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Development of novel ferulic acid derivatives as potent histone deacetylase inhibitors

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ABSTRACT

Histone deacetylase inhibitors (HDACIs) offer a promising strategy for cancer therapy. The discovery of potent ferulic acid-based HDACIs with hydroxamic acid or 2-aminobenzamide group as zinc binding group was reported. The halogeno-acetanilide was introduced as novel surface recognition moiety (SRM). The majority of title compounds displayed potent HDAC inhibitory activity. In particular, **FA6** and **FA16** exhibited significant enzymatic inhibitory activities, with IC_{50} values of 3.94 and 2.82 μM, respectively. Furthermore, these compounds showed moderate antiproliferative activity against a panel of human cancer cells. **FA17** displayed promising profile as an antitumor candidate. The results indicated that these ferulic acid derivatives could serve as promising lead compounds for further optimization.

1. Introduction

Histone deacetylases (HDACs) are zinc metalloenzyme which remove acetyl group of lysine residues located on nucleosomal histones. Histone acetylation and deacetylation are essential in modulation of chromatin topology and gene transcription. HDACs are critical in the epigenetic regulation of gene expression.[1] They could cause condensation of chromatin resulting in transcriptional repression. Therefore, HDACs play an essential role in cell proliferation, cell-cycle regulation and apoptosis.[2] Aberrant activity of HDACs has been found in several human cancers leading to development of histone deacetylase inhibitors (HDACIs). As clinically validated cancer targets, their inhibition has been proven to be successful strategy for the development of novel anticancer agents.[3]

Moreover, HDACIs exhibit attractive antitumor properties by inducing transcriptional events involved in growth arrest, cell proliferation, and apoptosis.[4] There are numbers of HDACIs emerging as an exciting novel class of antitumor agents (Fig. 1). Suberoylanilide hydroxamic acid (Vorinostat, SAHA) is the first HDACI approved by FDA in 2006. Belinostat and Panobinostat are also hydroxamate HDACIs which induce acetylation of histone at nanomolar concentrations. Entinostat is an oral benzamide HDACI with limited cardiac toxicity in preclinical studies.[5]

HDACIs are classified into different classes depending on their structures namely aliphatic acids, hydroxamic acids, 2-aminoanilides, cyclic peptides and electrophilic ketones.[6] These structures all shared common pharmacophore composed of four portions: (a) zinc binding group (ZBG), which chelates zinc ion at the bottom of pocket, (b) linker (scaffold), usually hydrophobic which occupies the narrow channel, (c) connect unit (CU), which connects SRM and linker, (d) surface recognition moiety (SRM), which interacts with residues on the rim of active site (Fig. 1). The common linkers are aliphatic chain, aromatic chain and vinyl-aromatic chain. The most common ZBGs are hydroxamic acid and 2-aminobenzamide.[7] In the past two decades, a number of HDACIs have been developed by modifying of SRM, linker and ZBG. However, recent studies have focused on varying SRM or linker portion. Based on the common pharmacophore, we designed and synthesized a series of ferulic acid-based HDACIs.

Ferulic acid (Fig. 2) is a natural product isolated from many staple foods, including fruits, vegetables, cereals, and coffee.[8] Ferulic acid and its derivatives displayed broad range of therapeutic effects, with applications including anticancer, antidiabetic, cardio protective, neuroprotective, and antiinflammatory activity. Herein, we introduced rigid ferulic acid as linker of HDACIs.

In our earlier work, structural optimization of natural alkaloid taspine afforded a novel antitumor agent (**HMQ1611**, Fig. 2).[9] It displayed antiproliferative activity against several human cancer cell lines. Moreover, numbers of acetanilides with halogen substituents were prepared and exhibited potent anticancer activity.[10] We supposed that halogeno-acetanilide might be suitable as SRM of HDACIs. We focused our attention on searching for novel ferulic acid derivatives with halogeno-acetanilide as SRM. It provides opportunities to develop potent HDACIs. These novel HDACIs comprising common hydroxamic acid or 2-aminobenzamide group as ZBG (Fig. 2).

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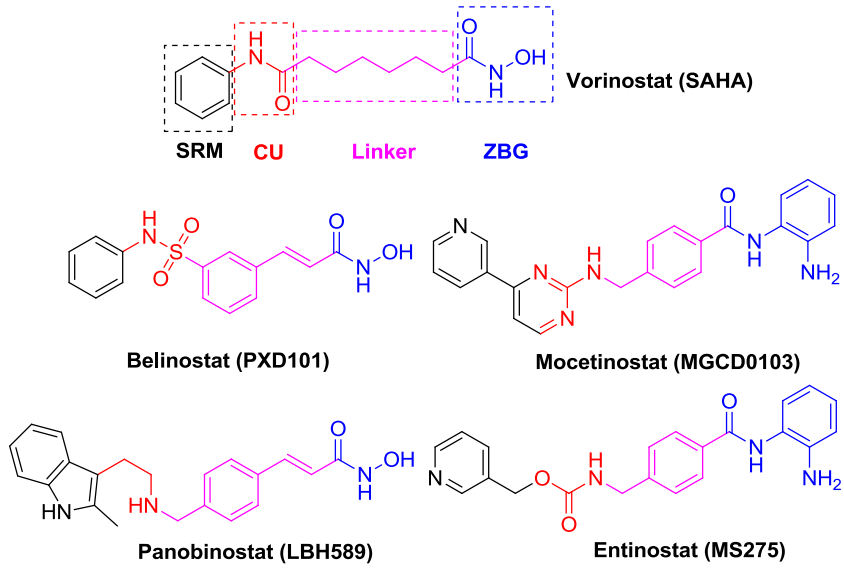


Figure 1. Structures and pharmacophore features of HDACIs.

