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Design, synthesis and biological evaluation of 3, 4-disubstituted-imidazolidine-2, 5-dione derivatives as HDAC6 selective inhibitors

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ABSTRACT

HDAC6 isoform selective inhibitors can be pursued as an alternative to pan-HDACs inhibitors due to their therapeutic effect and low toxicity. Efforts of the structure optimization of our previous compound **10c** (IC_{50} = 4.4 nM) resulted in a new series of 3, 4-disubstituted-imidazolidine-2, 5-dione based HDAC6 inhibitors with better HDAC6 inhibitory activities and improved selectivities. The most potent compound **71** exhibited a low nanomolar HDAC6 inhibitory activity (IC_{50} = 2.1 nM) and showed 5545-fold, 5864-fold as well as 1638-fold selectivity relative to HDAC1, HDAC2 and HDAC8, respectively. Western blot analysis further confirmed that compound **71** selectively increased the acetylation level of α-tubulin without affecting histone H3. Moreover, compound **71** also possesses good properties in term of caspase-3 activation, apoptosis induction, anti-proliferative activity, cytotoxicity and plasma stability. Therefore, compound **71** can be applied in cancer therapy or used as a lead compound to develop more potent HDAC6 selective inhibitor.

1. Introduction

As an epigenetic eraser, histone deacetylases (HDACs) together with histone acetyltransferases (HATs), maintain cellular acetylation homeostasis on histones and non-histone proteins [1,2]. According to the homology structure and cellular localization, 18 HDAC isoforms are phylogenetically divided into 4 classes: Class I (HDAC1, 2, 3 and 8), Class IIa (HDAC 4, 5, 7 and 9), Class IIb (HDAC6 and 10) and Class IV (HDAC11) are zinc-dependent enzymes, whereas Class III (SIRT 1–7) are NAD-dependent enzymes [3]. It is believed that HDACs overexpression is associated with the cancer initiation as well as progression and nowadays, HDACs have been validated as clinical promising targets for the treatment of diverse cancer [4–7]. Efforts of three decades have identified five approved HDACs inhibitors including vorinostat, romidepsin, belinostat, panobinostat and chidamide [8–12]. Although HDACs inhibitors achieve a great success in cancer therapy, approved pan-HDACs inhibitors resulted in severe side effects due to their indiscriminate inhibition toward zinc-dependent HDACs [13–17]. However, HDAC isoform selective inhibitor, which targets specific HDAC isoform, can be pursued as an alternative to pan-HDACs inhibitor [18,19].

As a pivotal member of the HDACs family, HDAC6 is of major significance to the progression, survival and migration of carcinoma cells [20,21]. Accumulating evidence suggested that the inhibition or knockout of HDAC6 could suppress the growth of carcinoma cells [22–24], whereas no obviously defective phenotypes or lethal effects were observed in HDAC6 knockout mice [25–27]. Above research results revealed that HDAC6 selective inhibitors could suppress the growth of carcinoma cells while attenuating the toxicity of current pan-HDAC inhibitors. And some HDAC6 isoform selective inhibitors have been developed, such as Ricolinostat (ACY-1215), Tubastatin A, NOC-7, Tubacin, Nexturastat A and HPOB (Fig. 1A).

Recently, we developed 2,4-imidazolinedione-derived HDAC6 selective inhibitors and compound **10c** showed nanomolar HDAC6 inhibitory activity (Fig. 1B, IC_{50} = 4.4 nM) [28]. To develop more potent and selective HDAC6 inhibitor, we optimized the structure of previous compound **10c.** Briefly, we replaced its long linker with *N*-hydroxybenzamide group, which favorably accommodates HDAC6's wide and shallow catalytic channel. Moreover, HDAC6 isoform selective inhibitors prefer large, bulky cap groups, which are believed to be tolerated by the outer region of HDAC6 binding pocket well. Therefore, imidazolidine-2, 5-dione scaffold with

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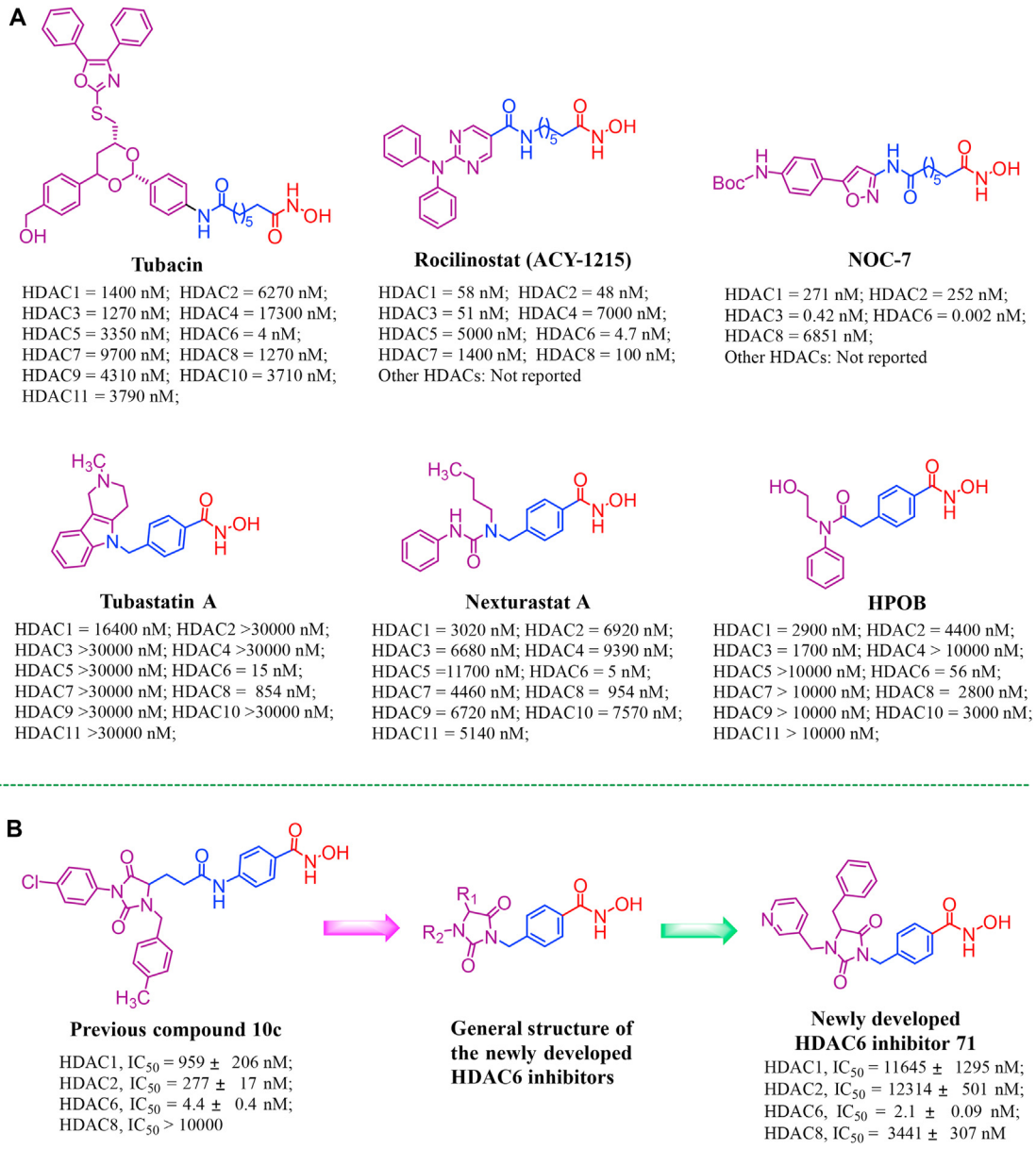


Fig. 1. (A) Reported selective HDAC6 inhibitors; **(B)** Structure optimization of previously reported compound **10c** and newly developed HDAC6 inhibitors.

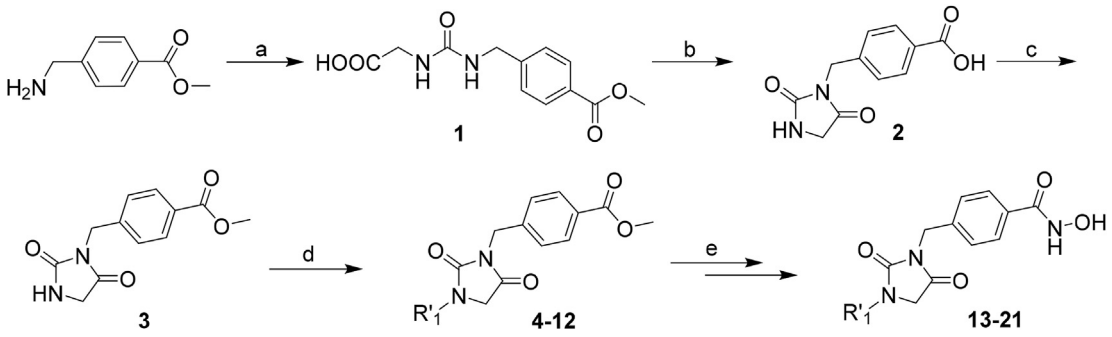
different aromatic rings was used as the cap group of our newly developed HDAC6 inhibitors. Biological evaluations suggested that the most potent compound **71** exhibited a low nanomolar HDAC6 inhibitory activity (IC_{50} = 2.1 nM) and over 1638-fold selectivity against HDAC1, 2 and 8 (Fig. 1B).

Herein, we report the structure optimization and biological evaluations of our newly developed HDAC6 selective inhibitors.

