Histone deacetylases inhibitors (HDACIs) have been widely recognized as significant therapeutic approach to cancers. In our efforts to develop novel histone deacetylases inhibitors (HDACIs) as potential anticancer agents, a series of $N^1$-hydroxyterephthalamide derivatives with an indole cap group were designed and synthesized. Compound 12m was identified to be the most potent one ($IC_{50} = 0.074 \mu M$ against HeLa nuclear extract) and showed higher inhibitory activity than the positive control SAHA ($IC_{50} = 0.131 \mu M$), which was also verified by further molecular docking studies into active site of HDAC2. The results of selectivity on the inhibition of HDACs exhibited 12m being with similar isoform selective profile with PXD101. In addition, the representative compounds (8d, 12d, 12j, 12m) based on the outcomes of preliminary tumor cell screening demonstrated more potent or comparable to SAHA in the next antiproliferative activity assays. Collectively, the results encouraged further development of this chemical template to provide more potent analogs as HDACIs.

**KEYWORDS**
antiproliferative activity, HDACIs, molecular docking, selectivity

The epigenetic abnormality is determined by chromatin structure including DNA methylation, histone variants and modifications, nucleosome remodeling as well as small non-coding regulatory RNAs and viewed as another pathway to initiation and progression of cancer based on genetic mutations.\(^1\) Histone deacetylases (HDACs) exert silencing effects on cell-cycle regulatory genes associated with cell proliferation, differentiation, and diminishing apoptosis which play a crucial role in the transition of normal cells into malignant cells.\(^2\) Thus far, 18 HDACs have been identified in humans and categorized into four classes due to their sequence homology to yeast orthologs.\(^3\) Class I, including HDACs 1, 2, 3, and 8, shares homology with Rpd3. Class II can be divided into two subclasses – IIa (HDACs 4, 7, and 9) and IIb (HDACs 6 and 10), which holds homology to HDAC1. Class IV covers the sole member of HDAC11 and possesses homology with both class I and class II. The 11 family members referred to as classical HDACs are metal-dependent enzymes inhibited by Zn\(^{2+}\)-ion-chelating compounds which differ in the catalytic mechanisms of class III HDACs as these enzymes with homology to the Sir2 (silent information regulator 2) family requiring NAD\(^+\) as an essential cofactor during catalysis.\(^4\) Although the biological functions of HDAC isoforms have not been fully understood yet, HDACs expression in specific tissues as well as organs and their different levels in various types of cancers both contribute to indicate the progress of diseases and develop agents with more precise therapeutic effects.\(^5\)

Up to date, four HDACIs, vorinostat (SAHA),\(^6\) romidepsin (FK228),\(^7\) belinostat (PXD101),\(^8,9\) and panobinostat

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Wang et al. (LBH589), [10] have been approved by the US FDA. SAHA and FK228 are approved for the clinical therapy of cutaneous T-cell lymphoma (CTCL), PXD101 is for the treatment of peripheral T-cell lymphoma (PTCL), and LBH589 is applied for combination therapy with bortezomib and dexamethasone for the treatment of recurrent multiple myeloma.[11] Additionally, over 20 HDACIs were in diverse clinical trials during the past 10 years. In general, numerous HDACIs share a common pharmacophore model which consists of three portions: zinc ion binding group (ZBG) that chelates zinc ion of HDACs active site; hydrophobic opposite capping group that enhances the affinity with residues of external HDACs, and a linker, connecting ZBG and cap group (Figure 1).[12]