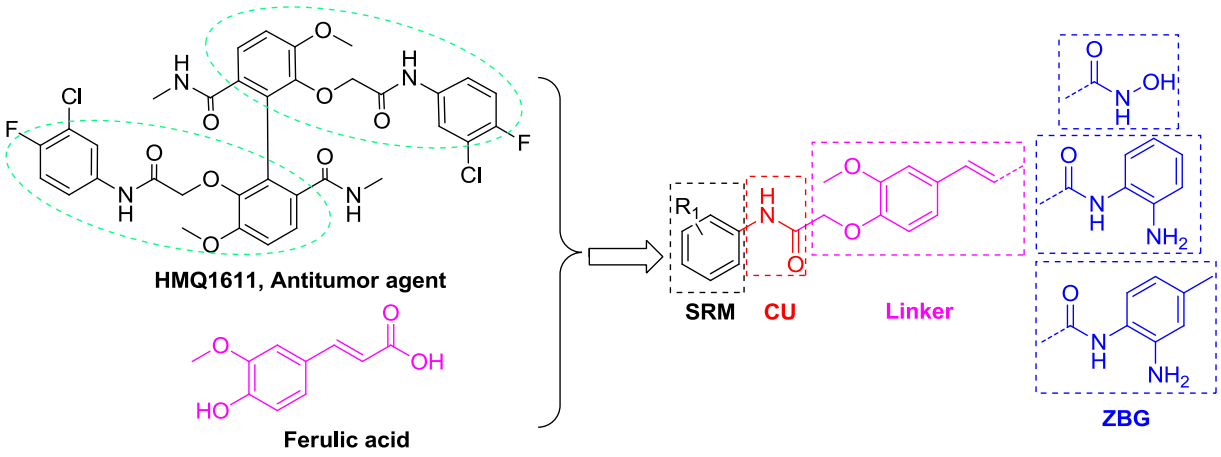


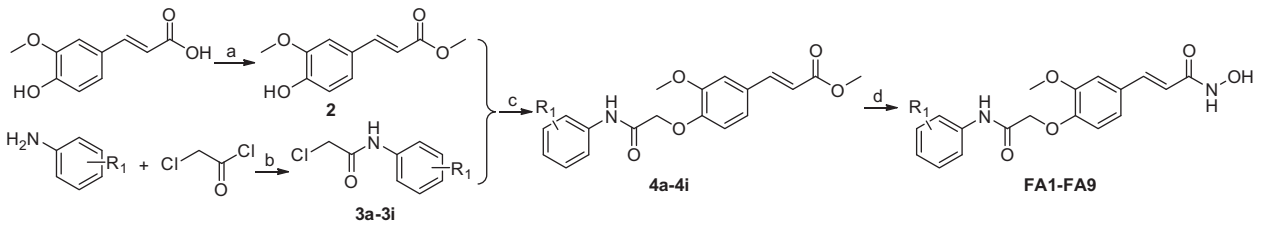
Figure 2. Design strategy and structures of target compounds.

As part of our ongoing effort to develop antitumor agents, we developed two series of ferulic acid derivatives bearing halogenoacetanilide as SRM. Various anilines were used to investigate the role of R_1 substituent. The structures of these compounds are quite consistent with common pharmacophore of HDACIs (Fig. 2). The binding mode of the two most potent compounds with HDAC was also established.

2. Chemistry

All the title compounds were prepared from commercial available ferulic acid. An efficient synthesis of hydroxamic acids was developed in 4-step reaction sequence (Scheme 1). Ferulic acid was esterified in the presence of concentrated H_2SO_4 to afford ferulic acid methylester **2**. Various substituted anilines were acylated with chloroacetyl chloride in polar solvent to provide intermediates **3a–3i**. The hydroxyl group in **2** was etherified with haloacylanilines **3a–3i** in anhydrous acetone in the presence of K_2CO_3 to afford corresponding intermediates **4a–4i**.[11] The resulting esters **4a–4i** were treated with methanolic NH_2OK at room temperature to yield corresponding hydroxamic acid derivatives **FA1–FA9**.[12]

Scheme 2 exhibited synthetic route of ferulic acid derivatives bearing 2-aminobenzamide. Ferulic acid was converted into its imidazolide derivative by reaction with *N,N′*-carbonyldiimidazole



Scheme 1. Preparation of compounds **FA1–FA9**. Reagents and conditions: (a) CH_3OH, H_2SO_4; (b) CH_2Cl_2, Et_3N; (c) K_2CO_3, acetone; (d) NH_2OK, NH_2OH, DMF.

(CDI) in THF at room temperature. This was further reacted with benzene-1,2-diamine or 4-methylbenzene-1,2-diamine in the presence of trifluoroacetic acid to afford key intermediates **5a–5b**.[13] The hydroxyl group in **5a**–**5b** was etherified with haloacylanilines **3a–3i** in anhydrous acetone in the presence of K_2CO_3 to afford corresponding 2-aminobenzamide-containing derivatives **FA10–FA27**.[14]

3. Results and discussion

These compounds were initially evaluated for their inhibitory activity against HDAC with SAHA as positive control. From the results listed in Table 1, majority of them displayed moderate to high inhibitory activity against HDAC. **FA6** was the most potent in hydroxamate series with an IC_{50} value of 3.94 μM, while **FA5** and **FA7** showed moderate inhibitory activities with IC_{50} values of 8.43 and 9.47 μM, respectively. The positions of halogen-substitution on aniline may be critical for activity. Benzamide series were afforded by introduce of 2-aminobenzamide as ZBG. Six compounds of them exhibited promising HDAC inhibitory activity. **FA16** displayed the highest inhibitory activity with IC_{50} value of 2.82 μM.

Two compounds (**FA6** and **FA16**) exhibited promising activity comparable to that of SAHA. According to the results, both substitution on aniline and structure of ZBG played important role in potency. It was indicated that compounds bearing substituents like fluorine, bromine and trifluoromethyl on aniline possessed potent anticancer activity.

To further investigate their antiproliferative activity, eight compounds were selected to test their anticancer potential by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method. The results were described in Table 2. It was found that majority of them displayed potent antiproliferative activities with IC_{50} values ranging from 0.76 to 100 μM. Some of them exhibited promising antiproliferative activity against MDA-MB-231. **FA5** and **FA7** showed potency comparable with SAHA in term of cancer cell growth inhibition.

