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# Design, synthesis and biological evaluation of tyrosine-based hydroxamic acid analogs as novel histone deacetylases (HDACs) inhibitors

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ABSTRACT

Histone deacetylases (HDACs) are a promising target for treating cancer and some other disorders. Herein, based on the structure of our previously reported tetrahydroisoquinoline-based hydroxamic acids, a novel series of tyrosine-based hydroxamic acid derivatives was designed and synthesized as HDACs inhibitors. Compared with tetrahydroisoquinoline-based hydroxamic acids, tyrosine-based hydroxamic acid derivatives exhibited more potent HDAC8 inhibitory activity. However, the antiproliferative activities and HeLa cell nuclear extract inhibition of several selected tyrosine-based hydroxamic acids were moderate.



## 1. Introduction

Cancer is a disease characterized by uncontrolled cell growth and proliferation, which often results from disordered gene expression, genetic and/or epigenetic. Epigenetic changes refer to heritable changes in gene expression caused by modifications of chromatin structure other than alteration in DNA sequence.[1,2] The fundamental repeating unit of chromatin is the nucleosome composed of core histone around which DNA coils.[3] Some histone amino acid residues, such as lysines, protrude the nucleosome and are subject to numerous posttranslational modifications.[4] Histone deacetylases (HDACs) are enzymes responsible for histone lysine residues deacetylation leading to condensation of chromosomal DNA and gene transcriptional repression.[5–7] Therefore, HDACs are regarded as promising targets for cancer therapy.

The human HDACs family can be divided into 4 classes. The enzymes of classes I (HDACs 1–3 and 8), II (HDACs 4–7, 9 and 10) and IV (HDACs 11) are all $Zn^{2+}$-dependent metalloproteases, whereas the class III HDACs (sirtuins 1–7) are $NAD^{+}$ dependent.[8,9] Indeed, only $Zn^{2+}$-dependent HDACs, especially class I and class II isozymes are involved in promoting tumor cells proliferation, angiogenesis, migration, resistance to chemotherapy and prohibiting apoptosis and differentiation.[10] Currently, over ten HDACs inhibitors (HDACi) are in clinical trials as antitumor agents[11] and two of them, SAHA (Zolinza®, Merck, Fig. 1)[12] and FK228 (Istodax®, Gloucester Pharmaceuticals/Celgene, Fig. 1),[13] are already on the market.

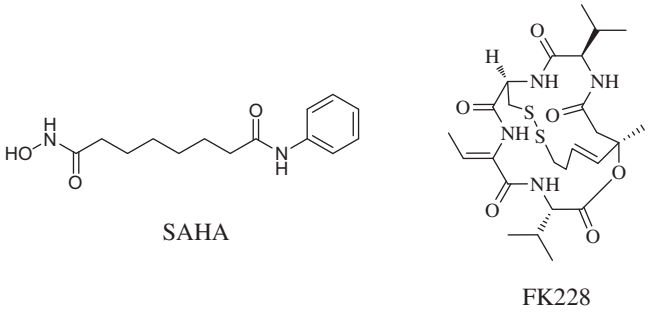


**Figure 1.** The structures of two approved drugs, SAHA and FK228.

In our previous study, we designed and synthesized a novel series of tetrahydroisoquinoline-based hydroxamic acids as potent HDACi (Fig. 2a), which exhibited excellent in vitro and in vivo antitumor activities.[14,15] In order to investigate the influence of molecular flexibility on HDACs inhibitory activity, the tetrahydroisoquinoline scaffold (Fig. 2a) was simplified to the tyrosine scaffold (Fig. 2b).

## 2. Chemistry

Target compounds **E**, **F** and **H** were synthesized according to the procedures described in Scheme 1. Boc (*tert*-butoxycarbonyl) group protection of the starting material L-tyrosine (compound **A**) led to compound **B**, which was condensed with phenylamine in the presence of DCC and HOBT to afford compound **C**. Alkylation of the

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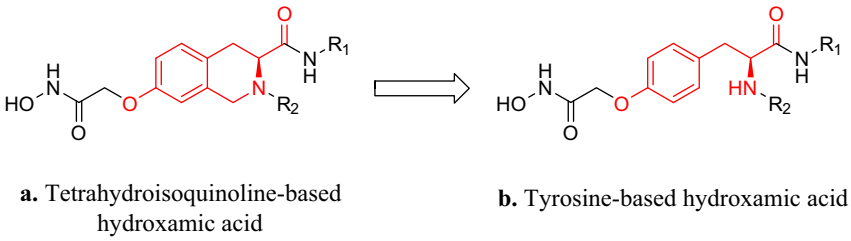
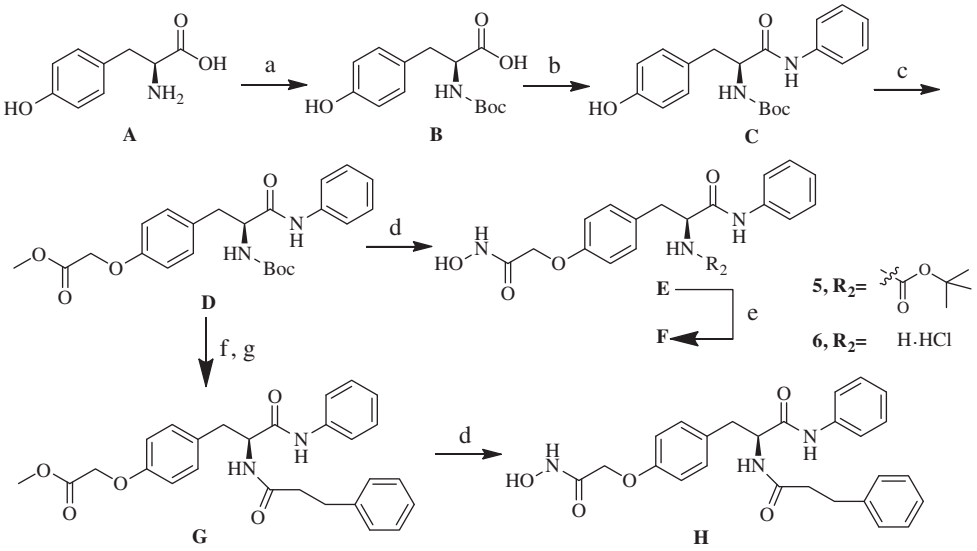
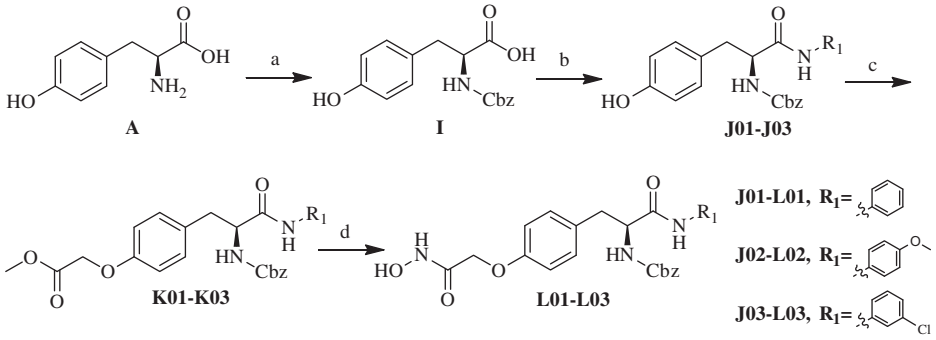