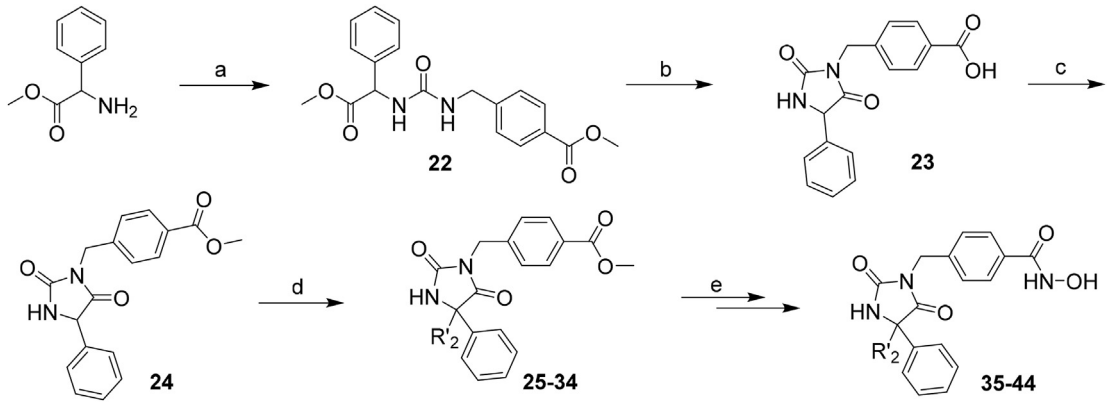
2. Results and discussion

2.1. Synthesis and characterization of target compounds

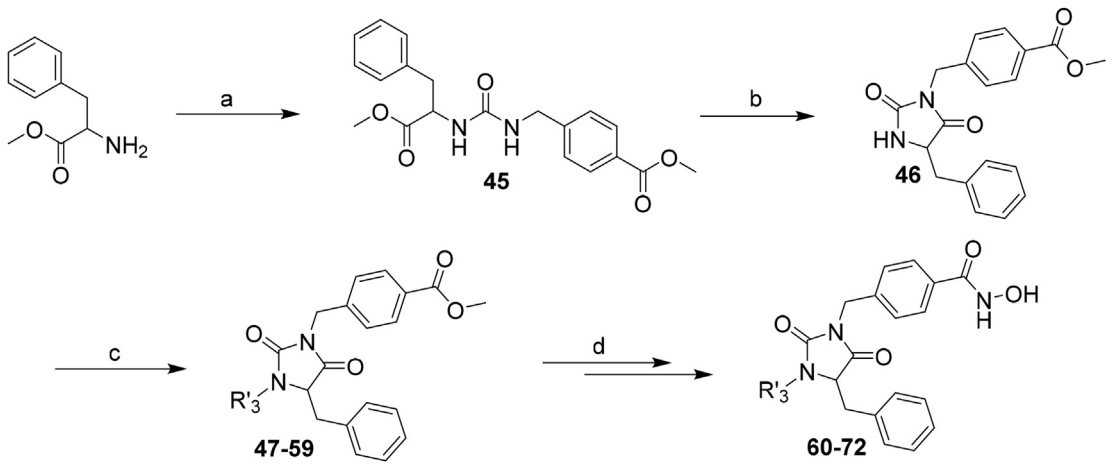
The synthetic methods of target compounds are displayed in Schemes 1–4. For the first series of compounds, intermediate **1** was prepared starting from methyl 4-(aminomethyl)benzoate and glycine. Then intermediate **1** was transformed into intermediate **2** using cyclization reaction in the presence of hydrochloric acid. Subsequently, different side chains were introduced into R_2 position of compound **3** using the *N*-alkylation reactions to synthesize the key intermediates **4**–**12,** which were converted into the first series target compounds **13**–**21** (Scheme 1**).** As for the second series of compounds, 4-(aminomethyl)benzoate and methyl 2-amino-2-phenylacetate were used as starting material for the synthesis of molecule **22,** which was used to prepare molecule **23** with cyclization reaction**.** After protecting the carboxyl group of molecule **23,** the *N*-alkylation reactions were performed to give molecules **25**–**34.** Finally, molecules **25**–**34** were converted into target compounds with transforming ester group into hydroxamic acid (Scheme 2). For the third series of compounds, the cyclization reaction of compound **45** was simply conducted to prepare intermediate **46** in the presence of sodium methoxide. Compound **46** was used to synthesize compounds **60**–**72** by introducing various side chains and transforming easter group into hydroxamic acid (Scheme 3). The fourth series of compounds were synthesized in a manner similar to the synthesis of the third series compounds (Scheme 4).



Scheme 1. Reagents and conditions: (a) (i) Triphosgene, TEA, CH_2Cl_2; (ii) glycine, 2 M NaOH, 0 °C, 4 h, (iii) 6 M HCl, 73%; (b) Hydrochloric acid, reflux, 3 h, 80%; (c) CH_3COCl, MeOH, reflux, 5 h, 98%; (d) R'$_1$-Br, K_2CO_3, KI, DMF, overnight, 75%–97%; (e) (i) LiOH, THF/H_2O, rt, 6 h; (ii) isobutyl chlorocarbonate, 4-Methylmorpholine, THF, $NH_2OH{\cdot}HCl$, KOH, MeOH, rt, 6 h, 39%–81%.



Scheme 2. Reagents and conditions: (a) (i) Triphosgene, TEA, CH_2Cl_2; (ii) Methyl 4-(aminomethyl)benzoate, TEA, 0 °C, 2 h, 74%; (b) Hydrochloric acid, reflux, 3 h, 95%; (c) CH_3COCl, MeOH, reflux, 5 h, 98%; (d) R'$_2$-Br, K_2CO_3, KI, DMF, overnight, 67%–91%; (e) (i) LiOH, THF/H_2O, rt, 6 h; (ii) isobutyl chlorocarbonate, 4-Methylmorpholine, THF, $NH_2OH{\cdot}HCl$, KOH, MeOH, rt, 6 h, 52%–69%.

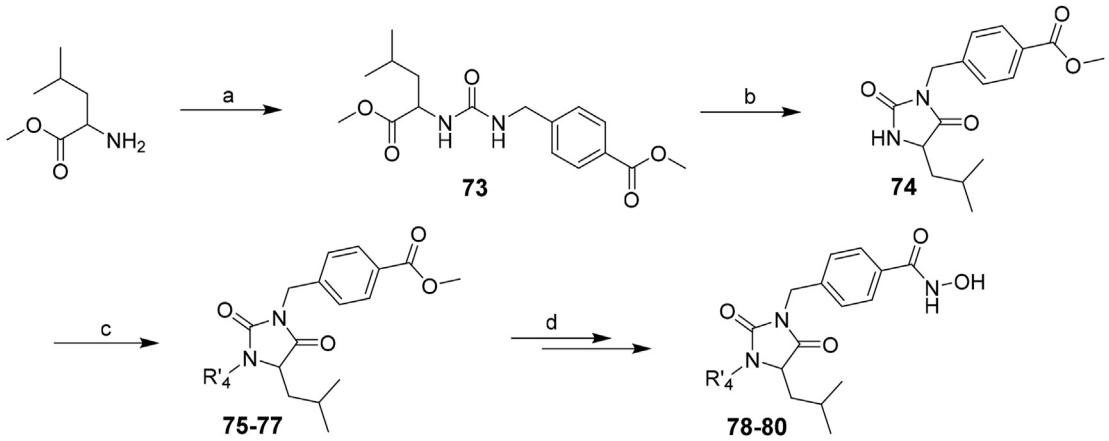


Scheme 3. Reagents and conditions: (a) (i) Triphosgene, TEA, CH_2Cl_2; (ii) Methyl 4-(aminomethyl)benzoate, TEA, 0 °C, 2 h, 71%; (b) CH_3ONa, THF, 1 h, 88%; (c) R'$_3$-Br, K_2CO_3, KI, DMF, overnight, 56%–95%; (d) (i) LiOH, THF/H_2O, rt, 6 h; (ii) isobutyl chlorocarbonate, 4-Methylmorpholine, THF, $NH_2OH{\cdot}HCl$, KOH, MeOH, rt, 6 h, 53%–76%.

2.2. HDAC6 inhibitory activity

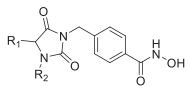
The HDAC6 inhibitory activities of all target compounds were evaluated *in vitro* using fluorescence assay with Tubastatin A and SAHA as the positive control. As shown in Table 1, most of the target compounds exhibited nanomolar HDAC6 inhibitory activities. Structure and activity relationship (SAR) analysis indicated that substituents attached to imidazolidine-2, 5-dione scaffold have influences on HDAC6 inhibitory activities. Compounds **60**–**72** with benzyl in the R_1 position achieve better HDAC6 inhibitory activities compared to compounds **78**–**80** with isobutyl in the R_1 position.

As for the substituents in the R_2 position, benzyl, 4-chlorobenzyl or naphthyl appear to be beneficial to HDAC6 inhibitory activities, whereas alkyl (methyl or propyl) or benzyl containing



Scheme 4. Reagents and conditions: (a) (i) Triphosgene, TEA, CH_2Cl_2; (ii) Methyl 4-(aminomethyl)benzoate, TEA, 0 °C, 2 h, 82%; (b) CH_3ONa, THF, 1 h, 97%; (c) R'$_4$-Br, K_2CO_3, KI, DMF, overnight, 81%–95%; (d) (i) LiOH, THF/H_2O, rt, 6 h; (ii) isobutyl chlorocarbonate, 4-Methylmorpholine, THF, $NH_2OH{\cdot}HCl$, KOH, MeOH, rt, 6 h, 58%–67%.

Table 1
HDAC6 inhibitory activities of target compounds.