Docking studies were carried out to understand interaction between inhibitors and HDAC. The most potent HDACIs in two series, **FA6** and **FA16**, were docked into active site of HDAC (PDB ID: 3F07). Molecular insights based on molecular docking indicated favorable binding models of them with HDAC (Fig. 3). The results suggested that hydroxamic group and 2-aminobenzamide group were bonded to zinc ion as ZBG. For **FA6** (left), hydroxamate OH made two hydrogen bond interactions with His142 and His143 with distance of 2.12 Å and 2.71 Å, respectively. N–H could also bind to His143 with distance of 1.79 Å. Carbonyl group accepted a hydrogen bond from Tyr306 with distance of 1.82 Å. The distance between zinc ion and two oxygen atoms were 1.88 Å and 3.08 Å, respectively.[15] For **FA16** (right), binding mode was consistent with **FA6**. One hydrogen atom of 2-amine formed two hydrogen bonds with His143 with distances of 1.90 Å and 2.74 Å, respectively. Another hydrogen atom could also bind to His143 with distance of 2.13 Å. Carbonyl group was identified to be involved in hydrogen bond with Tyr306 with distance of 2.07 Å. There was an additional hydrogen bond between oxygen atom of acetyl and Lys202. This interaction might contribute to affinity and activity of benzamides. The distance between zinc ion and oxygen atoms was 3.30 Å while distance with nitrogen of amino was 2.49 Å. The results indicated that these two compounds had similar binding mode and orientation as APHA in active site of HDAC. Both of them did not only chelate zinc ion but also form four hydrogen bonds with His142, His143 and Tyr306. In summary, docking results suggested that **FA6** and **FA16** fit comfortably inside active site of HDAC.

4. Conclusion

In conclusion, twenty-seven ferulic acid derivates with HDAC inhibitory property and antiproliferative activity were developed. These ferulic acid-based HDACIs comprised hydroxamic acid or 2-aminobenzamide group as ZBG. Ferulic acid was served as molecular scaffold and rigid linker. Both series displayed moderate to potent HDAC inhibitory activity, together with good levels of antiproliferative activity on several cancer cell lines. Benzamides were somewhat more potent than hydroxamates. Eight compounds (**FA5, FA6, FA7, FA12, FA13, FA16, FA17, FA27**) displayed significant enzymatic inhibitory activities, with IC_{50} values ranging from 2.82 μM to 10.3 μM. Among them, **FA16** exhibited potency comparable with SAHA. Moreover, **FA17** bearing 2-aminobenzamide exhibited potent antiproliferative activities against MCF-7, MDA-MB-231 and HeLa cell lines. In summary, these ferulic acid derivatives had strong potential to be further developed as novel HDACIs. Further structural optimization of these promising anticancer agents will be reported in due course.

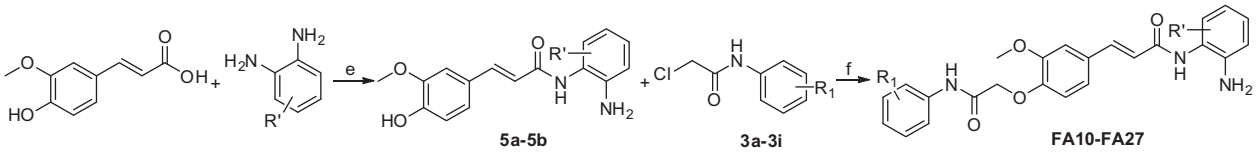
5. Experimental

5.1. Chemistry: general procedure

Solvents and reagents were purified according to standard procedure. All reactions except those in aqueous media were carried out by standard techniques for exclusion of moisture. Anhydrous reactions were carried out under nitrogen atmosphere. Reactions were monitored by thin layer chromatography on 0.25-mm silica gel plates (60GF-254) and visualized with UV light. Melting points were determined on electrothermal meliting point apparatus and are uncorrected. ^{1}H NMR spectra were measured at 400 MHz on Bruker Advance AC 400 instrument. Mass spectra were obtained on Shimadzu HPLC-MS-QP2010 instrument.

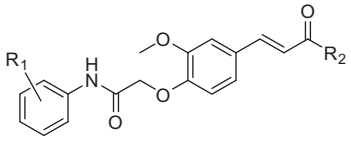
5.1.1. Methyl (2*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylate (2)[16]

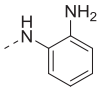
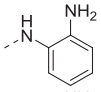
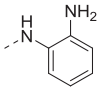
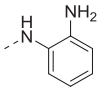
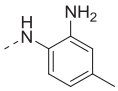
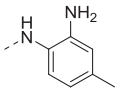
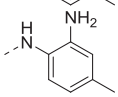
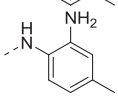
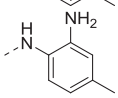
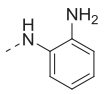
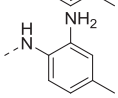
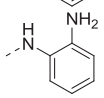
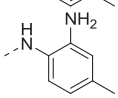
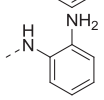
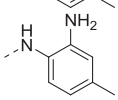
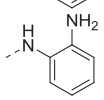
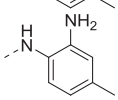
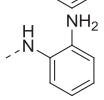
Ferulic acid (6.80 g, 35 mmol) was dissolved in methanol (80 mL) containing catalytic of 2 mL concentrated H_2SO_4, and then solution was heated at reflux for about 4 h. After cooling at room temperature, solvent was evaporated under vacuum. The residue was taken up in EtOAc (150 mL) and washed with saturated aqueous solution of $NaHCO_3$ until neutral pH. The organic layer was then washed with distilled water and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to afforded (**2**) (6.54 g, 89.7%) as white solid. mp: 62–63 °C.



Scheme 2. Preparation of compounds **FA10–FA27**. Reagents and conditions: (e) CDI, THF, *O*-phenylenediamine or 3,4-diaminotoluene, TFA; (f) K_2CO_3, acetone.