Olson and co-workers reported that compound 2b[13] exhibited potent HDACs inhibitory activity and excellent selectivity for HDAC2 (IC$_{50} = 0.61 \mu$m) and HDAC6 (IC$_{50} = 0.004 \mu$m), thus suggesting that the N$_1$-hydroxyterephthalamide could be an ideal moiety in the design of effective HDACIs. Indole structure appears frequently in molecule drug design[14,15] and has been successfully employed in design of potent HDACIs such as the FDA-approved panobinostat and quisinostat that is under clinical trial (JNJ-26481585).[16,17] Our laboratory is also interested in exploring the indole-containing cap group in designing novel HDACIs. For example, compound 14a[18] exhibited potent in vitro and in vivo anticancer activities. In continuation of our efforts to explore this structural feature and design of new HDACIs, herein, we reported the design, synthesis, and preliminary bioactivity evaluation of N$_1$-hydroxyterephthalamide derivatives with indole cap as HDACIs (Figure 2). Preliminary structure–activity relationship (SAR) studies were also discussed.

1 | EXPERIMENTAL SECTION

1.1 | Chemistry

All commercially available starting materials, reagents, and solvents were used without further purification unless otherwise stated. All reactions were monitored by TLC using 0.25-mm silica gel plates (60GF-254). UV light and ferric chloride were used to visualize the spots. $^1$H NMR spectra were obtained on a Bruker DRX spectrometer (Jinan, China) at 400 or 300 MHz with TMS as an internal standard, $\delta$ in parts per million, and $J$ in hertz. High-resolution mass spectrometry was performed by Shandong Analysis and Test Center in Jinan, China. ESI-MS spectra were recorded on an API 4000 spectrometer. Silica gel was used for column chromatography purification. Flash chromatography was accomplished using the automated Combi Flash Rf system from Teledyne ISCO and was performed using silica gel of 200–300 mesh. Melting points were determined on an electrothermal melting point apparatus.

1.1.1 | General procedure for the preparation of 2

(Tert-butoxycarbonyl)-L-tryptophan (2)

L-tryptophan (10.2 g, 50 mmol) was dissolved in 1 m NaOH (100 mL) aqueous solution, and then, solution of Boc$_2$O (13.08 g, 60 mmol) in THF was added dropwise. After the reaction finished, THF was evaporated. The residual aqueous solution was acidified with 1 N HCl until pH 3–4 and then extracted with EtOAc (3 × 100 mL). The organic layer was washed with brine (2 × 50 mL), dried over Na$_2$SO$_4$ overnight, and then evaporated under vacuum to obtained white solid 2, which was directly used in the next step without further purification.

**FIGURE 1** Pharmacophore model and HDACIs approved by FDA
1.1.2 | General procedure for the preparation of 3

(S)-benzyl 2-((tert-butoxycarbonyl)amino)-3-(1H-indol-3-yl)propanoate (3)

To a solution of 2 (9 g, 30 mmol) in anhydrous CH₂Cl₂ (150 mL) was added HOBT (4.8 g, 36 mmol) and EDCI (6.9 g, 36 mmol) at 0 °C, followed by Et₃N (3.6 g, 36 mmol). After 30 min, phenylmethanol (3.9 g, 36 mmol) was added. After 9 h, the solution of CH₂Cl₂ was washed with 1 M HCl (2 × 40 mL), saturated Na₂CO₃ (2 × 40 mL), and brine (2 × 40 mL) and dried over MgSO₄ overnight, and the solvent was evaporated under vacuum to afford white solid 3, which was directly used in the next step without further purification.

1.1.3 | General procedure for the preparation of 4

(S)-Benzy 1-amino-3-(1H-indol-3-yl)propanoatehydrochloride (4)

Compound 3 (9.9 g, 25 mmol) was dissolved in a solution of EtOAc (100 mL) saturated by dry HCl gas. The solution was stirred at room temperature overnight. The filtered precipitate was washed with diethyl ether to give the white solid powder 4, which was directly used in the next step without further purification.

