subject in need thereof, wherein said cytokine comprises IL-1, TNF-α, IL-6, M-CSF, VCAM-1, or MCP-1.

20. The use of claim 19, wherein said conditions are selected from a group consisting of coronavirus-induced pulmonary inflammation, acute respiratory distress syndrome, acute pulmonary inflammation, pulmonary fibrosis, liver fibrosis, and renal fibrosis.

21. The compound of any one of claims 1 to 12 or the pharmaceutical composition of claim 13, for use in therapy.