Table 1
The structures and inhibitory activity of ferulic acid derivatives (IC_{50})

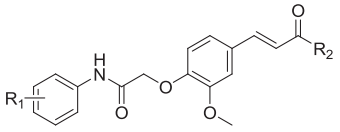


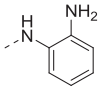
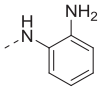
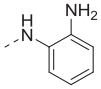
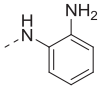
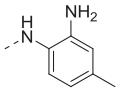
Compd	R_1	R_2	IC_{50} (μM)	Compd	R_1	R_2	IC_{50} (μM)
FA-1	3-Cl-4-F		49.3	**FA-15**	2-F		73.7
FA-2	3-CF_3		12.5	**FA-16**	3-F		2.82
FA-3	3,4-Cl		43.0	**FA-17**	3,5-CF_3		7.80
FA-4	4-OCH_3		10.8	**FA-18**	3-CF_3-5-Br		24.2
FA-5	4-Br		8.43	**FA-19**	3-Cl-4-F		15.4
FA-6	2-F		3.94	**FA-20**	3-CF_3		15.1
FA-7	3-F		9.47	**FA-21**	3,4-Cl		64.5
FA-8	3,5-CF_3		10.5	**FA-22**	4-OCH_3		118
FA-9	3-CF_3-5-Br		67.8	**FA-23**	4-Br		16.4
FA-10	3-Cl-4-F		11.5	**FA-24**	2-F		11.6
FA-11	3-CF_3		49.6	**FA-25**	3-F		66.6
FA-12	3,4-Cl		10.3	**FA-26**	3,5-CF_3		71.4
FA-13	4-OCH_3		8.95	**FA-27**	3-CF_3-5-Br		7.43
FA-14	4-Br		12.8		SAHA		2.59

5.1.2. Methyl (2*E*)-3-(4-{2-[(3-chloro-4-fluorophenyl)amino]-2-oxoethoxy}-3- methoxyphenyl)acrylate (4a)[17]

To a suspension of **2** (2.08 g, 10 mmol) in dehydrated acetone (70 mL) was added anhydrous potassium carbonate (4.14 g, 30 mmol). The mixture was stirred at room temperature for 30 min and then 2-chloro-*N*-(3-chloro-4-fluorophenyl)acetamide (2.44 g, 11 mmol) was added. The reaction mixture was refluxed for another 10 h. Filtration and evaporation of acetone was done in vacuum. The residue was extracted with EtOAc (120 mL). The combined layers were washed with water, 2 M NaOH, 2 M HCl and brine, dried over Na_2SO_4 and solvent was removed. The crude product was purified by silica gel column chromatography (Petro-

Table 2
Growth inhibition of HDACIs against a panel of cancer cells (IC_{50}, μM)



Compd	R_1	R_2	MCF-7	HeLa	MDA-MB-231
FA5	4-Br		73.6	>100	0.76
FA6	2-F		>100	11.07	8.30
FA7	3-F		39.5	34.50	1.45
FA12	3,4-diCl		>100	72.09	83.4
FA13	4-OCH_3		>100	>100	48.5
FA16	3-F		>100	28.09	>100
FA17	3,5-diCF_3		43.1	20.82	25.3
FA27	3-CF_3-5-Br		92.1	84.33	>100
SAHA			60.2	9.69	0.16

leum:AcOEt = 5:1 to 1:1) to yield **4a** as white solid (3.37 g, 85.65%). Mp: 156–158 °C. EI-MS (*m/z*): 393.1 (M^+). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 4 Hz, 1H), 7.66 (d, *J* = 8 Hz, 1H), 7.43 (d, *J* = 6 Hz, 1H), 7.29 (s, 1H), 7.17 (s, 1H), 7.14 (d, *J* = 4 Hz, 1H), 6.98 (d, *J* = 4 Hz, 1H), 6.39 (d, *J* = 8 Hz, 1H), 4.69 (s, 2H), 4.00 (s, 3H), 3.84 (s, 3H).

Compounds (**4b–4l**) were prepared by using the same procedure described above.

5.1.3. (2*E*)-3-(4-{2-[(3-Chloro-4-fluorophenyl)amino]-2-oxoethoxy}-3-methoxy phenyl)-*N*-hydroxyacrylamide (FA1)[18]

Preparation of NH_2OK/NH_2OH solution: $NH_2OH{\cdot}HCl$ (0.476 g, 6.85 mmol) was solubilized in methanol (2.4 mL) by heating to reflux. The solution was cooled to room temperature, and a solution of KOH (0.56 g, 9.98 mmol) in methanol (1.4 mL) was added in one portion to afford NH_2OK/NH_2OH solution.

To a solution of **4a** (1.97 g, 5 mmol) in 7 mL of anhydrous DMF was added NH_2OK/NH_2OH solution (10 mL). The mixture was stirred at room temperature for 3 days. The reaction mixture was taken up in dilute aqueous HCl (pH 2), extracted with EtOAc (150 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (AcOEt:-MeOH = 20:1) to give hydroxamic acid **FA1** as white solid (0.71 g, 35.34%). Mp: 177–179 °C. EI-MS (*m/z*):394.1 (M^+). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.95 (d, *J* = 4 Hz, 1H), 7.54 (d, *J* = 4 Hz, 1H), 7.41 (d, *J* = 4 Hz, 1H), 7.38 (s, 1H), 7.22 (s, 1H), 7.11 (d, *J* = 4 Hz, 1H), 6.97 (d, *J* = 4 Hz, 1H), 6.37 (d, *J* = 8 Hz, 1H), 4.74(s, 2H), 3.84 (s, 3H).

Compounds (**FA2**–**FA9**) were synthesized following the same procedure described above.

5.1.3.1. (2*E*)-*N*-Hydroxy-3-[3-methoxy-4-(2-oxo-2-{[3-(trifluoromethyl)phenyl]amino}ethoxy)phenyl]acrylamide (FA2).

Mp: 206–208 °C. EI-MS (*m/z*): 410.1 (M^+). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.12 (s, 1H) 7.83 (d, *J* = 4 Hz, 1H), 7.59 (d, *J* = 4 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H), 7.45 (d, *J* = 2 Hz, 1H), 7.38 (s, 1H), 7.23–7.19(m, 1H), 6.96 (d, *J* = 4 Hz, 1H), 6.48 (d, *J* = 8 Hz, 1H), 4.79(s, 2H), 3.86 (s, 3H).

5.1.3.2. (2*E*)-3-(4-{2-[(3,4-Dichlorophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)-*N*-hydroxyacrylamide (FA3).

Mp: 223–225 °C. EI-MS (*m/z*): 394.0[M-OH]$^+$. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.96(d, *J* = 4 Hz, 1H), 7.54(d, *J* = 4 Hz, 1H), 7.41(d, *J* = 4 Hz, 1H), 7.38(s, 1H), 7.22(s, 1H), 7.11(d, *J* = 4 Hz, 1H), 6.97(d, *J* = 4 Hz, 1H), 6.37(d, *J* = 8 Hz, 1H), 4.74(s, 2H), 3.84(s, 3H).

5.1.3.3. (2*E*)-*N*-Hydroxy-3-(3-methoxy-4-{2-[(4-methoxyphenyl)amino]-2-oxoethoxy}phenyl)acrylamide (FA4).