1.1.4 | General procedure for the preparation of 5

(S)-Methyl-4-((3-(1H-indol-3-yl)-1-oxo-1-(propylamino) propan-2-yl) carbamoyl) benzoate (5)

To a solution of 4-(methoxycarbonyl)benzoic acid (3.6 g, 20 mmol) in anhydrous CH₂Cl₂ was added 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU, 7.7 g, 24 mmol), followed by Et₃N (2.4 g, 24 mmol). After 30 min, compound 4 (6.6 g, 20 mmol) was added followed by Et₃N (2.4 g, 24 mm mol). After 4 h, the reaction solution was washed with 1 M HCl (2 × 40 mL), saturated Na₂CO₃ (2 × 40 mL), and brine (2 × 40 mL) and dried over MgSO₄ overnight and evaporated under vacuum. The desired compound 5 was derived by crystallization in EtOAc as white powder.

1.1.5 | General procedure for the preparation of 6

(S)-3-(1H-indol-3-yl)-2-(4-(methoxycarbonyl) benzamido) propanoic acid (6)

Compound 5 (6.8 g, 15 mmol) was dissolved in 200 mL MeOH, and then, Pd/C of 0.68 g was added. The solution was stirred at room temperature overnight under the atmosphere of hydrogen, was filtered with diatomite, evaporated under vacuum, and washed by diethyl ether to give white solid 6, which was directly used in the next step without further purification.

1.1.6 | General procedure for the preparation of 7b–h

(S)-Methyl-4-((3-(1H-indol-3-yl)-1-oxo-1-(propylamino) propan-2-yl) carbamoyl) benzoate (7b)

To a solution of compound 6 (0.73 g, 2 mmol) in anhydrous CH₂Cl₂ (20 ml) was added propan-1-amine (0.12 g, 2 mmol), benzotriazol-1-yl-oxytripyrrolidino-phosphonium hexafluorophosphate (PyBop, 1.0 g, 2 mmol) at 0 °C, followed by Et₃N (0.2 g, 2 mmol). The solution was stirred at room temperature overnight. The solution was washed with 1 M HCl (2 × 10 mL), saturated Na₂CO₃ (2 × 10 mL), and...
brine (2 × 10 mL) and dried over MgSO₄ overnight, and the solvent was evaporated under vacuum. The desired compound 7b was derived by crystallization in mixture of EtOAc and petroleum ether as white solid.

Compounds 7c–h were prepared using the same procedure as described above.

1.1.7 | General procedure for the preparation of 8a–h and 12a–p

(S)-N\(^1\)-(3-(1H-indol-3-yl)-1-oxo-1-(propylamino)propan-2-yl)-N\(^4\)-hydroxyterephthalalamide (8a)

KOH (38.64 g, 690 mmol) and NH\(_2\)OH HCl (23.35 g, 343 mmol) were dissolved, respectively, in 70 and 120 mL MeOH to obtain solution A and solution B. Next, solution A was added dropwise to solution B. After filtering the precipitate (KCl), a NH\(_2\)OK solution was obtained. Compound 6 (0.38 g, 1 mmol) was dissolved in the NH\(_2\)OK solution and stirred overnight. After the reaction was completed, it was evaporated under vacuum. The residue was acidified with 1 N HCl to a pH 3–4 and then extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine (2 × 30 mL) and dried over Na\(_2\)SO\(_4\) overnight. The crude material was purified via flash chromatography to afford the light brown solid 8a.

Compounds 8b–h and 12a–p were prepared using the same procedure as described above.

1.1.8 | General procedure for the preparation of 9a–h

(S)-tert-butyl (3-(1H-indol-3-yl)-1-oxo-1-(phenylamino)propan-2-yl)carbamate (9a)

Compound 2 (3.0 g, 10 mmol) was dissolved in anhydrous CH\(_2\)Cl\(_2\), and 2-(1H-benzotriazole-1-yl)-1, 3, 3-tetramethyluronium tetrafluoroborate (TBTU, 3.9 g, 12 mmol) was added, followed by Et\(_3\)N (1.2 g, 12 mmol). After 30 min, aniline (1.1 g, 12 mmol) was added. After 4 h, the reaction solution was washed with 1 m HCl (2 × 20 mL), saturated Na\(_2\)CO\(_3\) (2 × 20 mL), and brine (2 × 20 mL), and dried over MgSO\(_4\) overnight, and the solvent was evaporated under vacuum to afford white solid 9a, which was directly used in the next step without further purification.