**Figure 2.** The general structures of tetrahydroisoquinoline-based hydroxamic acids (**a**) and tyrosine-based hydroxamic acids (**b**).




**Scheme 1.** Reagents and conditions: (a) $(Boc)_2O$, 1 N NaOH, THF; (b) phenylamine, DCC, HOBT, anhydrous THF; (c) $BrCH_2COOCH_3$, $K_2CO_3$, anhydrous DMF; (d) $NH_2OK$, $CH_3OH$; (e) HC1, anhydrous EtOAc; (f) TFA, DCM, $Et_3N$; (g) 3-phenylpropionic acid, TBTU, $Et_3N$, THF.




**Scheme 2.** Reagents and conditions: (a) Cbz-Cl, 1 M NaOH; (b) R–$NH_2$, DCC, HOBT, anhydrous THF; (c) $BrCH_2COOCH_3$, $K_2C0_3$, anhydrous DMF; (d) $NH_2OK$, $CH_3OH$.

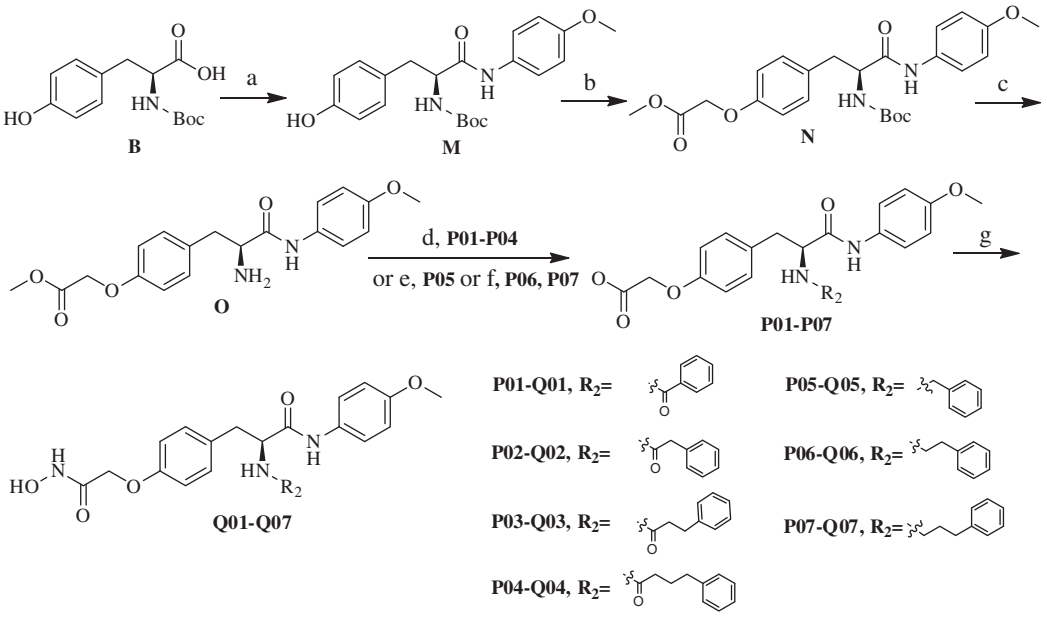
phenol group of compound **C** with methyl bromoacetate gave compound **D**, which was treated with $NH_2OK$ in methanol to furnish one target compound **E**. Boc group of compound **E** was cleaved in acidic conditions to give compound **F**. N-deprotection of compound **D** followed by acylation of the obtained free amine group with 3-phenylpropionic acid afforded compound **G**, which was converted to the hydroxamic acid derivative **H**.

Cbz (benzoyloxycarbonyl) group protection of L-tyrosine followed by condensation with several kinds of amines, alkylation of the phenol group and final aminolysis of the ester group furnished the desired hydroxamic acids **L01**–**L03** (Scheme 2).

Target compounds **Q1**–**Q7** were synthesized according to the procedures described in Scheme 3. Compound **B** was converted to compound **N** in two steps as described for compound **D**. The Boc protection group of compound **N** was cleaved by trifluoroacetic acid in $CH_2Cl_2$ giving the free amine intermediate **O**, which was subsequently functionalized through either acylation or alkylation to afford **P01**–**P07**. Compounds **P01**–**P07** were then treated with $NH_2OK$ in methanol to give corresponding hydroxamic acids **Q01**–**Q07**.

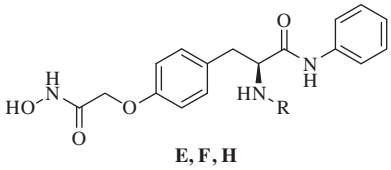
## 3. Result and discussion

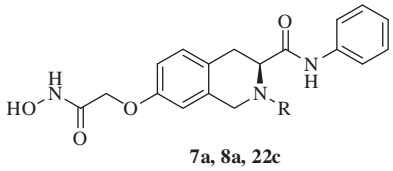
Considering that all zinc ion dependent HDACs were highly conserved in their active sites and HDAC8 could be expressed and purified in our laboratory, we used HDAC8 as the enzyme source to screen our target compounds efficiently. Enzyme inhibitory

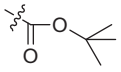
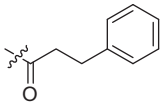



**Scheme 3.** Reagents and conditions: (a) 4-methoxyaniline, DCC, HOBT, anhydrous THF; (b) $BrCH_2COOCH_3$, $K_2CO_3$, anhydrous DMF; (c) TFA, DCM, saturated $Na_2CO_3$; (d) carboxylic acid, TBTU, $Et_3N$, THF; (e) benzyl bromide, $K_2CO_3$, DMF; (f) microwave, RBr, $K_2CO_3$, DMF; (g) $NH_2OK$, $CH_3OH$.