Mp: 165–167 °C. EI-MS (*m/z*): 372.1 (M^+). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.53(d, *J* = 8 Hz, 3H), 7.15(s, 1H), 7.13(d, *J* = 2 Hz, 1H), 6.97(d, *J* = 4 Hz, 1H), 6.94(d, *J* = 8 Hz, 1H), 6.91(d, *J* = 4 Hz, 3H), 4.71(s, 2H), 3.86(s, 3H), 3.72(s, 3H).

5.1.3.4. (2*E*)-3-(4-{2-[(4-Bromophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)-*N*-hydroxyacrylamide (FA5).

Mp: 215–217 °C. EI-MS (*m/z*): 420.0 (M^+). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 7.61(d, *J* = 6 Hz, 2H), 7.53(s, 1H), 7.52(d, *J* = 6 Hz, 2H), 7.40(d, *J* = 8 Hz, 1H), 7.20(d, *J* = 6 Hz, 1H), 7.11(d, *J* = 4 Hz, 1H), 6.95(d, *J* = 4 Hz, 1H), 4.65(s, 2H), 3.84(s, 3H).

5.1.3.5. (2*E*)-3-(4-{2-[(2-Fluorophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)-*N*-hydroxyacrylamide (FA6).

Mp: 204–

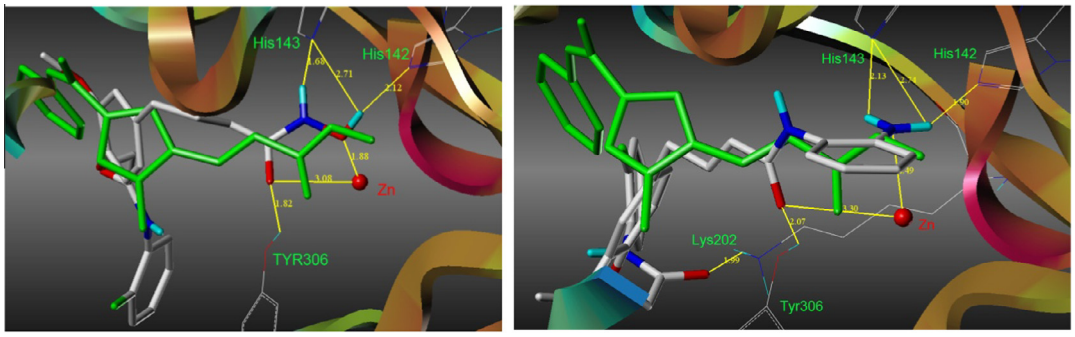


Figure 3. Molecular modeling of **FA6** (left) and **FA16** (right) binding to the active site of HDAC. The original ligands are shown in green. Metal coordination and hydrogen bond interactions are shown as dotted yellow lines.

207 °C. EI-MS (*m/z*): 345.1[M-CH_3]$^+$. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.95(s, 1H), 7.54 (d, *J* = 8 Hz, 1H), 7.42(d, *J* = 8 Hz, 1H), 7.30–7.28(m, 2H), 6.99(d, *J* = 6 Hz, 1H), 6.49(d, *J* = 8 Hz, 1H), 6.38(d, *J* = 8 Hz, 1H), 4.83(s, 2H), 3.86(s, 3H).

5.1.3.6. (2*E*)-3-(4-{2-[(3-Fluorophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)-*N*-hydroxyacrylamide (FA7). Mp: 176–178 °C. EI-MS (*m/z*):344.1[M-OH]$^+$. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.62(d, *J* = 6 Hz, 1H), 7.40(d, *J* = 6 Hz, 3H), 7.36(s, 1H), 7.22(s, 1H), 7.11(d, *J* = 4 Hz, 1H), 6.96–6.92(m, 1H), 6.37(d, *J* = 8 Hz, 1H), 4.75 (s, 2H), 3.85(s, 3H).

5.1.3.7. (2*E*)-3-[4-(2-{[3,5-Bis(trifluoromethyl)phenyl]amino}-2-oxoethoxy)-3-methoxyphenyl]-*N*-hydroxyacrylamide (FA8). Mp: 183–185 °C. EI-MS (*m/z*): 478.1 (M$^+$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.34(s, 2H), 7.83 (s, 1H), 7.41(d, *J* = 8 Hz, 1H), 7.23(s, 1H), 7.11(d, *J* = 4 Hz, 1H), 6.99(d, *J* = 6 Hz, 1H), 6.37(d, *J* = 8 Hz, 1H), 4.81(s, 2H), 3.85(s, 3H).

5.1.3.8. (2*E*)-3-[4-(2-{[3-Bromo-5-(trifluoromethyl)phenyl]amino}-2-oxoethoxy)-3-methoxyphenyl]-*N*-hydroxyacrylamide (FA9). Mp: 195–198 °C. EI-MS (*m/z*):471.9[M-OH]$^+$. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.17(s, 1H), 8.04(s, 1H), 7.69(s, 1H), 7.41(d, *J* = 8 Hz, 1H), 7.23(s, 1H), 7.11(d, *J* = 4 Hz, 1H), 6.96(d, *J* = 4 Hz, 1H), 6.37(d, *J* = 8 Hz, 1H), 4.78(s, 2H), 3.84(s, 3H).

5.1.4. (2*E*)-*N*-(2-Aminophenyl)-3-(4-hydroxy-3-methoxyphenyl)acrylamide (5a)

To a solution of ferulic acid (5.83 g, 30 mmol) in anhydrous THF (120 mL) was added CDI (5.35 g, 33 mmol) portionwise at room temperature. The reaction mixture was stirred for 1 h to form acylimidazole followed by addition of 1,2-phenylenediamine (25.96 g, 240 mmol)and TFA (3.49 g, 30 mmol). The reaction mixture was stirred at room temperature for another 16 h. The mixture was then filtered to give crude product which was purified by silica gel column chromatography (Petroleum:AcOEt = 3:1 to 1:3) to yield **5a** as white solid (6.87 g, 80.53%). Mp: 164–166 °C. EI-MS (*m/z*):284.1 (M$^+$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70(d, *J* = 8 Hz, 1H), 7.35(s, 1H), 7.12–7.09(m, 2H), 7.08(d, *J* = 6 Hz, 1H), 6.95(d, *J* = 4 Hz, 1H), 6.86(d, *J* = 2 Hz, 2H), 6.49(d, *J* = 4 Hz, 1H), 3.96(s, 3H).