Compounds 9b–h were prepared using the same procedure as described above.

1.1.9 | General procedure for the preparation of 10a–h

(S)-2-amino-3-((1H-indol-3-yl)-N-phenyl-propionamide hydrochloride (10a)

Compound 9a (3.0 g, 8 mmol) was dissolved in a solution of EtOAc (30 mL) saturated by dry HCl gas. The solution was stirred at room temperature overnight. The filtered precipitate was washed by EtOAc to give white solid powder 10a, which was directly used in the next step without further purification.

Compounds 10b–h were prepared using the same procedure as described above.

1.1.10 | General procedure for the preparation of 11a–h

(S)-Methyl-4-((3-(1H-indol-3-yl)-1-oxo-1-(phenylamino)propan-2-yl)carbamoyl)benzoate (11a)

To a solution of 4-(methoxycarbonyl)benzoic acid (0.9 g, 5 mmol) in anhydrous CH\(_2\)Cl\(_2\) was added 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU, 1.9 g, 6 mmol), followed by Et\(_3\)N (0.6 g, 6 mmol). After 30 min, compound 10a (1.6 g, 5 mmol) was added followed by Et\(_3\)N (0.6 g, 6 mmol). The solution was stirred at room temperature overnight, washed with 1 m HCl (2 × 20 mL), saturated Na\(_2\)CO\(_3\) (2 × 20 mL), and brine (2 × 20 mL), and dried over MgSO\(_4\) overnight, and the solvent was evaporated under vacuum to afford white solid 11a, which was directly used in the next step without further purification.

Compounds 11b–h were prepared using the same procedure as described above.

1.2 | In vitro HDACs inhibition fluorescence assay

In vitro HDACs inhibition assays were conducted as previously described.[16] In brief, 10 μL of HeLa nuclear extract was mixed with various concentrations of target compounds (50 μL), SAHA, using 100% and none HDACs groups as control group, and the mixture. After incubation at 37 °C for 10 min, fluorogenic substrate Boc-Lys (acetyl)-AMC (40 μL) was added and then the mixture was incubated at 37 °C for 30 min. The mixture was stopped by addition of 100 μL of developer containing trypsin and TSA afterward. Over the next incubation at 37 °C for 20 min, fluorescence intensity was measured using a microplate reader at excitation and emission wavelengths of 390 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.

1.3 | Molecular docking studies

Compounds were docked into the active site of HDAC2 (PDB entry: 4LXZ) using tripos sybyl x 2.0. (Certara USA, Inc., Princeton, NJ, USA) Before the docking process, the protein structure was treated by deleting water molecules,
adding hydrogen atoms, fixing atom types, and assigning AMBER7 FF99 charges. A 100-step minimization process was performed to further optimize the protein structure. The molecular structures were generated with the Sybyl/Sketch module and optimized using Powell’s method with the Tripos force field with convergence criterion set at 0.05 kcal/Å mol and assigned charges with the Gasteiger–Hückel method. Molecular docking was carried out via the Sybyl/FlexX module. Other docking parameters were kept to the default values.