Compound	R_1	R_2	IC_{50} (nM)[a]
13	H	methyl	118.5 ± 6.8
14	H	n-propyl	53.4 ± 1.8
15	H	Bn	12.5 ± 0.4
16	H	4-Cl-Bn	8.3 ± 0.9
17	H	4-CH_3-Bn	17.6 ± 1.3
18	H	4-OCH_3-Bn	28.2 ± 5.6
19	H	4-tert-butyl-Bn	40.7 ± 3.6
20	H	phenylethyl	21.7 ± 3.5
21	H	2-methylnaphthalen	13.1 ± 1.6
(±)-35	Ph, methyl	H	74.9 ± 2.5
(±)-36	Ph, n-propyl	H	50.9 ± 3.3
(±)-37	Ph, Bn	H	71.9 ± 9.2
(±)-38	Ph, 4-Cl-Bn	H	54.0 ± 3.3
(±)-39	Ph, 4-CH_3-Bn	H	82.4 ± 5.0
(±)-40	Ph, 4-OCH_3-Bn	H	72.4 ± 4.1
(±)-41	Ph, 4-tert-butyl-Bn	H	114.7 ± 5.9
(±)-42	Ph, phenylethyl	H	24.7 ± 4.4
(±)-43	Ph, 1-methylnaphthalen	H	91.9 ± 3.8
(±)-44	Ph, 2-methylnaphthalen	H	74.6 ± 2.1
(±)-60	Bn	methyl	107.5 ± 4.7
(±)-61	Bn	n-propyl	56.9 ± 6.7
(±)-62	Bn	Bn	21.3 ± 1.6
(±)-63	Bn	4-Cl-Bn	6.0 ± 0.8
(±)-64	Bn	4-CH_3-Bn	37.8 ± 1.8
(±)-65	Bn	4-OCH_3-Bn	102.3 ± 15.1
(±)-66	Bn	4-tert-butyl-Bn	139.3 ± 13.4
(±)-67	Bn	phenylethyl	20.2 ± 0.1
(±)-68	Bn	1-methylnaphthalen	28.8 ± 2.9
(±)-69	Bn	2-methylnaphthalen	25.1 ± 1.0
(±)-70	Bn	2-methylpyridine	4.8 ± 1.8
(±)-71	Bn	3-methylpyridine	2.1 ± 0.09
(±)-72	Bn	4-methylpyridine	13.9 ± 2.4
(±)-78	Isobutyl	methyl	251.4 ± 10.1
(±)-79	Isobutyl	n-propyl	174.0 ± 11.5
(±)-80	Isobutyl	Bn	129.2 ± 6.0
Tubastatin A	–	–	27.4 ± 0.7
SAHA	–	–	26.9 ± 3.2

[a] All compounds were assayed at least two times, and the results are expressed as mean ± standard error of the mean (SEM).

alkyl (4-methylbenzyl, 4-methoxybenzyl or 4-tert-butylbenzyl) impair the HDAC6 inhibitory activities. Above results indicated that the outer surface region of HDAC6 occupied by the R_2 group may be composed of polar residues and the hydrophobic alkyl or the benzyl containing alkyl are unable to favorably accommodate the polar pocket, thereby reducing their contributions to HDAC6 inhibitory activities. Therefore, we subsequently introduced pyridine ring, a polar group, into the R_2 position. *In vitro* evaluations suggested that

these compounds containing a pyridine ring (compounds **70, 71** and **72**) achieve better HDAC6 inhibitory activities. In our present study, the most potent compound **71** exhibits a low nanomolar HDAC6 inhibition (IC_{50} = 2.17 nM) and its HDAC6 inhibitory activity is 12-fold better than that of Tubastatin A (IC_{50} = 27.44 nM).

Subsequently, computational modelling of compound **71** was employed to investigate its good HDAC6 inhibitory activity. After protein preparation and grid generation, ***(R)*-71** or ***(S)*-71** was calculated into the HDAC6 (PDB ID: 5EDU) binding site by means of GLIDE (Glide, version 11.5, Schrodinger). Molecular docking studies suggested that the hydroxamate moiety of ***(R)*-71** or ***(S)*-71** chelates zinc ion well and the pyridine group of ***(R)*-71** or ***(S)*-71** forms hydrogen bond with H651 residue (Fig. 2). The presence of H651 residue at the outer surface region of HDAC6 explains why the introduction of the pyridine group could improve the HDAC6 inhibitory activity, while the introduction of alkyl or benzyl containing alkyl impair HDAC6 inhibitory activity.

2.3. HDAC isoform selectivity

For potent compounds (compounds **16, 63, 70** and **71**) with a low nanomolar HDAC6 inhibitory activities, we subsequently investigated their HDAC isoform selectivities against HDAC1, HDAC2 and HDAC8 (Table 2). The results indicated that R_1 group plays an essential role in HDAC6 isoform selectivity. Despite compound **16** with no substituent in R_1 position shows good HDAC6 isoform selectivity (103-fold, 130-fold and 119-fold selectivity toward HDAC1, HDAC2 and HDAC8, respectively), the introduction of benzyl group into R_1 position of compound **16** improves its HDAC6 isoform selectivity greatly (compound **63**, 1362-fold, 1377-fold and 664-fold selectivity against HDAC1, HDAC2 and HDAC8, respectively).

In addition, the most potent compound **71** possesses good HDAC6 isoform selectivity and it displays 5545-fold selectivity against HDAC1, 5864-fold selectivity against HDAC2 as well as 1638-fold selectivity relative to HDAC8. Given the good HDAC6 inhibitory activity and HDAC6 isoform selectivity of compound **71**, it was chosen for further biological evaluations.

2.4. In vitro anti-proliferative activity

HDAC6 isoform selective inhibitors have emerged as an alternative to pan-HDACs inhibitor for the anti-cancer therapy because they could attenuate the toxicity of current pan-HDACs inhibitors while remaining therapeutic effect. Therefore, we evaluated the anti-proliferative activity of compound **71**. As the results summarized in Table 3, compound **71** shows low micromolar anti-proliferative activities against various human leukemia cell lines (KG1, IC_{50} = 7.04 μM; Jurkat, IC_{50} = 9.29 μM; HEL, IC_{50} = 4.58 μM and HL-60, IC_{50} = 3.23 μM) and human multiple myeloma (NCI−H929, IC_{50} = 7.61 μM). Notably, compound **71** possessed better anti-proliferation activity than Tubastatin A.

2.5. Western blot

To confirm that the anti-proliferative activities of compound **71** are the effect of HDAC6 inhibition instead of HDAC1 or HDAC2 inhibition, Western blot analysis was performed. As shown in Fig. 3, compound **71**, strongly increase the acetylation level of α-tubulin (a major substrate for HDAC6) in a time-dependent and dose-dependent manner, whereas it has only a slight effect on the acetylation of histone H3 (a major substrate of HDAC1 and HDAC2). The results indicated that our HDAC6 inhibitor **71** could suppress the growth of carcinoma cells by inhibiting HDAC6 instead of HDAC1 or HDAC2.

2.6. Mitochondrial depolarization assay (mtΔΨ) and Caspase-3 activation assay in HL-60 cells

Literature revealed that HDAC6 inhibition induces the acetylation of Ku70, thus regulating the interaction between Ku70 and Bax, and initiates the dissociation of Bax from Ku70, followed by mitochondrial outer membrane permeabilization (MOMP), caspase cascade events and apoptosis [29−33]. Therefore, we explored the mitochondrial potential changes and caspase-3 activation in HL-60 cells treated with compound **71**.

Following incubation with 3 μM compound **71**, the mitochondrial potential change was determined using tetramethylrhodamine ethyl ester (TMRE). As shown in Fig. 4A, the significant mitochondrial potential loss was observed and compound **71** induced mitochondrial depolarization in a time-dependent manner.

As for caspase-3 activation, incubating compound **71** significantly increased the amount of activated caspase-3 in HL-60 cells compared with vehicle (0.2% DMSO). As the incubation time increases, more and more caspase-3 was activated. It is worth

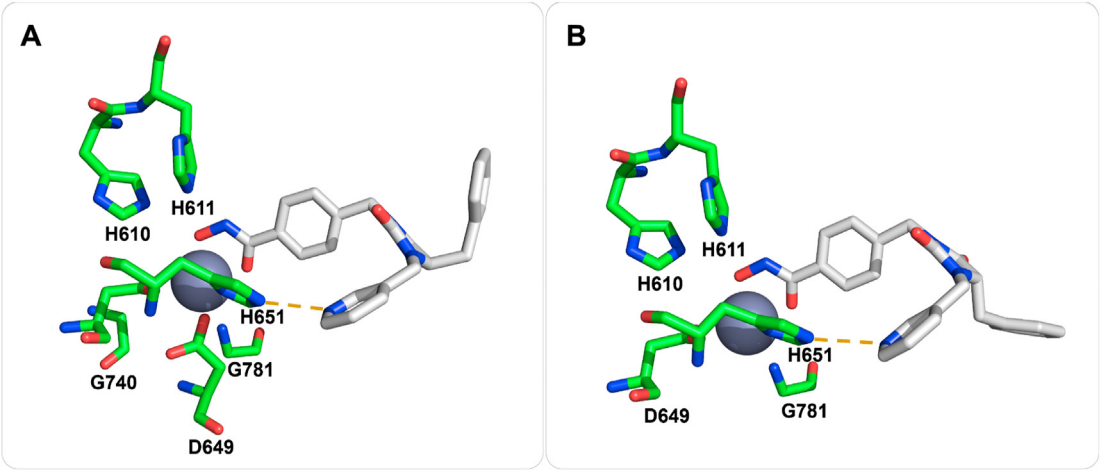


Fig. 2. (A) Proposed binding mode of **(*R*)-71** (depicted in gray) in the HDAC6 binding site; (B) Proposed binding mode of **(*S*)-71** (depicted in gray) in the HDAC6 binding site. Hydrogen bonds were shown as yellow dotted line and the zinc ion was shown as a gray sphere.

Table 2
HDACs isoform profiles of potent target compounds.

Compound	IC_{50} (nM) [a]			
	HDAC1	HDAC2	HDAC6	HDAC8
16	862.5 ± 17.5	1082.0 ± 145.0	8.3 ± 0.9	994.0 ± 18.1
63	8176.5 ± 1095.5	8263.9 ± 451.6	6.0 ± 0.8	3987.5 ± 298.5
70	3422.0 ± 235.0	5081.0 ± 178.9	4.8 ± 1.8	7826.0 ± 98.1
71	11645.0 ± 1295.0	12314.4 ± 501.0	2.1 ± 0.09	3441.0 ± 307.0
Tubastatin A	7582.5 ± 145.5	8674.5 ± 1119.5	27.4 ± 0.7	1899.0 ± 105.0
SAHA	45.5 ± 0.5	112.5 ± 2.5	26.9 ± 3.2	1279.3 ± 32.9

[a] The results are expressed as mean ± SEM (n ≥ 2).

Table 3
Anti-proliferative activity of compound 71.