**Table 1**
The structures and HDAC8 inhibitory activity comparison of compounds **E**, **F** and **H** with their parent compounds **7a**, **8a**, **22c** and the positive control SAHA




| Compounds | $IC_{50}$[c] of HDAC8 (μM) | R |
|---|---|---|
| SAHA[a] | 1.48 ± 0.20 | / |
| E | 0.227 ± 0.04 |  |
| **7a**[a] | 1.29 ± 0.15 | |
| F | 0.467 ± 0.07 | H·HCl |
| **8a**[a] | 8.21 ± 1.68 | |
| H | 0.151 ± 0.03 |  |
| **22c**[b] | 0.759 ± 0.12 | |

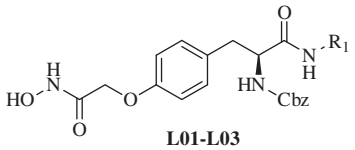
[a] Cited from Ref. 14.
[b] Cited from Ref. 15.
[c] Results expressed as the mean ± standard deviation of at least three separate determinations.

assay (Table 1) revealed that compounds **E**, **F** and **H** exhibited more potent HDAC8 inhibitory activities relative to SAHA and their corresponding tetrahydroisoquinoline analogs **7a**, **8a** and **22c**. Besides, the results that compounds **E** and **H** possessed lower $IC_{50}$ than compound **F** reminded us of the structure–activity relationship (SAR) obtained from the tetrahydroisoquinoline derivatives,[14,15] namely, N-substituents ($R_2$ group, such as the Boc group in compound **E** and the 3-phenylpropionyl group in compound **G**) were beneficial to the inhibitory activity.

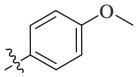
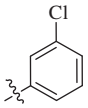
To further verify the above SAR and to identify an optimal $R_1$ group, compounds **L01**–**L03** were designed and synthesized following the methods in Scheme 2. HDAC8 inhibitory activity in Table 2 showed that compared with compound **H** (Table 1), compound **L01** exhibited superior activity due to the Cbz group located on the primary amine group. Different $R_1$ groups could also lead to different inhibitory potency, and compound **L02** with 4-methoxyphenyl group as $R_2$ group exhibited the most potent activity among these three compounds. These results promoted us to keep the 4-methoxyphenyl group fixed and substitute other functional groups for the Cbz group of **L02**.

Compounds synthesized in Scheme 3 were designed to preliminarily explore the effect of the N-substituent. The same as the conclusion drew from Table 1, tyrosine derivatives **Q1**–**Q7** all showed preferable HDAC8 inhibitory activities to their corresponding tetrahydroisoquinoline analogs (Table 3). Notably, four excellent inhibitors **Q1**–**Q7** with double-digit nanomolar $IC_{50}$ were obtained, and compounds **Q1**, **Q2** and **Q3** were almost 1 order of magnitude more potent than their corresponding secondary amine analogs

**Table 2**
The structures and HDAC8 inhibitory activity of compounds **L01**–**L03**



**L01-L03**

| Compounds | $R_1$ | $IC_{50}$[a] of HDAC8 (μM) |
|---|---|---|
| **L01** |  | 0.197 ± 0.04 |
| **L02** |  | 0.120 ± 0.03 |
| **L03** |  | 0.213 ± 0.04 |

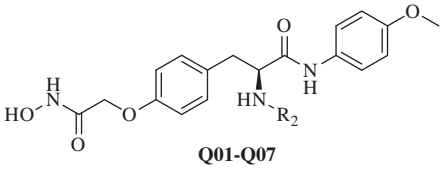
[a] Results expressed as the mean ± standard deviation of at least three separate determinations.

**Q5**, **Q6** and **Q7** (the $IC_{50}$ values of **Q1**, **Q2** and **Q3** were 0.087 ± 0.02 μM, 0.063 ± 0.01 μM and 0.090 ± 0.01 μM, whereas the $IC_{50}$ values of **Q5**, **Q6** and **Q7** were 1.18 ± 0.21 μM, 0.660 ± 0.11 μM and 0.922 ± 0.13 μM, respectively). This tendency was also observed in the tetrahydroisoquinoline analogs, which indicated that the oxygen atom of amide group was crucial for enzyme inhibition.

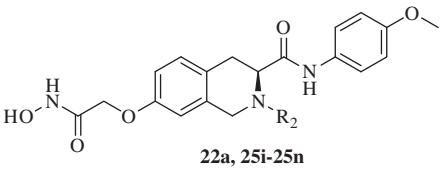
The potent anti-HDACs activities of compounds **Q1–Q4** promoted us to evaluate their in vitro antiproliferative activities against human breast tumor cell line (MDA-MB-231), lung tumor cell line (A549) and colon tumor cell line (HCT-116) since these three kinds of tumor cell lines were sensitive to our tetrahydroisoquinoline-based hydroxamic acid HDACi.[14,15] As can be seen in Table 4, although the HDAC8 inhibitory activities of these compounds were all superior to that of SAHA, their antiproliferative activities were not comparable with that of SAHA. To preliminarily explore the reason why the antiproliferative activities of the tyrosine derivatives were disappointing, we tested our compounds against HeLa cell nuclear extract (which contains the panel of HDACs, primarily HDAC1 and HDAC2) and found that the antiproliferative potency correlated well with their HeLa cell nuclear extract inhibitory activity. To be specific, the potent antiproliferative activity of SAHA was in line with its robust inhibition against HeLa cell nuclear extract ($IC_{50}$ = 0.107 ± 0.02 μM), and among the four tyrosine derivatives, compound **Q1** with the most similar $IC_{50}$ value against HeLa cell nuclear extract to SAHA, exhibited the most effective antiproliferative activity. However, it should be kept in mind that linking the enzyme inhibitory activity of HDACi with their cellular potency is difficult because several other variables should be considered, such as enzyme isoform selectivity, cellular membrane permeability, metabolic stability, subcellular localization and cellular xenobiotics-exporting mechanisms.