1.4 | In vitro antiproliferative assay

In vitro antiproliferative assays were determined by the MTT (3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyl-2H-tetrazolium bromide) method as previously described. All cell lines were maintained in RPMI1640 medium containing 10% FBS at 37 °C in a 5% CO₂ humidified incubator. Cell proliferation assay was determined by the MTT method. Briefly, cells were passaged the day before dosing into a 96-well cell plate, allowed to grow for 12 h, and then treated with different concentrations of compound sample for 48 h. A 0.5% MTT solution was added to each well. After incubation for another 4 h, formazan formed from MTT was extracted by adding 150 μL of DMSO rocking for 15 min. Absorbance was then determined using an ELISA reader at 570 nm.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

Given the reports above, we decided to keep N1-hydroxylterephthalamide with indole cap group as active structural fragments and designed compounds with different substituents, mainly including aliphatic amine and aromatic amine, to evaluate the impact of various functional groups on the inhibitory activities to HDACs. The synthesis of target compounds 8a–h was described in Scheme 1. Briefly, the starting compound of L-tryptophan gave 2 by Boc protection. Compound 2 was reacted with benzyl alcohol to give the ester intermediate 3. Deprotection followed by the coupling reaction with mono-methyl terephthalate in the presence of TBTU afforded 5. Hydrogenation in the presence of Pd/C followed by ester amide exchange reaction produced target compound 8a. On another route, coupling of 6 with various aliphatic amines followed by ester amide exchange reaction with acid yielded 8b–h in good yield. The synthesis of 12a–p followed similar reactions to the synthetic method for compounds 8a–h.

2.2 | HeLa cell extract inhibition of the target compounds

As shown in Table 1, within the aliphatic amide analogs, the chain length seemed to impact the potency dramatically with
the shorter chain analog (8b) being more potent. Compounds 8e–h exhibited comparable potent on the inhibition of HDACs, and this might suggest that steric or hydrophobic interactions were preferred at this specific position. The results of compounds 12b and 12c also supported this notion by showing submicromolar potency. Notably, aromatic amide analogs overall exhibited better inhibitory activities with the exception of compound 12p. When the substitution pattern was compared within this series, the para-substituents gave more potent analogs. Further evaluation revealed that halogenated analogs were preferred at this position and compound 12l with para-iodine was the most potent one with nanomolar potency. This may suggest the substituent size is important at the para-position of the phenyl ring. To extend the confirmation of this notion, compounds 12m–p were designed and evaluated. The results demonstrated that inhibitory potency of 12m to HDACs was comparable to that of 12l and compounds with more bulky substituents such as 12n–p showed decreased potency. Collectively, this may suggest that the optimal size and this position are needed to produce optimal interactions and consequently inhibitory activities.

2.3 Molecular docking of 12m to HDAC2

To better understand the inhibition of 12m to HDACs, docking studies were conducted employing structure of HDAC2.

**TABLE 1** The chemical structures and HDACs inhibitory activities of N1-hydroxyterephthalamide derivatives

| Compound | R   | IC50 of HeLa extract (μM) | Compound | R   | IC50 of HeLa extract (μM) |
|----------|-----|--------------------------|----------|-----|--------------------------|
| 8a       | HO  | 0.227                    | 12f      | Cl  | 0.360                    |
| 8b       |     | 1.654                    | 12g      | Br  | 0.189                    |
| 8c       |     | 1.742                    | 12h      | O   | 0.435                    |
| 8d       |     | >25                      | 12i      |     | 0.202                    |
| 8e       |     | 0.527                    | 12j      |     | 0.150                    |
| 8f       |     | 0.504                    | 12k      |     | 0.096                    |
| 8g       |     | 0.683                    | 12l      | I   | 0.078                    |
| 8h       |     | 0.416                    | 12m      |     | 0.074                    |
| 12a      |     | 0.361                    | 12n      |     | 0.413                    |
| 12b      |     | 0.346                    | 12o      |     | 0.335                    |
| 12c      |     | 0.301                    | 12p      |     | 1.287                    |
| 12d      |     | 0.225                    | SAHA     |     | 0.131                    |
| 12e      |     | 0.234                    |          |     |                          |