Compound	IC_{50} (μM)[a]				
	KG1	HEL	Jurkat	HL-60	NCI−H929
71	7.04 ± 1.03	4.58 ± 0.06	9.29 ± 1.61	3.23 ± 0.09	7.61 ± 0.76
Tubastatin A	8.82 ± 0.36	8.09 ± 0.24	14.58 ± 1.03	4.09 ± 0.09	15.42 ± 1.48

[a] The results are expressed as mean ± SEM (n ≥ 3).

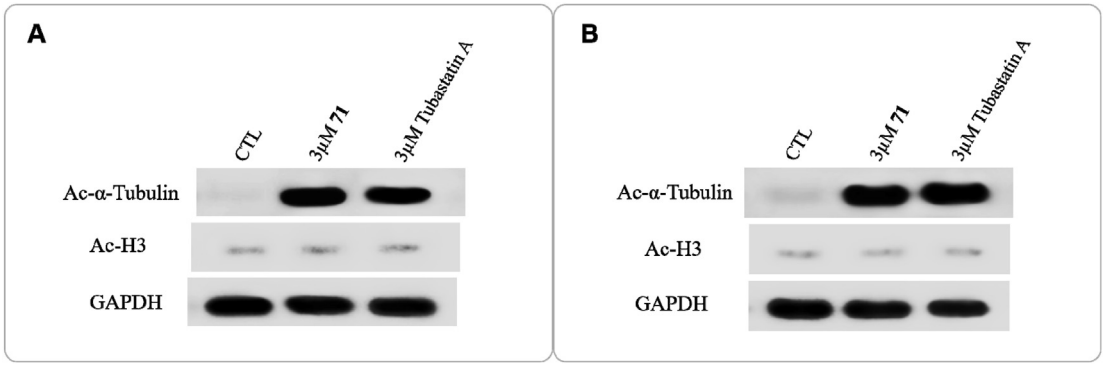


Fig. 3. The acetylation of α-tubulin and histone H3 induced by compound **71** or Tubastatin A for 12 h **(A)** and 24 h **(B)** in HL-60 cells.

mentioning that compound **71** exhibits the better property in term of caspase-3 activation compared with Tubastatin A (Fig. 4B).

2.7. TUNEL assay on HL-60 cells

Subsequently, TUNEL assay was designed to investigate the ability of compound **71** to induce apoptosis in HL-60 cells. As illustrated in Fig. 5, weak green fluorescence was observed in HL-60 cells incubated Tubastatin A, whereas the HL-60 cells treated with compound **71** were labeled with stronger green fluorescence. In other words, compound **71** has the stronger ability to induce apoptosis compared to Tubastatin A in HL-60 cells.

2.8. Flow cytometry analysis on HL-60 cells

To further determine the apoptotic rate of HL-60 cells in response to compound **71** or Tubastatin A, flow cytometry analysis was performed (Fig. 6). Upon treatment with Tubastatin A or compound **71** for 48 h, HL-60 cells displayed modest apoptosis (apoptotic rates are 12.36% and 20.50%, respectively). The results are consistent of TUNEL assay.

2.9. Cytotoxicity studies

We also evaluated the cytotoxicity of compound **71** and Tubastatin A toward normal-tissue cells (HUVECs and GEC-1 cells). Compound **71** and Tubastatin A exhibit acceptable cytotoxicity toward HUVECs (Fig. 7A) and GEC-1 cells (Fig. 7B). Notably, our compound **71** could kill HL-60 cells selectively and spare normal-tissue cell lines.

2.10. Stability of compound 71 in rabbit plasma

Finally, we preliminarily investigated the plasma stability of compound **71**. Upon treatment compound **71** with rabbit plasma for indicated times (0, 0.5, 1, 3, 6, 9, and 12 h), the recovered compound was measured using HPLC and a small amount of compound **71** was degraded (Fig. 8). The result indicates that compound **71** possesses good plasma stability.

3. Conclusion

Efforts of the structure optimization of previous compound **10c** (IC_{50} = 4.4 nM) resulted in a series of more potent and selective HDAC6 inhibitors. Compound **71,** the most potent molecule, has a low nanomolar inhibitor activity for HDAC6 (IC_{50} = 2.1 nM), and improved selectivity against HDAC1, HDAC2 and HDAC8, respectively. Western blot analysis further confirmed that compound **71** selectively increased the acetylation level of α-tubulin with a slight effect on the acetylation of histone H3. Moreover, compound **71** can induce mitochondrial outer membrane permeabilization (MOMP), caspase-3 activation and apoptosis. In the other hand, compound

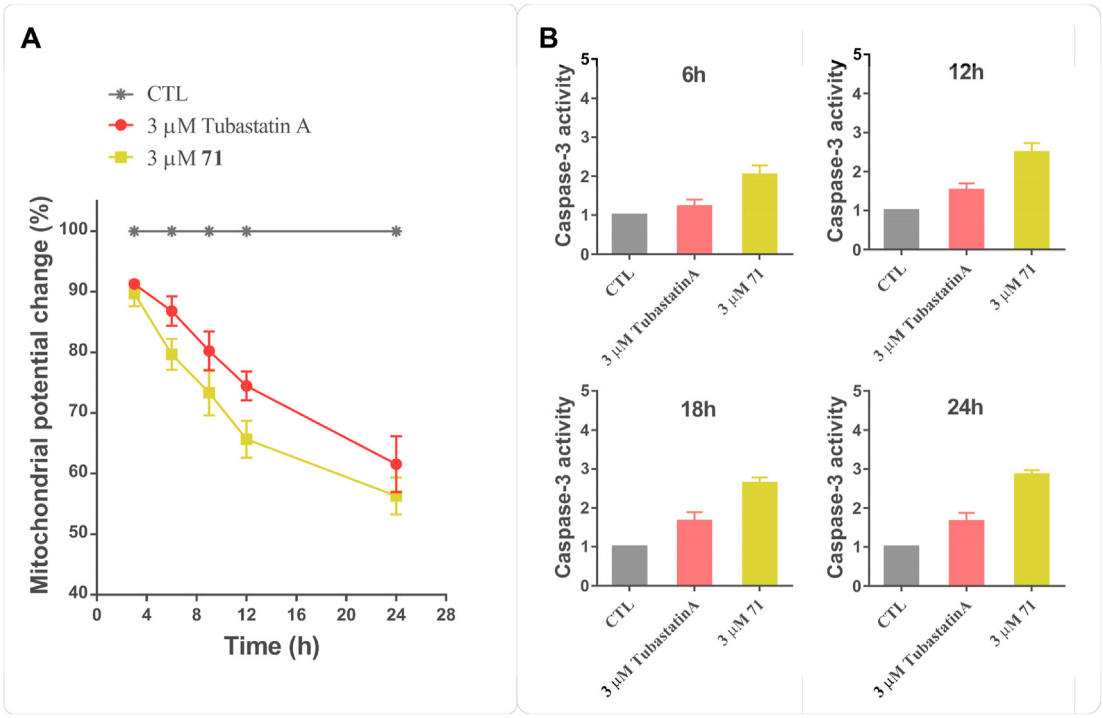


Fig. 4. Mitochondrial potential changes **(A)** and caspase-3 activation **(B)** in HL-60 cells treated compound **71** or Tubastatin A for indicated time.

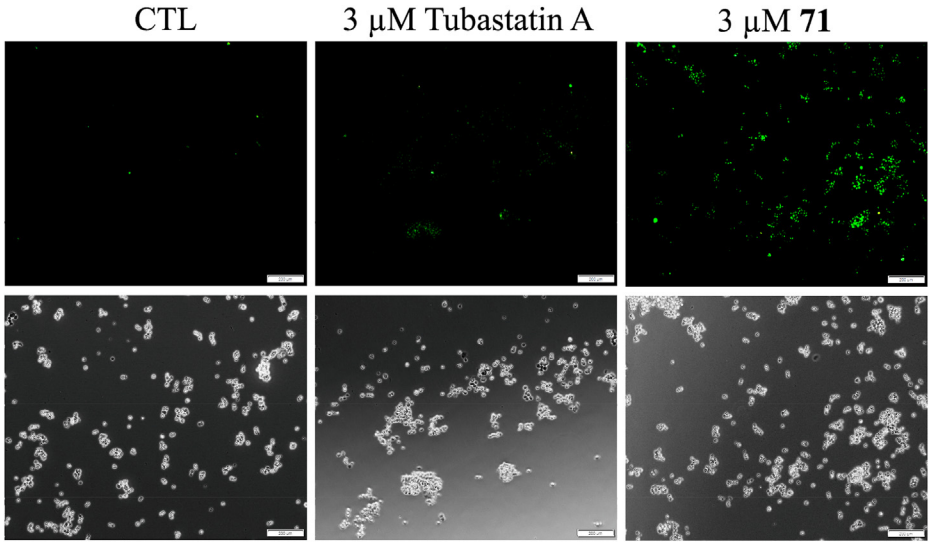


Fig. 5. TUNEL assay in HL-60 cells treated with compound **71** and Tubastatin A.

71 also possesses good properties in term of anti-proliferative activities, plasma stability and cytotoxicity. In summary, our compound **71** demonstrates a paradigm for anti-cancer therapy using HDAC6 selective inhibitor and it can also be used as lead compound to develop more potent and selective HDAC6 inhibitor.

4. Materials and methods

4.1. Biological evaluations

4.1.1. HDAC6 inhibitory activities

The HDAC6 inhibitory activities of all target compounds were evaluated using a fluorescence assay with Tubastatin A as the positive control. Generally, HDAC6 enzyme was incubated with a range of concentrations of test compounds for 10 min at 37 °C, followed by the addition of fluorogenic substrates (Ac-LeuGlyLys(Ac)-AMC). After incubating for 2 h, the reaction was quenched by developer containing TSA and trypsin. Incubate the mixture at 37 °C for another 30 min, and measure the fluorescence intensity with the excitation and emission wavelength of 390 nm and 460 nm using a Thermo Varioskan microtiter plate reader. The data was analyzed to calculate the inhibition ratios and IC_{50} values.