The results listed in Table 4 revealed that different with SAHA, our tyrosine-based hydroxamic acid derivatives exhibited preferable HDAC8 inhibition. Moreover, compared with the tetrahydroisoquinoline-based hydroxamic acid scaffold with little selectivity against individual HDACs,[15] the tyrosine-based hydroxamic acid scaffold exhibited HDAC8 isoform selectivity to some degree,

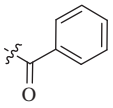
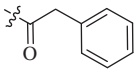
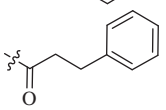
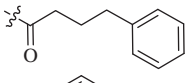
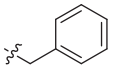
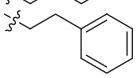
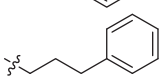
**Table 3**
The structures and HDAC8 inhibitory activity of compounds **Q01–Q07** with their parent compounds **25i–25n** and **22a**



**Q01-Q07**



**22a, 25i-25n**

| Compounds | $IC_{50}$[b] of HDAC8 (μM) | $R_2$ |
|---|---|---|
| **Q01**<br>**25j**[a] | 0.087 ± 0.02<br>0.164 ± 0.028 |  |
| **Q02**<br>**25i**[a] | 0.063 ± 0.01<br>0.141 ± 0.020 |  |
| **Q03**<br>**22a**[a] | 0.090 ± 0.01<br>0.502 ± 0.17 |  |
| **Q04**<br>**25k**[a] | 0.086 ± 0.02<br>0.114 ± 0.018 |  |
| **Q05**<br>**25n**[a] | 1.18 ± 0.21<br>1.92 ± 0.35 |  |
| **Q06**<br>**25m**[a] | 0.660 ± 0.11<br>1.02 ± 0.23 |  |
| **Q07**<br>**25l**[a] | 0.922 ± 0.13<br>1.72 ± 0.36 |  |

[a] Cited from Ref. 15.
[b] Data represent mean values of at least three independent experiments and standard deviations are calculated based on the results of these experiments.

**Table 4**
Antiproliferative and HDACs inhibitory activities of compounds **Q01–Q04** with SAHA as positive control

| Compounds | $IC_{50}$[a] (μM) | | | | |
|---|---|---|---|---|---|
| | MDA-MB-231 | A549 | HCT-116 | HeLa cell nuclear extract | HDAC8 |
| **Q01** | 2.98 ± 0.24 | 24.0 ± 3.6 | 1.53±0.23 | 0.358 ± 0.04 | 0.087 ± 0.02 |
| **Q02** | 22.3 ± 3.1 | >100 | >100 | 1.23 ± 0.24 | 0.063 ± 0.01 |
| **Q03** | 6.59 ± 0.97 | 54.6 ± 7.9 | 6.24 ± 1.1 | 0.889 ± 0.12 | 0.090 ± 0.01 |
| **Q04** | 14.3 ± 2.2 | 97.2 ± 17.9 | 57.3 ± 9.8 | 1.32 ± 0.25 | 0.086 ± 0.02 |
| SAHA | 1.18 ± 0.16 | 0.69 ± 0.09 | 0.34 ± 0.07 | 0.107 ± 0.02[b] | 1.48 ± 0.20[b] |

[a] Results expressed as the mean ± standard deviation of at least three separate determinations.
[b] Cited from Ref. 15.

which could be further derivatized to give rise to HDAC8 selective inhibitors. Currently, class-selective, even isoform selective HDACs inhibitors are of great interest, not only as therapeutic agents with few side effects, but also as molecular probes for exploring the biological functions of HDAC isoforms.[10,16–18]

## 4. Conclusions

In summary, on the basis of the structure of our previously reported tetrahydroisoquinoline-based hydroxamic acids, a novel series of tyrosine-based hydroxamic acid derivatives as HDACi was designed and synthesized. Interestingly, some structure–activity relationships (SARs) were generally applicable for both series compounds, for example, the N-substitutes ($R_2$ group) were beneficial to the inhibitory activity and the derivatives with N-acylation were more potent than their corresponding analogs with N-alkylation. Although the tyrosine-based hydroxamic acid derivatives exhibited more robust HDAC8 inhibitory activity relative to their parent tetrahydroisoquinoline analogs and the positive control SAHA, their antiproliferative potency and HeLa cell nuclear extract inhibition were moderate. Taken together, we speculated that tyrosine-based hydroxamic acid scaffold could be used to design HDAC8 isoform selective inhibitors. Related research is under way in our laboratory.

## 5. Experimental section

### 5.1. Chemistry: General procedures

All commercially available starting materials, reagents and solvents were used without further purification unless otherwise stated. All reactions were monitored by TLC with 0.25 mm silica gel plates (60GF-254). UV light, iodine stain and ferric chloride were used to visualize the spots. Silica gel was used for column chromatography purification. Microwave-aided synthesis was performed using CEM Discover-S microwave synthesis system. Melting points were determined uncorrected on an electrothermal melting point apparatus. $^1$H NMR spectra were recorded on a Bruker DRX spectrometer at 600 MHz, $\delta$ in parts per million and $J$ in hertz, using TMS as an internal standard. High-resolution mass spectra were conducted by Shandong Analysis and Test Center in Ji'nan, China. ESI-MS spectra were recorded on an API 4000 spectrometer.

#### 5.1.1. (*S*)-2-((*tert*-Butoxycarbonyl)amino)-3-(4-hydroxyphenyl) propanoic acid (B)

To a solution of compound **A** (3.62 g, 20.0 mmol) in 44 mL of 1 N NaOH, was added a solution of $(Boc)_2O$ (4.80 g, 22.0 mmol) in THF (10 mL). The solution was kept between pH 9 and 11 by addition of 1 N NaOH. After stirring the mixture at room temperature for 8 h, THF was evaporated in vacuum with the residues being adjusted to pH 4–5 with 1 N aqueous citric acid. Then the mixture was extracted with EtOAc (3 × 25 mL). The extractions were combined, washed with brine (3 × 20 mL), dried over $MgSO_4$ and evaporated to give 5.30 g of crude product compound **B** as a white solid. This product was used for the following reaction without further purification. ESI-MS *m/z*: 282.1 $[M+H]^+$.

#### 5.1.2. (*S*)-*tert*-Butyl (3-(4-hydroxyphenyl)-1-oxo-1-(phenylamino)propan-2-yl)carbamate (C)

At 0 °C, to a solution of compound **B** (2.81 g, 10.0 mmol) and HOBT (1.49 g, 11.0 mmol) in 50 mL of anhydrous THF, was added a solution of DCC (2.27 g, 11.0 mmol) in 10 mL of anhydrous THF, and after 20 min, the aniline (1.02 g, 11.0 mmol). After stirring the mixture at room temperature over night, THF was evaporated with the residues being taken up in EtOAc (40 mL) and freezed in refrigerator. Then DCU was filtered off, the filtrate washed with saturated $Na_2CO_3$ (3 × 10 mL), 1 N HCl (3 × 10 mL), brine (3 × 10 mL) and dried over $MgSO_4$. The solvent was evaporated to give 3.1 g of crude product compound **C** as a yellow solid. This product was used for the following reaction without further purification. ESI-MS *m/z*: 356.2 $[M+H]^+$.