*Assays were performed in replicate (n ≥ 2); the SD values are < 20% of the mean.
As shown in Figure 3, the linker of 12m stretches to the bottom of the tunnel and the hydroxamic acid moiety orient can chelate properly with the zinc ion, which is consistent with the chelating type of SAHA. Compared to the sole hydrophobic interaction between the phenyl of SAHA and the amino acid residues around the external motif, the p-methylphenyl and the indole ring of 12m can potentially double-enhance the ligand–receptor bindings of the surface plot near the opening of the tunnel. In addition, the hydroxyl and carbonyl oxygens of 12m have four H-bond interactions with His145, His146, Tyr308, and Asp104, while only two H-bond interactions of SAHA with His146 and Asp104 were displayed. Moreover, the benzene ring, as part linker of 12m, has π–π stacking interactions with the phenyl group of Phe155, which also improves its binding ability to the active site of HDAC2. All the information observed above could rationalize the better inhibitory activity of 12m than SAHA.

### 2.4 HDAC isoform selectivity of 12m

The studies employing the cellular extract demonstrated that compound 12m was the most potent analog and slightly potent than SAHA under these experimental conditions. To further ascertain HDAC isoform selectivity of 12m, we conducted enzymatic inhibitory assays against HDAC1 (class I), HDAC8 (class I), HDAC6 (class IIb), HDAC4 (class IIa), and HDAC11 (class IV). Compound 12m exhibited almost no inhibition to HDAC4 at the concentration of 100 μm and displayed IC₅₀ values close to the magnitude of micromole or nanomole versus other HDAC isoforms, which demonstrated that 12m showed similar selectivity profile with control PXD101 (Table 2).

![Figure 3](image1.png)

**Figure 3** The docking modes of compounds 12m (yellow molecular) and SAHA (green molecular) in the active site of HDAC2, derived by modification of PDB code 4LXZ with tripolar x2.0 (zinc ion is indicated green in the bottom of the tunnel).

![Figure 4](image2.png)

**Figure 4** Inhibition rate of synthesized compounds to U937 and HEL at 5 μm.
2.5  |  In vitro antiproliferative assay

HDACs have been indicated significant roles in the proliferation and differentiation of cancer cells. In the following research, we conducted in vitro antiproliferative evaluation of target compounds in cellular assays. Firstly, we tested the inhibition rate of all synthesized compounds at 5 μM against two human leukemia cell lines (U937 and HEL) as preliminary results shown in Figure 4, compounds 8d, 12d, 12j, and 12m were selected as the representative ones for further antiproliferative evaluation in vitro against five frequently used cancer cell lines (Table 3) and exhibited comparable potency to SAHA in suppressing the growth of HL60 cells, but less inhibition in cellular extract assay, while overall displayed similar activities compared to SAHA in vitro antiproliferative assay. It was likely 8d interacted with complicated binding sites in cancer cells of which main ingredients distinguished from the HeLa cellular extract.

3  |  CONCLUSIONS

In this article, a series of N-hydroxyterephthalamide derivatives with indole cap analogs were designed, synthesized, and biologically characterized as HDACIs. Compounds 12k, 12l, and 12m displayed potent HDAC inhibitory activity compared with control drug SAHA in vitro HeLa cell extract inhibitory fluorescence assay. The most potent compound 12m was also verified by molecular docking studies in the active site of HDAC2 and showed similar overall selectivity profile with control PXD101 in HDAC isoform selectivity assay. Four selected compounds (8d, 12d, 12j, and 12m) demonstrated more potent or comparable antiproliferative activities to SAHA in vitro antiproliferative assay. We found antiproliferative activity of 12m was less potent than SAHA, which was inferior to their enzyme inhibitory activity. One main reason could be that 12m was limited by its poor transcellular permeability so that its specific binding with HDACs was weaker in cells. In addition, 12m was likely to be disintegrated by other enzymes in cells before approaching active site of HDACs. To summarize, the results revealed that N-hydroxyterephthalamide with an indole cap could serve as novel chemical scaffold to develop more potent HDACIs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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**SUPPORTING INFORMATION**

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