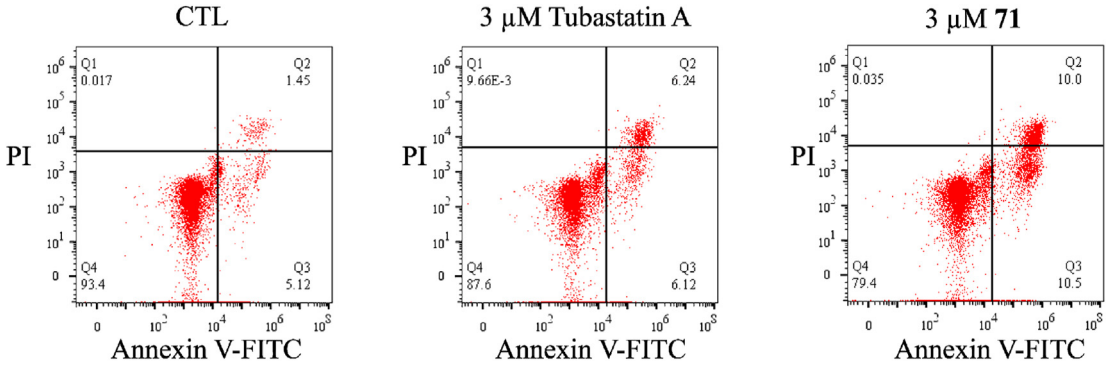


Fig. 6. Flow cytometry analysis of HL-60 cells treated with compound **71** or Tubastatin A.

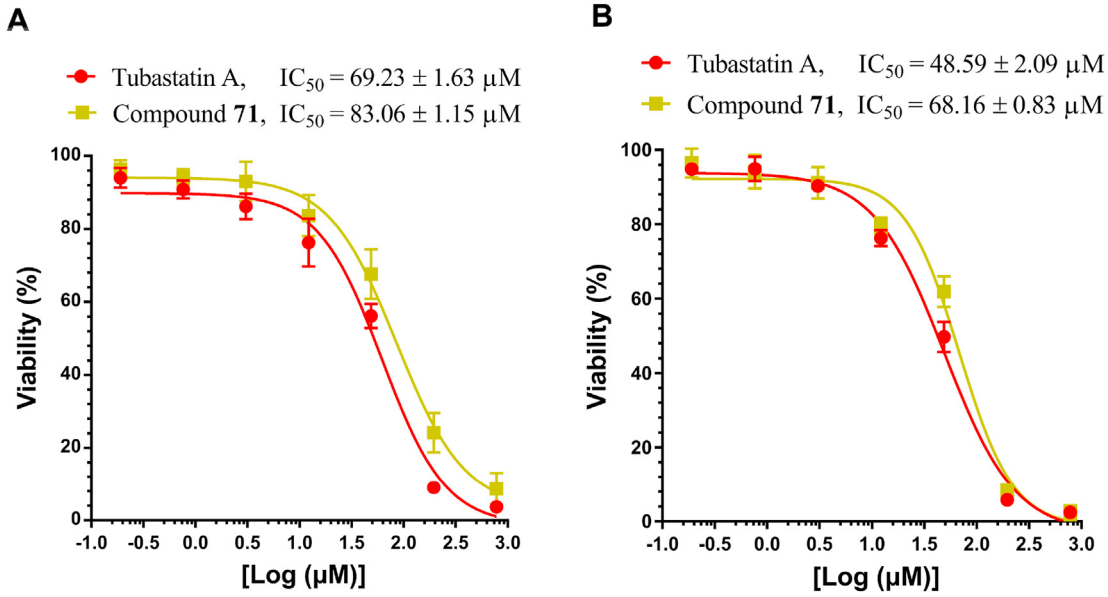


Fig. 7. Cytotoxicity of compound **71** and Tubastatin A against HUVECs (**A**) and GEC-1 cells (**B**).

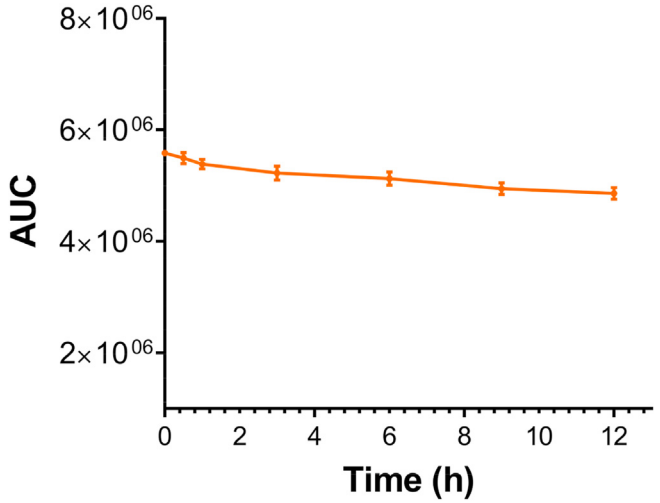


Fig. 8. The stability of compound **71** in rabbit plasma.

4.1.2. HDACs isoform selectivity

HDAC1, 2 and 8 were incubated with a serial dilutions of the tested compounds for 10 min, and the fluorogenic substrate (Ac-LeuGlyLys(Ac)-AMC substrate for HDAC1 and 2; Ac-LeuGlyLys(tfa)-AMC substrate for HDAC 8) were added, followed by incubation for 1 h. After quenching the reaction with developer, incubate the mixture at 37 °C for another 30 min. Subsequently, measure the fluorescence intensity with a Thermo microtiter plate reader with an excitation of 390 nm and an emission wavelength of 460 nm. Then Varioskan Prism Graph Pad software was used to calculate the IC_{50} values.

4.1.3. In vitro Antiproliferative activities

All of the cell lines were cultured with RPMI1640 medium (10% FBS) at 37 °C in a 5% CO_2 humidified incubator. After seeding the cells in 96-well plates at 3500−4000 cells per well (100 μL/well), the cells were cultured overnight, followed by treatment with the indicated dilutions of compound **71** (100 μL/well) for 48 h. Add 10 μL 0.5% MTT to each well and incubate the mixture for another 4 h. Subsequently, centrifuge and remove the supernatant carefully, followed by the addition of 150 μL DMSO. A Thermo Varioskan microtiter-plate reader was used to analyze the absorbance at 570 nm. The inhibition ratios and IC_{50} values were calculated with Prism Graph Pad software.

4.1.4. Western blot

Treated HL-60 cells were harvested (800 rpm, 5 min) and lysed with 1 × RIPA buffer containing 1 mM PMSF on ice for 30 min. Collect the supernatant (4 °C, 14000 rpm, 10 min) and boil it in loading buffer. Then samples were electrophoretically separated on 12.5% SDS PAGE gel and transferred to PVDF membrane, followed by being blocked with 5% nonfat dry milk for 1 h. Subsequently, the membranes were washed with TBST and incubated with primary anti-bodies of Ac- α-tubulin Ac-H3 and GAPDH overnight at 4 °C. Finally, wash the membranes with TBST for another three times and incubate them with the secondary antibody for 1 h, followed by ECL reaction. Images of the member were monitored with an Amersham Imager 680.

4.1.5. TUNEL assay

TUNEL assay was designed to detect apoptotic HL-60 cells. HL-60 cells (1×10^6 cells/well) in 6-well clear bottom plates were incubated with 3 μM compound **71**, 3 μM Tubastatin A or vehicle (0.2% DMSO) for 48 h. Above cells were washed with pre-chilled PBS and incubated with paraformaldehyde for 30 min. Then they were treated with 0.5% Tritonx-100 in PBS for 5 min and washed with cold PBS. After adding FITC-12-Dutp and terminal deoxynucleotidyl transferase, the cells were incubated for 60 min. Wash the cells two times with cold PBS buffer to eliminate background fluorescence and the green fluorescence was monitored with a Zeiss Axio Observer A1 fluorescence microscope.

4.1.6. Flow-cytometry analysis

Flow-cytometry analysis was performed on HL-60 cells. Cells (1×10^6 cells/well) in 6-well clear bottom plates were incubated with indicated dilutions of tested compounds for 48 h and then cells were collected and washed with PBS. Subsequently, resuspend cells with 195 μL Annexin V-FITC binding buffer, followed by the addition of 5 μL propidium iodide (PI) and 2.5 μL Annexin V-FITC. After incubating for 15 min, the samples were analyzed with flow cytometry.

4.1.7. Mitochondrial depolarization assay (mtΔΨ)

1×10^6 HL-60 cells were seeded in 6-well plate and then they were cultured overnight. Following treatment with compound **71**, Tubastatin A or vehicle (0.2% DMSO) for indicated time, cells were incubated with tetramethylrhodamine ethyl ester (100 nM) for 30 min at 37 °C. Subsequently, collect and wash cells with PBS for three times and then transfer them into a black 96-well plate, followed by the analysis of the fluorescence intensity (Ex: 540 nm, Em: 579 nm).

4.1.8. Caspase 3 activation assay

The caspase-3 activation in treated HL-60 cells was measured using GreenNuc™ Caspase-3 Assay Kit for Live Cells. HL-60 cells were seeded in 6-well clear bottom plate for 8 h. Upon treatment with indicated concentrations of tested compounds or vehicle (0.2% DMSO) for different time (6 h, 12 h, 18 h and 24 h), cells were harvested and washed with PBS buffer. After incubating with GreenNuc™ Caspase-3 substrate for 30 min, transfer the cells into a black 96-well plate and measure the fluorescence intensity (Ex: 485 nm, Em: 515 nm). The results are expressed as fold increase in caspase activity of apoptotic cells over that of non-induced cells.

4.1.9. Stability of compound 71 in rat plasma

200 μL rabbit plasma was incubated with the solution of compound **71** (50 μL, 2 mg/mL in DMSO) at 37 °C for indicated time (0 h, 0.5 h, 1 h, 3 h, 6 h, 9 h and 12 h). Add 600 μL acetonitrile and then the suspension was centrifuged and filtered. HPLC was performed to analyze the samples with a C_{18} column (150 mm × 4.6 mm, 5 μm) at a flow rate of 1 mL/min. The mobile phase consists of 42% acetonitrile and 58% H_2O containing 0.1% formic acid.