Compound **5b** was prepared following the same procedure as **5a**. Then it was purified by silica gel column chromatography (Petroleum:AcOEt = 3:1 to 1:3).

5.1.5. (2*E*)-*N*-(2-Aminophenyl)-3-(4-{2-[(3-chloro-4-fluorophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)acrylamide (FA10)

To a suspension of **5a** (1.43 g, 5 mmol) in dehydrated acetone (70 mL) was added anhydrous potassium carbonate (2.07 g, 15 mmol). The mixture was stirred at room temperature for 30 min and then 2-chloro-*N*-(3-chloro-4-fluorophenyl)acetamide (3.33 g, 15 mmol) was added. The reaction mixture was refluxed for another 10 h. Filtration and evaporation of acetone was done in vacuum. The residue was extracted with EtOAc (150 mL). The combined layers were washed with water, 2 M NaOH, 2 M HCl and brine, dried over Na_2SO_4 and solvent was removed. The crude product was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 80:1 to 20:1) to yield **FA10** as white solid (1.33 g, 56.45%). Mp: 177–178 °C. EI-MS (*m/z*): 469.0(M$^+$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.90(d, *J* = 4 Hz, 1H), 7.51(d, *J* = 8 Hz, 2H), 7.42(d, *J* = 4 Hz, 1H), 7.39–7.34(m, 1H), 7.29(s, 1H), 7.17(d, *J* = 4 Hz, 1H), 6.99(d, *J* = 4 Hz, 1H), 6.82(s, 1H), 6.77(d, *J* = 4 Hz, 1H), 6.63–6.59(m, 1H), 6.49(d, *J* = 4 Hz, 1H), 4.77(s, 2H), 3.87(s, 3H).

Compounds (**FA11–FA27**) were prepared following the procedure described above.

5.1.5.1. (2*E*)-*N*-(2-Aminophenyl)-3-[3-methoxy-4-(2-oxo-2-{[3-(trifluoromethyl)phenyl]amino}ethoxy)phenyl]acrylamide (FA11). Mp: 212–214 °C. EI-MS (*m/z*): 485.1 (M$^+$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.54(d, *J* = 8 Hz, 2H), 7.48(s, 1H), 7.35(d, *J* = 8 Hz, 1H), 7.28(s, 1H), 7.18(d, *J* = 12 Hz, 1H), 7.00(d, *J* = 8 Hz, 1H), 6.91(d, *J* = 8 Hz, 3H), 6.82–6.74(m, 2H), 6.60–6.56(m, 1H), 4.72(s, 2H), 3.88(s, 3H).

5.1.5.2. (2*E*)-*N*-(2-Aminophenyl)-3-(4-{2-[(3,4-dichlorophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)acrylamide (FA12). Mp: 195–197 °C. EI-MS (*m/z*):485.0 (M$^+$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.03(s, 1H), 7.61(d, *J* = 4 Hz, 1H), 7.56(d, *J* = 4 Hz, 1H), 7.51(d, *J* = 8 Hz, 1H), 7.35(d, *J* = 4 Hz, 1H), 7.29(s, 1H), 7.17(d, *J* = 4 Hz, 1H), 6.99(d, *J* = 4 Hz, 1H), 6.94–6.90(m, 1H), 6.80(d, *J* = 8 Hz, 1H), 6.76(d, *J* = 4 Hz, 1H), 6.60–6.57(m, 1H), 4.78(s, 2H), 3.87(s, 3H).

5.1.5.3. (2*E*)-*N*-(2-Aminophenyl)-3-(3-methoxy-4-{2-[(4-methoxyphenyl)amino]-2-oxoethoxy}phenyl)acrylamide (FA13). Mp: 189–191 °C. EI-MS (*m/z*): 447.1(M$^+$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.54(d, *J* = 6 Hz, 2H), 7.51(d, *J* = 6 Hz, 1H), 7.35(d, *J* = 4 Hz, 1H), 7.28(s, 1H), 7.18(d, *J* = 4 Hz, 1H), 7.01–6.95(m, 2H), 6.91(d, *J* = 4 Hz, 2H), 6.80(d, *J* = 8 Hz, 2H), 6.65(d, *J* = 4 Hz, 1H), 4.72(s, 2H), 3.88(s, 3H), 3.73(s, 3H).

5.1.5.4. (2*E*)-*N*-(2-Aminophenyl)-3-(4-{2-[(4-bromophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)acrylamide (FA14). Mp: 194–195 °C. EI-MS (*m/z*): 495.1(M$^+$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.62(d, *J* = 6 Hz, 2H), 7.52(d, *J* = 4 Hz, 2H), 7.50(d, *J* = 4 Hz, 1H), 7.35(d, *J* = 4 Hz, 1H), 7.28(s, 1H), 7.17(d, *J* = 4 Hz, 1H), 6.99(d, *J* = 4 Hz, 1H), 6.94–6.90(m, 1H), 6.80(d, *J* = 8 Hz, 1H), 6.76(d, *J* = 4 Hz, 1H), 6.61–6.57(m, 1H), 4.76(s, 2H), 3.87(s, 3H).

5.1.5.5. (2*E*)-*N*-(2-Aminophenyl)-3-(4-{2-[(2-fluorophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)acrylamide (FA15). Mp: 194–195 °C. EI-MS (*m/z*):435.0 (M$^+$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.52(d, *J* = 8 Hz, 1H), 7.36–7.30(m, 3H), 7.18(d, *J* = 2 Hz, 4H), 7.03(d, *J* = 4 Hz, 1H), 6.94–6.92(m, 1H), 6.81(d, *J* = 8 Hz, 2H), 6.63(s, 1H), 4.76(s, 2H), 3.87(s, 3H).

5.1.5.6. (2*E*)-*N*-(2-Aminophenyl)-3-(4-{2-[(3-fluorophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)acrylamide (FA16). Mp: 177–178 °C. EI-MS (*m/z*): 435.1(M$^+$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.63(d, *J* = 6 Hz, 1H), 7.55(d, *J* = 6 Hz, 1H), 7.38(d, *J* = 6 Hz, 1H), 7.36(s, 1H), 7.35(d, *J* = 4 Hz, 1H), 7.29 (s, 1H), 7.17(d, *J* = 4 Hz, 1H), 6.99(d, *J* = 4 Hz, 1H), 6.93(d, *J* = 4 Hz, 1H), 6.91(d, *J* = 4 Hz, 1H), 6.82–6.75(m, 2H), 6.61–6.57(m, 1H), 4.78(s, 2H), 3.88(s, 3H).