Compounds **J01–J03**, **M** were synthesized according to the same procedure as compound **C**.

#### 5.1.3. (*S*)-Methyl 2-(4-(2-((*tert*-butoxycarbonyl)amino)-3-oxo-3-(phenylamino)propyl)phenoxy)acetate (D)

A mixture of **C** (2.47 g, 6.93 mmol), $K_2CO_3$ (1.91 g, 13.86 mmol) and methyl bromoacetate (2.12 g, 13.86 mmol) in 40 mL of anhydrous DMF was stirred at room temperature for 3 h. The mixture was poured to 300 mL of $H_2O$ and extracted with EtOAc (3 × 40 mL). The organic layers were combined, washed with brine (3 × 20 mL), dried over $MgSO_4$ and evaporated under vacuum. The crude product was purified by recrystallization in EtOAc to get 2.8 g of compound **D** as a white powder. Yield: 65%, $^1$H NMR (DMSO-$d_6$) $\delta$ 1.33 (s, 9H), 2.78 (dd, $J$ = 13.8 Hz, $J$ = 10.2 Hz, 1H), 2.93 (dd, $J$ = 13.8 Hz, $J$ = 4.8 Hz, 1H), 3.69 (s, 3H), 4.28 (dd, $J$ = 4.8 Hz, $J$ = 10.2 Hz, 1H), 4.75 (s, 2H), 6.85 (d, $J$ = 8.4 Hz, 2H), 7.06 (t, $J$ = 7.2 Hz, 1H), 7.24 (d, $J$ = 8.4 Hz, 2H), 7.31 (t, $J$ = 7.2 Hz, 2H), 7.59 (d, $J$ = 8.4 Hz, 2H), 10.03 (s, 1H). ESI-MS *m/z*: 429.2 $[M+H]^+$.

Compounds **K01–K03**, **N** were synthesized according to the same procedure as compound **D**.

#### 5.1.4. (*S*)-*tert*-Butyl (3-(4-(2-(hydroxyamino)-2-oxoethoxy)-phenyl)-1-oxo-1-(phenylamino)propan-2-yl)carbamate (E)

To a solution of compound **D** (0.86 g, 2.0 mmol) in 10 mL of anhydrous methanol, was added a solution of $NH_2OK$ (0.14 g, 6 mmol) in 3.5 mL of anhydrous methanol. The mixture was stirred for 0.5 h and the solvent was evaporated under vacuum. The residues were acidified with 2 N HCl until pH 3–4 then extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (3 × 10 mL), dried over $MgSO_4$ and evaporated with the residues being recrystallized with EtOH to give 0.21 g of title compound **E** as a white powder. Yield: 24%, mp: 152–154 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 1.24+1.33 (s, 9H, cis/trans), 2.77 (dd, $J$ = 13.8 Hz, 10.8 Hz, 1H), 2.92 (dd, $J$ = 13.8 Hz, 4.8 Hz, 1H), 4.23–4.27 (m, 1H), 4.41 (s, 2H), 6.87 (d, $J$ = 8.4 Hz, 2H), 7.05 (t, $J$ = 7.8 Hz, 1H), 7.07 (d, $J$ = 9.0 Hz, 1H), 7.23 (d, $J$ = 8.4 Hz, 2H), 7.31 (t, $J$ = 7.8 Hz, 2H), 7.58 (d, $J$ = 7.8 Hz, 2H), 8.95 (s, 1H), 10.02

(s, 1H), 10.80 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{22}H_{27}N_3NaO_6$ $[M+Na]^+$ 452.1798. Found: 452.1830.

Compounds **H**, **L01–L03**, **Q1–Q7** were synthesized according to the same procedure as compound **E**.

**5.1.4.1. (*S*)-3-(4-(2-(Hydroxyamino)-2-oxoethoxy)phenyl)-*N*-phenyl-2-(3-phenylpropanamido)propanamide (H).** Mp: 148–150 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.39 (t, $J$ = 7.8 Hz, 2H), 2.73 (t, $J$ = 7.8 Hz, 2H), 2.77 (dd, $J$ = 13.8 Hz, 9.6 Hz, 1H), 2.95 (dd, $J$ = 13.8 Hz, 5.4 Hz, 1H), 4.40 (s, 2H), 4.61–4.65 (m, 1H), 6.85 (d, $J$ = 8.4 Hz, 2H), 7.05 (t, $J$ = 7.2 Hz, 1H), 7.14–7.15 (m, 4H), 7.17 (t, $J$ = 7.8 Hz, 1H), 7.22 (t, $J$ = 7.2 Hz, 2H), 7.31 (t, $J$ = 7.8 Hz, 2H), 7.58 (d, $J$ = 8.4 Hz, 2H), 8.27 (d, $J$ = 7.8 Hz, 1H), 8.96 (s, 1H), 10.10 (s, 1H), 10.81 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{26}H_{28}N_3O_5$ $[M+H]^+$ 462.2029. Found: 462.2057.

**5.1.4.2. (*S*)-Benzyl (3-(4-(2-(Hydroxyamino)-2-oxoethoxy)phenyl)-1-oxo-1-(phenylamino) propan-2-yl)carbamate (L01).** Mp: 142–144 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.78 (dd, $J$ = 13.8 Hz, 10.8 Hz, 1H), 2.96 (dd, $J$ = 13.8 Hz, 4.8 Hz, 1H), 4.33–4.37 (m, 1H), 4.41 (s, 2H), 4.97–5.03 (m, 2H), 6.87 (d, $J$ = 8.4 Hz, 2H), 7.06 (t, $J$ = 7.2 Hz, 1H), 7.25 (d, $J$ = 8.4 Hz, 2H), 7.28 (d, $J$ = 7.8 Hz, 2H), 7.32–7.36 (m, 5H), 7.60 (d, $J$ = 7.8 Hz, 2H), 7.67 (d, $J$ = 8.4 Hz, 1H), 8.96 (s, 1H), 10.11 (s, 1H), 10.81 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{25}H_{26}N_3O_6$ $[M+H]^+$ 464.1822. Found: 464.1836.