4.1.10. Cytotoxicity studies

Normal-tissue cells (HUVECs and GEC-1 cells) was selected to evaluate the cytotoxicity of tested compounds. HUVECs were cultured with RPMI1640 medium containing 10% FBS as well as 0.1% heparin and GEC-1 cell lines were cultured with RPMI1640 medium containing 10% FBS. HUVECs and GEC-1 cells were seeded in a 96-well plate for 8 h and then treated with the indicated dilution of tested compounds for 48 h. Following incubation with 0.5% MTT for 4 h, the supernatant was removed and DMSO was added. Finally, the absorbance was determined using a Thermo Varioskan microtiter-plate reader at 570 nm.

4.1.11. Molecular docking

The crystal structure of human HDAC6 (PDB ID: 5EDU) was selected for molecular docking studies using GLIDE (Glide, version 11.5, Schrodinger). After protein preparation and grid generation, ***(S)*-71 or *(R)*-71** was calculated into HDAC6 binding site and the top scored binding poses were chosen as proposed binding modes.

4.2. Chemistry

All chemical reagents are analytical grade and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates (60 GF-254). Melting points were determined by the RY-1 electrothermal melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Brucker DRX spectrometer at 400 MHz. High-resolution mass spectra (HRMS) were conducted on an Agilent 6510 quadrupole time-off light liquid chromatography/mass spectrometer (LC/MS) delivered with electrospray ionization (ESI). The purities of target compounds were determined by reversed-phase (RP)-HPLC and they achieved a minimum of 95% purity.

4.2.1. ((4-(methoxycarbonyl)benzyl)carbamoyl)glycine (1)

To the solution of triphosgene (23.74 g, 80 mmol) in CH_2Cl_2, the solution of methyl 4-(aminomethyl)benzoate (33.04 g, 200 mmol) with triethylamine (55.60 mL, 400 mmol) was added slowly under ice bath. Stir the mixture for 30 min at 0 °C and then the solvent was removed to give methyl 4-(isocyanatomethyl)benzoate. Glycine (30.03 g, 400 mmol) was dissolved with 2 M NaOH (200 mL) and the solution of methyl 4-(isocyanatomethyl)benzoate in toluene (200 mL) was added. After stirring the mixture for 3 h, the water phase was acidified (pH = 2) with 6 M HCl and the product was obtained by filtration. White solid, yield: 73%, mp 191–192 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (s, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 6.78 (t, J = 5.9 Hz, 1H), 6.29 (t, J = 5.6 Hz, 1H), 4.29 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 3.72 (d, J = 5.8 Hz, 2H).

4.2.2. 4-((2,5-dioxoimidazolidin-1-yl)methyl)benzoic acid (2)

The intermediate **1** (39.93 g, 150 mmol) was dissolved using hydrochloric acid (300 mL), followed by refluxing for 3 h. After cooling the reaction solution down, the white crystal precipitation was isolated to give compound **2**. White solid, yield: 80%, mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 8.18 (s, 1H), 7.91 (d, J = 8.4, 2.0 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.60 (s, 2H), 4.01 (s, 2H).

4.2.3. Methyl 4-((2,5-dioxoimidazolidin-1-yl)methyl)benzoate (3)

To the solution of compound **2** (32.78 g, 140 mmol) in MeOH, acetyl chloride (25.2 mL, 350 mmol) was slowly added at 0 °C and the mixture was refluxed for 5 h. Cool the reaction solution down

and the solvent was evaporated under vacuum. The crude product was washed with n-hexane to give a white solid, yield: 98%, mp 178–180 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 6.10 (s, 1H), 4.71 (s, 2H), 4.01 (d, J = 1.1 Hz, 2H), 3.91 (s, 3H).

4.2.4. Methyl 4-((3-methyl-2,5-dioxoimidazolidin-1-yl)methyl) benzoate (4)

Compound **4** was mixed with K_2CO_3 (2.48 g, 10 mmol) and iodomethane (0.74 g, 12 mmol) in 50 mL DMF for 6 h. Poured the mixture into cool water and extracted three times with ethyl acetate. Dry the organic phases over with $MgSO_4$ and then the organic solvent was concentrated to give the crude product, which was purified by silica gel column chromatography. White solid, yield: 97%, mp 119–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 4.69 (s, 2H), 3.98–3.84 (m, 5H), 3.00 (s, 3H).

4.2.5. Methyl 4-((2,5-dioxo-3-propylimidazolidin-1-yl)methyl) benzoate (5)

The title compound was synthesized from **3** and 1-iodopropane in a manner similar to that described for the preparation of **4.** White solid, yield: 75%, mp 73–74 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 4.62 (s, 2H), 4.06 (s, 2H), 3.84 (s, 3H), 3.26 (s, 2H), 1.52 (q, J = 7.3 Hz, 2H), 0.85 (t, J = 7.4 Hz, 3H).

4.2.6. Methyl 4-((3-benzyl-2,5-dioxoimidazolidin-1-yl)methyl) benzoate (6)

The title compound was synthesized from **3** and benzyl bromide in a manner similar to that described for the preparation of **4.** White solid, yield: 94%, mp 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.40–7.32 (m, 3H), 7.24 (dd, J = 7.9, 1.7 Hz, 2H), 4.73 (s, 2H), 4.56 (s, 2H), 3.91 (s, 3H), 3.76 (s, 2H).

4.2.7. Methyl 4-((3-(4-chlorobenzyl)-2,5-dioxoimidazolidin-1-yl) methyl)benzoate (7)

The title compound was synthesized from **3** and *1-(bromomethyl)-4-chlorobenzene* in a manner similar to that described for the preparation of **4.** White solid, yield: 94%, mp 121–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 4.72 (s, 2H), 4.53 (s, 2H), 3.91 (s, 3H), 3.75 (s, 2H).

4.2.8. Methyl 4-((3-(4-methylbenzyl)-2,5-dioxoimidazolidin-1-yl) methyl)benzoate (8)

The title compound was synthesized from **3** and *1-(bromomethyl)-4-methylbenzene* in a manner similar to that described for the preparation of **4.** White solid, yield: 95%, mp 132–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.14 (q, J = 8.1 Hz, 4H), 4.72 (s, 2H), 4.51 (s, 2H), 3.91 (s, 3H), 3.73 (s, 2H), 2.34 (s, 3H).

4.2.9. Methyl 4-((3-(4-methoxybenzyl)-2,5-dioxoimidazolidin-1-yl) methyl)benzoate (9)

The title compound was synthesized from **3** and *1-(bromomethyl)-4-methoxybenzene* in a manner similar to that described for the preparation of **4.** White solid, yield: 94%, mp 129–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.71 (s, 2H), 4.49 (s, 2H), 3.91 (s, 3H), 3.80 (s, 3H), 3.73 (s, 2H).

4.2.10. Methyl 4-((3-(4-(tert-butyl)benzyl)-2,5-dioxoimidazolidin-1-yl)methyl)benzoate (10)

The title compound was synthesized from **3** and *1-(bromomethyl)-4-(tert-butyl)benzene* in a manner similar to that described for the preparation of **4.** White solid, yield: 95%, mp 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 4.72 (s, 2H), 4.53 (s, 2H), 3.91 (s, 3H), 3.76 (s, 2H), 1.31 (s, 9H).

4.2.11. Methyl 4-((2,5-dioxo-3-phenethylimidazolidin-1-yl)methyl) benzoate (11)

The title compound was synthesized from **3** and *(2-bromoethyl) benzene* in a manner similar to that described for the preparation of **4.** White solid, yield: 83%, mp 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 13.7, 8.2 Hz, 2H), 7.44–7.35 (m, 2H), 7.35–7.27 (m, 3H), 7.19–7.14 (m, 2H), 4.66 (d, J = 2.4 Hz, 2H), 4.52 (s, 1H), 3.91 (s, 2H), 3.66 (s, 3H), 3.08 (d, J = 6.9 Hz, 1H), 2.89 (t, J = 7.1 Hz, 2H).

4.2.12. Methyl 4-((3-(naphthalen-1-ylmethyl)-2,5-dioxoimidazolidin-1-yl)methyl) benzoate (12)

The title compound was synthesized from **3** and *1-(bromomethyl)naphthalene* in a manner similar to that described for the preparation of **4.** White solid, yield: 82%, mp 197–199 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–8.06 (m, 1H), 8.00 (d, J = 8.1 Hz, 2H), 7.93–7.84 (m, 2H), 7.58–7.52 (m, 2H), 7.44 (dd, J = 10.7, 8.2 Hz, 3H), 7.38 (dd, J = 7.0, 1.4 Hz, 1H), 5.02 (s, 2H), 4.72 (s, 2H), 3.91 (s, 3H), 3.61 (s, 2H).

4.2.13. N-hydroxy-4-((3-methyl-2,5-dioxoimidazolidin-1-yl) methyl)benzamide (13)

To the solution of compound **4** (1.57 g, 6 mm0l) in THF, the aqueous solution of LiOH was added and the mixture was stirred for 6 h. After removing THF, the water phase was acidified, followed by extracting three times using ethyl acetate. Then, the organic solvent was evaporated under vacuum to give the hydrolysate without further purification.

Subsequently, the hydrolysate (0.74 g, 3 mmol) was dissolved with THF and then isobutyl chloroformate (0.42 mL, 3.3 mmol) as well as *N*-methylmorpholine (0.43 mL, 3.9 mmol) were added. After stirring the mixture for 30 min, the freshly prepared hydroxylamine (0.40 g, 12 mmol) in methanol was added and the reaction solution was stirred for another 6 h at room temperature. The solvent was concentrated and the residue was dissolved in 50 ml ethyl acetate, followed by washing with 1 M HCl and saturated brine. The crude product was purified by silica gel column chromatography to give a white solid, yield: 39%, mp 194–196 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.02 (s, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.58 (s, 2H), 4.04 (s, 2H), 2.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.75, 164.45, 156.71, 140.23, 132.37, 127.79, 127.55, 51.88, 41.63, 29.71. HRMS (AP-ESI) m/z, calculated for $C_{12}H_{13}N_3O_4$, ($[M + H]^+$): 264.0979, found: 264.0981. HPLC t_R = 5.33 min (97.12% purity).