5.1.5.7. (2*E*)-*N*-(2-Aminophenyl)-3-[4-(2-{[3,5-bis(trifluoromethyl)phenyl]amino}-2-oxoethoxy)-3-methoxyphenyl]acrylamide (FA17). Mp: 190–192 °C. EI-MS (*m/z*):553.0 (M$^+$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.35(s, 2H), 7.83(s, 1H), 7.51(d, *J* = 8 Hz, 1H), 7.35(d, *J* = 4 Hz, 1H), 7.30(s, 1H), 7.17(d, *J* = 4 Hz, 1H), 7.02(d, *J* = 4 Hz, 1H), 6.94–6.90(m, 1H), 6.81(d, *J* = 8 Hz, 1H), 6.76(d, *J* = 4 Hz, 1H), 6.61–6.57(m, 1H), 4.84(s, 2H), 3.88(s, 3H).

5.1.5.8. (2*E*)-*N*-(2-Aminophenyl)-3-[4-(2-{[3-bromo-5-(trifluoromethyl)phenyl]amino}-2-oxoethoxy)-3-methoxyphenyl]acrylamide (FA18). Mp: 209–211 °C. EI-MS (*m/z*): 563.0(M$^+$). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.18(s, 1H), 8.05(s, 1H), 7.69(s, 1H), 7.51(d, *J* = 8 Hz, 1H), 7.32(d, *J* = 8 Hz, 2H), 7.16(s, 1H), 7.01–6.92(m, 2H), 6.79(d, *J* = 8 Hz, 2H), 6.58(d, *J* = 2 Hz, 1H), 4.81(s, 2H), 3.87(s, 3H).

5.1.5.9. (2*E*)-*N*-(2-Amino-4-methylphenyl)-3-(4-{2-[(3-chloro-4-fluorophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)acrylamide (FA19). Mp: 187–188 °C. EI-MS (*m/z*): 483.2(M^+). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.96(d, *J* = 4 Hz, 1H), 7.52(d, *J* = 4 Hz, 1H), 7.47(s, 1H), 7.42(d, *J* = 4 Hz, 1H), 7.28(s, 1H), 7.20 (d, *J* = 4 Hz, 1H), 7.17(d, *J* = 6 Hz, 1H), 6.99(d, *J* = 4 Hz, 1H), 6.78(d, *J* = 8 Hz, 1H), 6.58(s, 1H), 6.43(d, *J* = 2 Hz, 1H), 4.76(s, 2H), 3.87(s, 3H), 2.18(s, 3H).

5.1.5.10. (2*E*)-*N*-(2-Amino-4-methylphenyl)-3-[3-methoxy-4-(2-oxo-2-{[3-(trifluoromethyl)phenyl]amino}ethoxy)phenyl]acrylamide (FA20). Mp: 200–202 °C. EI-MS (*m/z*): 499.1(M^+). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.84(d, *J* = 4 Hz, 1H), 7.77(d, *J* = 4 Hz, 1H), 7.60 (d, *J* = 4 Hz, 1H), 7.58(d, *J* = 4 Hz, 1H), 7.51(s, 1H), 7.28(s, 1H), 7.17(d, *J* = 6 Hz, 1H), 7.08–7.05(m, 1H), 7.00(d, *J* = 4 Hz, 1H), 6.78(d, *J* = 8 Hz, 1H), 6.56(s, 1H), 6.39(d, *J* = 4 Hz, 1H), 4.76(s, 2H), 3.85(s, 3H), 2.17(s, 3H).

5.1.5.11. (2*E*)-*N*-(2-Amino-4-methylphenyl)-3-(4-{2-[(3,4-dichlorophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)acrylamide (FA21). Mp: 207–209 °C. EI-MS (*m/z*):499.1 (M^+). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.03(s, 1H), 7.61(d, *J* = 6 Hz, 1H), 7.56(d, *J* = 4 Hz, 1H), 7.49 (d, *J* = 8 Hz, 1H), 7.28(s, 1H), 7.20(d, *J* = 4 Hz, 1H), 7.16 (d, *J* = 4 Hz, 1H), 6.99(d, *J* = 4 Hz, 1H), 6.78(d, *J* = 8 Hz, 1H), 6.56(s, 1H), 6.39(d, *J* = 4 Hz, 1H), 4.78(s, 2H), 3.87(s, 3H), 2.17(s, 3H).

5.1.5.12. (2*E*)-*N*-(2-Amino-4-methylphenyl)-3-(3-methoxy-4-{2-[(4-methoxyphenyl)amino]-2-oxoethoxy}phenyl)acrylamide (FA22). Mp: 192–194 °C. EI-MS (*m/z*):461.2 (M^+). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.54(d, *J* = 4 Hz, 2H), 7.49(d, *J* = 8 Hz, 1H), 7.27(s, 1H), 7.20(d, *J* = 4 Hz, 1H), 7.18 (d, *J* = 6 Hz, 1H), 7.00(d, *J* = 4 Hz, 1H), 6.91(d, *J* = 4 Hz, 2H), 6.78(d, *J* = 8 Hz, 1H), 6.57(s, 1H), 6.41(d, *J* = 4 Hz, 1H), 4.72(s, 2H), 3.87(s, 3H), 3.73(s, 3H), 2.17(s, 3H).

5.1.5.13. (2*E*)-*N*-(2-Amino-4-methylphenyl)-3-(4-{2-[(4-bromophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)acrylamide (FA23). Mp: 184–186 °C. EI-MS (*m/z*): 509.0(M^+). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.61(d, *J* = 4 Hz, 2H), 7.52(d, *J* = 4 Hz, 2H), 7.27(s, 1H), 7.20(d, *J* = 6 Hz, 1H), 7.17 (d, *J* = 6 Hz, 1H), 6.99(d, *J* = 4 Hz, 1H), 6.80(d, *J* = 2 Hz, 1H), 6.75(d, *J* = 6 Hz, 1H), 6.56(s, 1H), 6.39(d, *J* = 4 Hz, 1H), 4.76(s, 2H), 3.87(s, 3H), 2.17(s, 3H).