**5.1.4.3. (*S*)-Benzyl (3-(4-(2-(Hydroxyamino)-2-oxoethoxy)-phenyl)-1-((4-methoxyphenyl) amino)-1-oxopropan-2-yl)carbamate (L02).** Mp: 179–181 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.77 (dd, $J$ = 13.2 Hz, 10.8 Hz, 1H), 2.96 (dd, $J$ = 13.2 Hz, 4.2 Hz, 1H), 3.72 (s, 3H), 4.30–4.33 (m, 1H), 4.41 (s, 2H), 4.94–4.99 (m, 2H), 6.86 (d, $J$ = 8.4 Hz, 2H), 6.89 (d, $J$ = 9.0 Hz, 2H), 7.24 (d, $J$ = 8.4 Hz, 2H), 7.29 (t, $J$ = 7.2 Hz, 2H), 7.30 (t, $J$ = 7.2 Hz, 1H), 7.34 (t, $J$ = 7.2 Hz, 2H), 7.49 (d, $J$ = 9.0 Hz, 2H), 7.63 (d, $J$ = 8.4 Hz, 1H), 8.96 (s, 1H), 9.96 (s, 1H), 10.81 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{26}H_{28}N_3O_7$ $[M+H]^+$ 494.1927. Found: 494.1944.

**5.1.4.4. (*S*)-Benzyl (1-((2-Chlorophenyl)amino)-3-(4-(2-(hydroxyamino)-2-oxoethoxy) phenyl)-1-oxopropan-2-yl)carbamate (L03).** Mp: 160–162 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.78 (dd, $J$ = 13.8 Hz, 10.8 Hz, 1H), 2.96 (dd, $J$ = 13.8 Hz, 4.8 Hz, 1H), 4.31–4.33 (m, 1H), 4.41 (s, 2H), 4.93–4.99 (m, 2H), 6.87 (d, $J$ = 8.4 Hz, 2H), 7.12–7.17 (m, 2H), 7.23 (d, $J$ = 8.4 Hz, 2H), 7.25–7.37 (m, 6H), 7.44–7.46 (m, 1H), 7.72 (d, $J$ = 8.4 Hz, 1H), 8.97 (s, 1H), 10.32 (s, 1H), 10.82 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{25}H_{25}ClN_3O_6$ $[M+H]^+$ 498.1432. Found: 498.1443.

**5.1.4.5. (*S*)-*N*-(3-(4-(2-(Hydroxyamino)-2-oxoethoxy)phenyl)-1-((4-methoxyphenyl)amino)-1-oxopropan-2-yl)benzamide (Q1).** Mp: 207–209 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 3.01–3.08 (m, 2H), 3.72 (s, 3H), 4.39 (s, 2H), 4.73–4.79 (m, 1H), 6.87 (d, $J$ = 8.4 Hz, 2H), 6.90 (d, $J$ = 9.0 Hz, 2H), 7.32 (d, $J$ = 8.4 Hz, 2H), 7.45 (t, $J$ = 7.8 Hz, 2H), 7.52 (d, $J$ = 9.0 Hz, 2H), 7.53 (t, $J$ = 7.8 Hz, 1H), 7.83 (d, $J$ = 7.8 Hz, 2H), 8.69 (d, $J$ = 8.4 Hz, 1H), 8.95 (s, 1H), 10.08 (s, 1H), 10.78 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{25}H_{26}N_3O_6$ $[M+H]^+$ 464.1822. Found: 464.1841.

**5.1.4.6. (*S*)-3-(4-(2-(Hydroxyamino)-2-oxoethoxy)phenyl)-*N*-(4-methoxyphenyl)-2-(2-phenylacetamido)propanamide (Q2).** Mp: 197–199 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.80 (dd, $J$ = 13.8 Hz, 9.6 Hz, 1H), 2.97 (dd, $J$ = 13.8 Hz, 4.8 Hz, 1H), 3.39–3.47 (m, 2H), 3.72 (s, 3H), 4.40 (s, 2H), 4.57–4.61 (m, 1H), 6.83 (d, $J$ = 8.4 Hz, 2H), 6.88 (d, $J$ = 9.0 Hz, 2H), 7.13 (d, $J$ = 7.2 Hz, 2H), 7.17 (d, $J$ = 8.4 Hz, 2H), 7.18 (t, $J$ = 7.2 Hz, 1H), 7.24 (t, $J$ = 7.2 Hz, 2H), 7.47 (d, $J$ = 9.0 Hz, 2H), 8.43 (d, $J$ = 8.4 Hz, 1H), 8.98 (s, 1H), 9.97 (s, 1H), 10.83 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{26}H_{27}N_3NaO_6$ $[M+Na]^+$ 500.1798. Found: 500.1818.

**5.1.4.7. (*S*)-3-(4-(2-(Hydroxyamino)-2-oxoethoxy)phenyl)-*N*-(4-methoxyphenyl)-2-(3-phenylpropanamido)propanamide (Q3).** Mp: 183–185 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.39 (t, $J$ = 7.8 Hz, 2H), 2.73 (t, $J$ = 7.8 Hz, 2H), 2.76 (dd, $J$ = 13.8 Hz, 9.6 Hz, 1H), 2.94 (dd, $J$ = 13.8 Hz, 4.8 Hz, 1H), 3.72 (s, 3H), 4.40 (s, 2H), 4.58–4.61 (m, 1H), 6.84 (d, $J$ = 8.4 Hz, 2H), 6.88 (d, $J$ = 9.0 Hz, 2H), 7.14–7.17 (m, 5H), 7.23 (t, $J$ = 7.8 Hz, 2H), 7.47 (d, $J$ = 9.0 Hz, 2H), 8.23 (d, $J$ = 8.4 Hz, 1H), 8.96 (s, 1H), 9.93 (s, 1H), 10.81 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{27}H_{30}N_3O_6$ $[M+H]^+$ 492.2135. Found: 492.2165.

**5.1.4.8. (*S*)-*N*-(3-(4-(2-(Hydroxyamino)-2-oxoethoxy)phenyl)-1-((4-methoxyphenyl)amino)-1-oxopropan-2-yl)-4-phenylbutanamide (Q4).** Mp: 173–175 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 1.69–1.70 (m, 2H), 2.09 (t, $J$ = 7.8 Hz, 3H), 2.44 (t, $J$ = 7.2 Hz, 3H), 2.77 (dd, $J$ = 13.8 Hz, 9.6 Hz, 1H), 2.95 (dd, $J$ = 13.8 Hz, 4.8 Hz, 1H), 3.71 (s, 3H), 4.37 (s, 2H), 4.58–4.62 (m, 1H), 6.84 (d, $J$ = 8.4 Hz, 2H), 6.88 (d, $J$ = 9.0 Hz, 2H), 7.12 (d, $J$ = 7.8 Hz, 2H), 7.16 (t, $J$ = 7.8 Hz, 1H), 7.21 (d, $J$ = 7.8 Hz, 2H), 7.26 (t, $J$ = 7.8 Hz, 2H), 7.48 (d, $J$ = 9.0 Hz, 2H), 8.18 (d, $J$ = 7.8 Hz, 1H), 8.96 (s, 1H), 9.95 (s, 1H), 10.80 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{28}H_{32}N_3O_6$ $[M+H]^+$ 506.2291. Found: 506.2307.