4.2.14. 4-((2,5-dioxo-3-propylimidazolidin-1-yl)methyl)-N-hydroxybenzamide (14)

The title compound was synthesized from **5** in a manner similar to that described for the preparation of **13**. White solid, yield: 81%, mp 182–184 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.03 (s, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 4.58 (s, 2H), 4.06 (s, 2H), 3.25 (t, J = 7.2 Hz, 2H), 1.53 (p, J = 7.3 Hz, 2H), 0.85 (q, J = 7.4, 6.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.86, 164.37, 156.52, 140.23, 132.39, 127.76, 127.56, 49.84, 44.23, 41.59, 20.91, 11.50. HRMS (AP-ESI) m/z, calculated for $C_{14}H_{17}N_3O_4$, ($[M + H]^+$): 292.1292, found: 292.1289. HPLC t_R = 7.32 min (99.43% purity).

4.2.15. 4-((3-benzyl-2,5-dioxoimidazolidin-1-yl)methyl)-N-hydroxybenzamide (15)

The title compound was synthesized from **6** in a manner similar

to that described for the preparation of **13**. White solid, yield: 48%, mp 188–189 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 9.05 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.45–7.34 (m, 4H), 7.30 (td, J = 6.2, 1.7 Hz, 3H), 4.63 (s, 2H), 4.52 (s, 2H), 3.98 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 170.56, 164.44, 156.80, 140.15, 136.86, 132.44, 129.15, 128.10, 128.00, 127.82, 127.60, 50.09, 46.42, 41.80. HRMS (AP-ESI) m/z, calculated for $C_{18}H_{17}N_3O_4$, ([M + H]$^+$): 340.1292, found: 340.1283. HPLC t_R = 9.24 min (99.27% purity).

4.2.16. 4-((3-(4-chlorobenzyl)-2,5-dioxoimidazolidin-1-yl)methyl)-N-hydroxybenzamide (16)

The title compound was synthesized from **7** in a manner similar to that described for the preparation of **13**. White solid, yield: 51%, mp 186–188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 9.04 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.40–7.30 (m, 4H), 4.62 (s, 2H), 4.51 (s, 2H), 4.00 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 170.56, 164.45, 156.84, 140.12, 135.97, 132.62, 132.44, 130.03, 129.07, 127.82, 127.61, 50.14, 45.77, 41.81. HRMS (AP-ESI) m/z, calculated for $C_{18}H_{16}ClN_3O_4$, ([M + H]$^+$): 374.0902, found: 374.0899. HPLC t_R = 19.05 min (99.87% purity).

4.2.17. N-hydroxy-4-((3-(4-methylbenzyl)-2,5-dioxoimidazolidin-1-yl)methyl)benzamide (17)

The title compound was synthesized from **8** in a manner similar to that described for the preparation of **13**. White solid, yield: 44%, mp 192–193 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.02 (s, 1H), 7.83–7.62 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.27–7.08 (m, 4H), 4.62 (s, 2H), 4.46 (s, 2H), 3.95 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.54, 164.43, 156.72, 140.16, 137.20, 133.76, 132.45, 129.71, 128.16, 127.81, 127.60, 49.93, 46.14, 41.77, 21.16. HRMS (AP-ESI) m/z, calculated for $C_{19}H_{19}N_3O_4$, ([M + H]$^+$): 354.1448, found: 354.1446. HPLC t_R = 16.08 min (98.49% purity).

4.2.18. N-hydroxy-4-((3-(4-methoxybenzyl)-2,5-dioxoimidazolidin-1-yl)methyl)benzamide (18)

The title compound was synthesized from **9** in a manner similar to that described for the preparation of **13**. White solid, yield: 61%, mp 183–185 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 9.03 (s, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 8.1 Hz, 2H), 4.61 (s, 2H), 4.44 (s, 2H), 3.93 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 170.54, 164.41, 159.20, 156.64, 140.15, 132.43, 129.65, 128.64, 127.81, 127.59, 114.54, 55.55, 49.81, 45.83, 41.75. HRMS (AP-ESI) m/z, calculated for $C_{19}H_{19}N_3O_5$, ([M + H]$^+$): 370.1398, found: 370.1406. HPLC t_R = 9.38 min (97.30% purity).

4.2.19. 4-((3-(4-(tert-butyl)benzyl)-2,5-dioxoimidazolidin-1-yl)methyl)-N-hydroxybenzamide (19)

The title compound was synthesized from **10** in a manner similar to that described for the preparation of **13**. White solid, yield: 55%, mp 142–144 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 9.03 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 8.8 Hz, 4H), 7.21 (d, J = 8.1 Hz, 2H), 4.62 (s, 2H), 4.47 (s, 2H), 3.98 (s, 2H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 170.52, 164.45, 156.72, 150.39, 140.15, 133.83, 132.45, 127.93, 127.86, 127.63, 125.89, 50.06, 46.07, 41.80, 34.66, 31.57. HRMS (AP-ESI) m/z, calculated for $C_{22}H_{25}N_3O_4$, ([M + H]$^+$): 396.1918, found: 396.1913. HPLC t_R = 10.06 min (98.89% purity).

4.2.20. 4-((2,5-dioxo-3-phenethylimidazolidin-1-yl)methyl)-N-hydroxybenzamide (20)

The title compound was synthesized from **11** in a manner similar to that described for the preparation of **13**. White solid, yield: 67%, mp 188–190 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 9.02 (s, 1H), 7.69 (d, J = 8.1 Hz, 2H), 7.39–7.13 (m, 7H), 4.54 (s, 2H), 4.01 (s, 2H), 3.56 (t, J = 7.2 Hz, 2H), 2.84 (t, J = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 170.62, 164.42, 156.28, 140.15, 139.06, 132.36, 129.16, 128.89, 127.63, 127.55, 126.82, 49.94, 43.88, 41.52, 33.65. HRMS (AP-ESI) m/z, calculated for $C_{19}H_{19}N_3O_4$, ([M + H]$^+$): 354.1448, found: 354.1443. HPLC t_R = 19.14 min (98.23% purity).

4.2.21. N-hydroxy-4-((3-(naphthalen-2-ylmethyl)-2,5-dioxoimidazolidin-1-yl)methyl)benzamide (21)

The title compound was synthesized from **12** in a manner similar to that described for the preparation of **13**. White solid, yield: 57%, mp 183–185 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 9.03 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 8.05–7.85 (m, 2H), 7.72 (d, J = 7.9 Hz, 2H), 7.58 (q, J = 6.1, 4.5 Hz, 2H), 7.50 (d, J = 5.1 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 4.99 (s, 2H), 4.65 (s, 2H), 3.92 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 170.44, 164.45, 156.60, 140.16, 133.94, 132.46, 132.06, 131.30, 129.18, 128.95, 127.78, 127.62, 127.11, 127.06, 126.53, 125.98, 123.61, 50.02, 44.57, 41.79. HRMS (AP-ESI) m/z, calculated for $C_{22}H_{19}N_3O_4$, ([M + H]$^+$): 390.1448, found: 390.1444. HPLC t_R = 4.82 min (98.89% purity).

4.2.22. Methyl 4-((3-(2-methoxy-2-oxo-1-phenylethyl)ureido)methyl)benzoate (22)

To the solution of triphosgene (23.74 g, 80 mmol) in CH_2Cl_2, the solution of methyl 2-amino-2-phenylacetate (33.02 g, 200 mmol) with triethylamine (55.60 mL, 400 mmol) was added slowly. When the titration was completed, stir the mixture for 30 min at 0 °C. Subsequently, methyl 4-(aminomethyl)benzoate (33.02 g, 200 mmol) in CH_2Cl_2 was added and the reaction solution was stirred for another 30 min. Wash the organic phase with 1 M HCl as well as saturated brine and the solvent was concentrated to give the title compound. White solid, yield: 80%, mp 144–146 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 8.3 Hz, 2H), 7.47–7.30 (m, 7H), 6.98 (d, J = 7.7 Hz, 1H), 6.65 (t, J = 6.1 Hz, 1H), 5.30 (d, J = 7.7 Hz, 1H), 4.31 (d, J = 6.1 Hz, 2H), 3.84 (s, 3H), 3.62 (s, 3H).

4.2.23. 4-((2,5-dioxo-4-phenylimidazolidin-1-yl)methyl)benzoic acid (23)

The title compound was synthesized from compound **22** in a manner similar to that described for the preparation of compound **2**. White solid, yield: 95%, mp 230–231 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 8.86 (s, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.55–7.23 (m, 7H), 5.34 (s, 1H), 4.64 (s, 2H).

4.2.24. Methyl 4-((2,5-dioxo-4-phenylimidazolidin-1-yl)methyl)benzoate (24)

The title compound was synthesized from compound **23** in a manner similar to that described for the preparation of compound **3**. White solid, yield: 98%, mp 178–180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.53–7.37 (m, 5H), 7.37–7.30 (m, 2H), 5.34 (s, 1H), 4.65 (s, 2H), 3.84 (s, 3H).

4.2.25. Methyl 4-((4-methyl-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl)benzoate (25)

The title compound was synthesized from compound **24** and iodomethane in a manner similar to that described for the preparation of compound **4**. White solid, yield: 79%, mp 228–230 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.52–7.45 (m, 2H), 7.45–7.37 (m, 3H), 7.34 (dd, J = 7.7, 3.0 Hz, 2H), 4.64 (s, 2H), 3.84 (s, 3H), 1.72 (s, 3H).

4.2.26. Methyl 4-((2,5-dioxo-4-phenyl-4-propylimidazolidin-1-yl)methyl)benzoate (26)

The title compound was synthesized from compound **24** and 1-iodopropane in a manner similar to that described for the preparation of compound **4**. White solid, yield: 67%, mp 70–72 °C. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.3 Hz, 2H), 7.52–7.47 (m, 2H), 7.41–7.31 (m, 5H), 6.37 (s, 1H), 4.73–4.62 (m, 2H), 3.90 (s, 3H), 2.22–1.98 (m, 2H), 1.33–1.21 (m, 1H), 1.19–1.08 (m, 1H), 0.88 (t, J = 7.3 Hz, 3H).