5.1.5.14. (2*E*)-*N*-(2-Amino-4-methylphenyl)-3-(4-{2-[(2-fluorophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)acrylamide (FA24). Mp: 187–189 °C. EI-MS (*m/z*): 449.1(M^+). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.96(s, 1H), 7.49(d, *J* = 8 Hz, 2H), 7.33–7.28(m, 2H), 7.20(d, *J* = 4 Hz, 2H), 7.18(d, *J* = 4 Hz, 1H), 7.03 (d, *J* = 4 Hz, 1H), 6.79(d, *J* = 8 Hz, 1H), 6.56(s, 1H), 6.39(d, *J* = 4 Hz, 1H), 4.83(s, 2H), 3.88(s, 3H), 2.17(s, 3H).

5.1.5.15. (2*E*)-*N*-(2-Amino-4-methylphenyl)-3-(4-{2-[(3-fluorophenyl)amino]-2-oxoethoxy}-3-methoxyphenyl)acrylamide (FA25). Mp: 205–207 °C. EI-MS (*m/z*):449.1 (M^+). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.63(d, *J* = 6 Hz, 1H), 7.58(d, *J* = 6 Hz, 1H), 7.49(d, *J* = 8 Hz, 1H), 7.38(d, *J* = 4 Hz, 1H), 7.37(s, 1H), 7.28(s, 1H), 7.20(d, *J* = 6 Hz, 1H), 7.17(d, *J* = 4 Hz, 1H), 6.99 (d, *J* = 4 Hz, 1H), 6.80–6.76(m, 1H), 6.58(s, 1H), 6.41(d, *J* = 4 Hz, 1H), 4.77(s, 2H), 3.87(s, 3H), 2.18(s, 3H).

5.1.5.16. (2*E*)-*N*-(2-Amino-4-methylphenyl)-3-[4-(2-{[3,5-bis(trifluoromethyl)phenyl]amino}-2-oxoethoxy)-3-methoxyphenyl]acrylamide (FA26). Mp: 204–206 °C. EI-MS (*m/z*): 567.1(M^+). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.35(s, 2H), 7.83(s, 1H), 7.49(d, *J* = 8 Hz, 1H), 7.29(s, 1H), 7.19(d, *J* = 2 Hz, 1H), 7.17(d, *J* = 6 Hz, 1H), 7.02(d, *J* = 4 Hz, 1H), 6.78(d, *J* = 8 Hz, 1H), 6.56(s, 1H), 6.39(d, *J* = 4 Hz, 1H), 4.83(s, 2H), 3.87(s, 3H), 2.17(s, 3H).

5.1.5.17. (2*E*)-*N*-(2-Amino-4-methylphenyl)-3-[4-(2-{[3-bromo-5-(trifluoromethyl)phenyl]amino}-2-oxoethoxy)-3-methoxyphenyl]acrylamide (FA27). Mp: 193–195 °C. EI-MS (*m/z*): 579.0(M^+). ^{1}H NMR (400 MHz, $(CD_3)_2SO$ δ 8.18(s, 1H), 8.05(s, 1H), 7.69(s, 1H), 7.49(d, *J* = 8 Hz, 1H), 7.28(s, 1H), 7.20(d, *J* = 4 Hz, 1H), 7.16(d, *J* = 4 Hz, 1H), 7.00(d, *J* = 4 Hz, 1H), 6.78(d, *J* = 8 Hz, 1H), 6.56(s, 1H), 6.39(d, *J* = 4 Hz, 1H), 4.80(s, 2H), 3.87(s, 3H), 2.17(s, 3H).

5.2. HDAC inhibitory activity assays[19]

The HDAC inhibitory activities of title compounds were measured using Color-de-Lys™ HDAC colorimetric activity assay kit (Enzo Life Sciences, Inc.) according to the manufacturer's instructions. The kit is useful for inhibitors screening using HDAC from HeLa nuclear extract. The *Color de Lys*™ substrate which comprises an acetylated lysine is incubated with sample containing HDAC activity. Deacetylation of substrate sensitizes the substrate. The mixing with the *Color de Lys*™ developer causes an increase in color intensity at 405 nm.

The title compounds and SAHA were diluted in buffer to various concentrations (20 μg/mL, 4 μg/mL, 0.8 μg/mL, 0.16 μg/mL). HDACs (5 μL) were incubated at 37 °C with 10 μL of compounds and 25 μL of substrate on 96-well plates. After incubation for 30 min, *Color de Lys*™ developer (50 μL/well) was added to stop HDAC reactions. Incubate plate at 37 °C for 15 min and read plate in microtiter-plate reader at 405 nm. The inhibition rates were calculated from ultraviolet absorption readings of inhibited wells related to those of control wells. The IC_{50} values were calculated according to inhibition ratios.

5.3. Cell growth inhibitory activity in cancer cells

The eight potent compounds were evaluated against breast cancer cell lines (MCF-7, MDA-MB-231) and cervical cancer cell (HeLa) using MTT assay to assess cell proliferation. Exponentially growing cells were harvested and plated in 96-well plates at a concentration of 1×10^4 cells/well, and then incubated for 24 h at 37 °C. The cells in wells were treated with target compounds respectively at various concentrations for 48 h. Then, 20 mL MTT (5 mg/mL) was added to each well and incubated for 4 h at 37 °C. Supernatant was discarded, and 150 mL DMSO was added to each well. Absorbance values were determined by microplate reader at 570 nm. The IC_{50} values were calculated according to inhibition ratios.

5.4. Molecular docking modeling[20]

Molecule docking was performed using Sybyl/Surflex-dock based on crystal structures of HDAC (PDB ID: 3F07). Hydrogen was added and minimized using Tripos force field and Pullman charges. All the waters were removed as well as all ions except for catalytic zinc ion. The residues in a radius 5.0 Å around APHA (ligand of HDAC in crystal complex) were selected as active site. Compounds **FA6** and **FA16** were depicted with Sybyl/Sketch module (Tripos Inc.) and optimized applying Powell's method with Tripos force field with convergence criterion set at 0.05 kcal/(Åmol), and assigned with Gasteiger-Hückel method. Other docking parameters were kept at default.

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