**5.1.4.9. (*S*)-2-(Benzylamino)-3-(4-(2-(hydroxyamino)-2-oxoethoxy)phenyl)-*N*-(4-methoxyphenyl)propanamide (Q5).** Mp: 72–74 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.39 (s, 1H), 2.76–2.79 (m, 1H), 2.86–2.89 (m, 1H), 3.35–3.36 (m, 1H), 3.54–3.56 (m, 1H), 3.71–3.73 (m, 1H), 3.72 (s, 3H), 4.41 (s, 2H), 6.84–6.88 (m, 4H), 7.14–7.24 (m, 5H), 7.25–7.27 (m, 2H), 7.47–7.48 (m, 2H), 8.96 (s, 1H), 9.73 (s, 1H), 10.81 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{25}H_{27}N_3NaO_5$ $[M+Na]^+$ 472.1848. Found: 472.1847.

**5.1.4.10. (*S*)-3-(4-(2-(Hydroxyamino)-2-oxoethoxy)phenyl)-*N*-(4-methoxyphenyl)-2-(phenethylamino)propanamide (Q6).** Mp: 148–150 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.05 (s, 1H), 2.63–2.71 (m, 4H), 2.72–2.75 (m, 1H), 2.83–2.87 (m, 1H), 3.36–3.39 (m, 1H), 3.71 (s, 3H), 4.40 (s, 2H), 6.82–6.86 (m, 4H), 7.11–7.18 (m, 5H), 7.23–7.26 (m, 2H), 7.39–7.40 (m, 2H), 8.96 (s, 1H), 9.62 (s, 1H), 10.81 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{26}H_{29}N_3NaO_5$ $[M+Na]^+$ 486.2005. Found: 486.2049.

**5.1.4.11. (*S*)-3-(4-(2-(Hydroxyamino)-2-oxoethoxy)phenyl)-*N*-(4-methoxyphenyl)-2-((3-phenylpropyl)amino)propanamide (Q7).** Mp: 87–89 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 1.63–1.68 (m, 2H), 1.95 (s,1H), 2.39–2.55 (m, 4H), 2.70–2.74 (m, 1H), 2.82–2.85 (m, 1H), 3.26–3.31 (m, 1H), 3.71 (s, 3H), 4.39 (s, 2H), 6.84–6.87 (m, 4H), 7.11–7.16 (m, 5H), 7.21–7.24 (m, 2H), 7.45–7.46 (m, 2H), 8.96 (s, 1H), 9.68 (s, 1H), 10.80 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{27}H_{31}N_3NaO_5$ $[M+Na]^+$ 500.2161. Found: 500.2192.

**5.1.5. (*S*)-2-Amino-3-(4-(2-(hydroxyamino)-2-oxoethoxy)-phenyl)-*N*-phenylpropanamide hydrochloride (F)**

To a solution of compound **E** (0.17 g, 0.40 mmol) in 6 mL of dry EtOAc, was added a solution of EtOAc (10 mL) saturated by dry HCl gas. The reaction solution was stirred at room temperature for 7 h when the precipitation appeared. The suspension was filtered with the filter being washed with ether to give 0.13 g of desired compound **F** as a white powder. Yield: 89%, mp: 168–170 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ 3.03 (dd, $J$ = 13.8 Hz, 7.8 Hz, 1H), 3.15 (dd, $J$ = 13.8 Hz, 6.0 Hz, 1H), 4.18–4.20 (m, 1H), 4.42 (s, 2H), 6.91 (d, $J$ = 9.0 Hz, 2H), 7.11 (t, $J$ = 7.2 Hz, 1H), 7.22 (d, $J$ = 9.0 Hz, 2H), 7.35 (t, $J$ = 7.2 Hz, 2H), 7.57 (d, $J$ = 7.2 Hz, 2H), 8.33 (br s, 3H), 8.98 (s, 1H), 10.73 (s, 1H), 10.86 (s, 1H). HRMS (AP-ESI) *m/z* calcd for $C_{17}H_{20}N_3O_4$ $[M+H]^+$ 330.1454. Found: 330.1471.

#### 5.1.6. (*S*)-Methyl 2-(4-(3-oxo-3-(phenylamino)-2-(3-phenylpropanamido)propyl)phenoxy)acetate (G)

To a solution of compound **D** (4.28 g, 10.0 mmol) in anhydrous $CH_2Cl_2$ (40 mL), was added 20 mL of trifluoroacetic acid. When the reaction was finished, saturated $Na_2CO_3$ was added to the solution until the pH reach weak basic. The mixture was separated with separatory funnel, the organic layer was washed with distilled water, dried over $MgSO_4$ and evaporated under vacuum to get 2.90 g of white solid. This product was used for the following reaction without further purification. At room temperature, to a solution of 3-phenylpropionic acid (0.75 g, 5.0 mmol) in anhydrous THF (20 mL), was added $Et_3N$ (0.56 g, 5.5 mmol) followed by 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU, 1.78 g, 5.5 mmol). After 15 min, the amine (1.67 g, 5.0 mmol) was added. The stirring was continued for 8 h and then THF was evaporated. The residues were taken up in EtOAc (40 mL), washed with 1 N HCl (3 × 10 mL), saturated $Na_2CO_3$ (3 × 10 mL), brine (3 × 10 mL), dried over $MgSO_4$ and evaporated under vacuum. The crude product was purified by recrystallization in EtOAc to get 2.0 g of compound **G** as a white powder. Yield: 43%, $^1$H NMR (DMSO-$d_6$) $\delta$ 2.38 (t, $J$ = 7.8 Hz, 2H), 2.72 (t, $J$ = 7.8 Hz, 2H), 2.75–7.79 (m, 1H), 2.92–2.95 (m, 1H), 3.72 (s, 3H), 4.59–4.60 (m, 1H), 4.74 (s, 2H), 6.82 (d, $J$ = 9.0 Hz, 2H), 6.88 (d, $J$ = 9.0 Hz, 2H), 7.14 (d, $J$ = 7.8 Hz, 2H), 7.16 (d, $J$ = 9.0 Hz, 2H), 7.17–7.20 (m, 1H), 7.23 (d, $J$ = 7.8 Hz, 2H), 7.47 (d, $J$ = 9.0 Hz, 2H), 8.24 (s, 1H), 9.94 (s, 1H). ESI-MS $m/z$: 461.2 $[M+H]^+$.

Compounds **P01–P04** were synthesized according to the same procedure as compound **G**.

#### 5.1.7. (*S*)-2-(((Benzyloxy)carbonyl)amino)-3-(4-hydroxyphenyl)propanoic acid (I)

At 0 °C, to a solution of compound **A** (1.15 g, 6.38 mmol) in 7 mL of 1 N NaOH, was added Cbz-Cl (1.20 g, 7.01 mmol) dropwise. The solution was kept between pH 9 and 11 by addition of 1 N NaOH. After stirring the mixture for 3 h, the solution was adjusted to pH 4–5 with 1 N HCl. Then the mixture was extracted with EtOAc (3 × 10 mL). The extractions were combined, washed with brine (3 × 10 mL), dried over $MgSO_4$ and evaporated to give 1.85 g of crude product compound **I** as light yellow oil. This product was used for the following reaction without further purification. ESI-MS $m/z$: 316.1 $[M+H]^+$.

#### 5.1.8. (*S*)-Methyl 2-(4-(2-amino-3-((4-methoxyphenyl)amino)-3-oxopropyl)phenoxy)acetate (O)

To a solution of compound **N** (4.58 g, 10.0 mmol) in anhydrous $CH_2Cl_2$ (40 mL), was added 20 mL of trifluoroacetic acid. When the reaction was finished, saturated $Na_2CO_3$ was added to the solution until the pH reach weak basic. The mixture was separated with separatory funnel, the organic layer was washed with distilled water, dried over $MgSO_4$ and evaporated under vacuum to get 3.10 g of white solid **O**. This product was used for the following reaction without further purification. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.66 (dd, $J$ = 13.8 Hz, $J$ = 7.8 Hz, 1H), 2.93 (dd, $J$ = 13.8 Hz, $J$ = 5.4 Hz, 1H), 3.40 (br s, 2H), 3.47 (dd, $J$ = 7.8 Hz, $J$ = 5.4 Hz, 1H), 3.69 (s, 3H), 3.72 (s, 3H), 4.74 (s, 2H), 6.83 (d, $J$ = 8.4 Hz, 2H), 6.88 (d, $J$ = 8.4 Hz, 2H), 7.16 (d, $J$ = 8.4 Hz, 2H), 7.50 (d, $J$ = 8.4 Hz, 2H), 9.71 (s, 1H). ESI-MS $m/z$: 359.2 $[M+H]^+$.

#### 5.1.9. (*S*)-Methyl 2-(4-(2-(benzylamino)-3-((4-methoxyphenyl)-amino)-3-oxopropyl)phenoxy)acetate (P05)

A mixture of **O** (0.39 g, 1.08 mmol), potassium carbonate powder (0.22 g, 1.62 mmol) and benzyl bromide (0.28 g, 1.62 mmol) in anhydrous DMF (15 mL) was stirred at room temperature for 4 h. The mixture was poured into 60 mL of water and extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine (3 × 15 mL), dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (petroleum ether/EtOAc 3:1) to give 0.39 g of desired compound **P05** as a white solid. Yield: 81%, $^1$H NMR (DMSO-$d_6$) $\delta$ 2.37 (s, 1H), 2.77–2.80 (m, 1H), 2.85–2.89 (m, 1H), 3.33–3.35 (m, 1H), 3.53–3.55 (m, 1H), 3.68 (s, 3H), 3.69–3.70 (m, 1H), 3.72 (s, 3H), 4.75 (s, 2H), 6.82–6.88 (m, 4H), 7.13–7.22 (m, 5H), 7.25–7.27 (m, 2H), 7.46–7.48 (m, 2H), 9.85 (s, 1H). ESI-MS $m/z$: 449.2 $[M+H]^+$.

#### 5.1.10. (*S*)-Methyl 2-(4-(3-((4-methoxyphenyl)amino)-3-oxo-2-(phenethylamino)propyl)phenoxy)acetate (P06)

A sealed tube containing compound **O** (0.15 g, 0.41 mmol), potassium carbonate powder (0.084 g, 0.61 mmol), (2-bromoethyl)benzene (0.11 g, 0.61 mmol) and DMF (4 mL) was subjected to microwave irradiation at 70 °C for 20 min, at 100 W. After cooling, the mixture was poured into 20 mL of water and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (3 × 10 mL), dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (petroleum ether/EtOAc 3:1) to give 0.13 g of desired compound **P06** as a white solid. Yield: 71%, $^1$H NMR (DMSO-$d_6$) $\delta$ 2.05 (s, 1H), 2.63–2.71 (m, 4H), 2.72–2.75 (m, 1H), 2.84–2.88 (m, 1H), 3.37–3.39 (m, 1H), 3.69 (s, 3H), 3.71 (s, 3H), 4.78 (s, 2H), 6.80–6.86 (m, 4H), 7.12–7.18 (m, 5H), 7.23–7.25 (m, 2H), 7.40–7.42 (m, 2H), 8.96 (s, 1H), 9.63 (s, 1H). ESI-MS $m/z$: 463.2 $[M+H]^+$.

Compounds **P07** were synthesized according to the same procedure as compound **P06**.

### 5.2. Biological materials and methods

#### 5.2.1. In vitro HDACs inhibition fluorescence assay

In vitro HDACs inhibition assays were conducted as previously described.[15] In brief, 10 μL of enzyme solution (HeLa nuclear extract or HDAC8) was mixed with various concentrations of tested compound (50 μL). Five minutes later, fluorogenic substrate Boc-Lys (acetyl)-AMC (40 μL) was added, and the mixture was incubated at 37 °C for 30 min and then stopped by addition of 100 μL of developer containing trypsin and TSA. After incubation at 37 °C for 20 min, fluorescence intensity was measured using a microplate reader at excitation and emission wavelengths of 390 nm and 460 nm, respectively. The inhibition ratios were calculated from the fluorescence intensity readings of tested wells relative to those of control wells, and the $IC_{50}$ values were calculated using a regression analysis of the concentration/inhibition data.

#### 5.2.2. MTT assay

In vitro antiproliferative assays were determined as previously described.[15] Briefly, all cell lines were maintained in RPMI1640 medium containing 10% FBS at 37 °C in 5% $CO_2$ humidified incubator. Cells were passaged the day before dosing into a 96-well cell plate, allowed to grow for a minimum of 4 h prior to addition of compounds. After compounds addition, the plates were incubated for an additional 48 h, and then 0.5% MTT (3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyl-2*H*-tetrazolium bromide) solution was added to each well. After further incubation for 4 h, formazan formed from MTT was extracted by adding 200 μL of DMSO for 15 min. Absorbance was then determined using an ELISA reader at 570 nm and the $IC_{50}$ values were calculated according to the inhibition ratios.

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