4.2.27. Methyl 4-((4-benzyl-2,5-dioxo-4-phenylimidazolidin-1-yl) methyl)benzoate (27)

The title compound was synthesized from compound **24** and (bromomethyl)benzene in a manner similar to that described for the preparation of compound **4**. White solid, yield: 91%, mp 172–174 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 7.77–7.66 (m, 4H), 7.52–7.43 (m, 2H), 7.39 (s, 1H), 7.33–7.20 (m, 5H), 6.75 (d, J = 8.3 Hz, 2H), 4.40 (d, J = 16.1 Hz, 1H), 4.32 (d, J = 16.1 Hz, 1H), 3.84 (s, 3H), 3.57 (d, J = 13.5 Hz, 1H), 3.07 (d, J = 13.6 Hz, 1H).

4.2.28. Methyl 4-((4-(4-chlorobenzyl)-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl) benzoate (28)

The title compound was synthesized from compound **24** and 1-(bromomethyl)-4-chlorobenzene in a manner similar to that described for the preparation of compound **4**. White solid, yield: 80%, mp 184–186 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 7.79 (d, J = 8.3 Hz, 2H), 7.72–7.66 (m, 2H), 7.47 (td, J = 7.3, 6.3, 1.4 Hz, 2H), 7.42–7.37 (m, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 8.2 Hz, 2H), 4.38 (d, J = 15.3 Hz, 2H), 3.84 (s, 3H), 3.55 (d, J = 13.5 Hz, 1H), 3.05 (d, J = 13.6 Hz, 1H).

4.2.29. Methyl 4-((4-(4-methylbenzyl)-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl) benzoate (29)

The title compound was synthesized from compound **24** and 1-(bromomethyl)-4-methylbenzene in a manner similar to that described for the preparation of compound **4**. White solid, yield: 86%, mp 199–201 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 7.77–7.64 (m, 4H), 7.46 (dd, J = 8.4, 6.8 Hz, 2H), 7.42–7.35 (m, 1H), 7.09 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 7.8 Hz, 2H), 6.75 (d, J = 8.1 Hz, 2H), 4.41 (d, J = 16.0 Hz, 1H), 4.32 (d, J = 16.0 Hz, 1H), 3.85 (s, 3H), 3.50 (d, J = 13.6 Hz, 1H), 3.00 (d, J = 13.5 Hz, 1H), 2.29 (s, 3H).

4.2.30. Methyl 4-((4-(4-methoxybenzyl)-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl) benzoate (30)

The title compound was synthesized from compound **24** and *1-(bromomethyl)-4-methoxybenzene* in a manner similar to that described for the preparation of compound **4**. White solid, yield: 82%, mp 220–222 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 7.69 (t, J = 7.8 Hz, 4H), 7.46 (t, J = 7.7 Hz, 2H), 7.41–7.36 (m, 1H), 7.15 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.67 (d, J = 8.1 Hz, 2H), 4.43 (d, J = 16.2 Hz, 1H), 4.32 (d, J = 16.1 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.48 (d, J = 13.7 Hz, 1H), 3.00 (d, J = 13.9 Hz, 1H).

4.2.31. Methyl 4-((4-(4-(tert-butyl)benzyl)-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl) benzoate (31)

The title compound was synthesized from compound **24** and *1-(bromomethyl)-4-(tert-butyl)benzene* in a manner similar to that described for the preparation of compound **4**. White solid, yield: 94%, mp 199–201 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (s, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.52–7.44 (m, 2H), 7.44–7.35 (m, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 4.44 (d, J = 16.0 Hz, 1H), 4.34 (d, J = 16.0 Hz, 1H), 3.84 (s, 3H), 3.54 (d, J = 13.7 Hz, 1H), 3.00 (d, J = 13.7 Hz, 1H), 1.26 (s, 9H).

4.2.32. Methyl 4-((2,5-dioxo-4-phenethyl-4-phenylimidazolidin-1-yl)methyl)benzoate (32)

The title compound was synthesized from compound **24** and *(2-bromoethyl)benzene* in a manner similar to that described for the preparation of compound **4**. White solid, yield: 72%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.84 (m, 2H), 7.44–7.41 (m, 2H), 7.40–7.32 (m, 5H), 7.21 (ddd, J = 11.2, 5.3, 3.3 Hz, 3H), 7.10–7.06 (m, 1H), 7.03 (dd, J = 6.9, 1.8 Hz, 1H), 4.80–4.71 (m, 2H), 3.90 (s, 3H), 3.13 (ddd, J = 14.1, 9.3, 6.7 Hz, 1H), 2.96 (ddd, J = 13.4, 9.5, 6.7 Hz, 1H), 1.78–1.67 (m, 1H), 1.51–1.38 (m, 1H).

4.2.33. Methyl 4-((4-(naphthalen-1-ylmethyl)-2,5-dioxo-4-phenylimidazolidin-1-yl) methyl) benzoate (33)

The title compound was synthesized from compound **24** and *1-(bromomethyl)naphthalene* in a manner similar to that described for the preparation of compound **4**. White solid, yield: 82%, mp 167–169 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.33–8.18 (d, J = 7.2 Hz, 1H), 7.93–7.88 (m, 1H), 7.87–7.78 (m, 3H), 7.60–7.54 (m, 2H), 7.55–7.45 (m, 5H), 7.45–7.34 (m, 2H), 6.50 (d, J = 8.2 Hz, 2H), 4.32 (d, J = 16.0 Hz, 1H), 4.22 (d, J = 13.6 Hz, 2H), 3.85 (s, 3H), 3.52 (d, J = 14.2 Hz, 1H).

4.2.34. Methyl 4-((4-(naphthalen-2-ylmethyl)-2,5-dioxo-4-phenylimidazolidin-1-yl) methyl)benzoate (34)

The title compound was synthesized from compound **24** and *2-(bromomethyl)naphthalene* in a manner similar to that described for the preparation of compound **4**. White solid, yield: 85%, mp 233–235 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.85–7.69 (m, 5H), 7.55 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.52–7.47 (m, 3H), 7.43–7.40 (m, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.44 (d, J = 8.2 Hz, 2H), 4.42–4.23 (m, 2H), 3.82 (s, 3H), 3.74 (d, J = 13.5 Hz, 1H), 3.25 (d, J = 13.5 Hz, 1H).

4.2.35. N-hydroxy-4-((4-methyl-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl)benzamide (35)

The title compound was synthesized from compound **25** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 59%, mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 9.07 (s, 1H), 9.02 (s, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.48 (dt, J = 6.4, 1.4 Hz, 2H), 7.44–7.38 (m, 2H), 7.37–7.31 (m, 1H), 7.25 (d, J = 8.2 Hz, 2H), 4.59 (s, 2H), 1.71 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.63, 164.34, 155.86, 140.17, 139.90, 132.46, 129.09, 128.52, 127.67, 127.50, 125.84, 63.47, 41.40, 25.42. HRMS (AP-ESI) m/z, calculated for $C_{18}H_{17}N_3O_4$, ($[M + H]^+$): 340.1292, found: 340.1291. HPLC t_R = 32.41 min (96.68% purity).

4.2.36. 4-((2,5-dioxo-4-phenyl-4-propylimidazolidin-1-yl)methyl)-N-hydroxybenzamide (36)

The title compound was synthesized from compound **26** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 52%, mp 148–150 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.14 (s, 1H), 9.03 (s, 1H), 7.69 (d, J = 7.9 Hz, 2H), 7.52 (d, J = 7.7 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 4.59 (s, 2H), 2.05 (ddd, J = 13.8, 10.2, 6.0 Hz, 1H), 1.95 (ddd, J = 13.7, 10.7, 5.8 Hz, 1H), 1.16 (q, J = 5.9 Hz, 2H), 0.85 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.01, 164.41, 156.19, 140.15, 139.18, 132.47, 129.03, 128.42, 127.73, 127.65, 125.84, 67.12, 41.44, 40.85, 17.23, 14.13. HRMS (AP-ESI) m/z, calculated for $C_{20}H_{21}N_3O_4$, ($[M + H]^+$): 368.1605, found: 368.1602. HPLC t_R = 9.52 min (96.96% purity).

4.2.37. 4-((4-benzyl-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl)-N-hydroxybenzamide (37)

The title compound was synthesized from compound **27** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 60%, mp 208–210 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.23 (s, 1H), 9.01 (s, 1H), 7.71–7.67 (m, 2H), 7.52 (d, J = 8.1 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.42–7.36 (m, 1H), 7.34–7.18 (m, 5H), 6.67 (d, J = 8.1 Hz, 2H), 4.40–4.22 (m, 2H), 3.56 (d, J = 13.5 Hz, 1H), 3.07 (dd, J = 13.7, 3.0 Hz, 1H). ^{13}C NMR (101 MHz,

DMSO) δ 173.98, 164.40, 155.53, 139.68, 139.54, 134.88, 131.93, 130.97, 129.79, 129.09, 128.60, 127.69, 127.41, 126.81, 126.12, 68.09, 44.15, 41.16. HRMS (AP-ESI) *m/z*, calculated for $C_{24}H_{21}N_3O_4$, ([M + H]$^+$): 416.1605, found: 416.1603. HPLC t_R = 15.07 min (99.67% purity).

4.2.38. 4-((4-(4-chlorobenzyl)-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl)-N- hydroxybenzamide (38)

The title compound was synthesized from compound **28** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 52%, mp 220–222 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.13 (s, 1H), 9.19 (s, 1H), 9.00 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.1 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 8.1 Hz, 2H), 4.45–4.26 (m, 2H), 3.56 (d, *J* = 13.5 Hz, 1H), 3.05 (d, *J* = 13.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 173.84, 164.59, 155.57, 139.45, 139.29, 133.79, 132.65, 132.31, 129.14, 128.75, 128.58, 127.41, 127.17, 126.10, 67.85, 43.29, 41.29. HRMS (AP-ESI) *m/z*, calculated for $C_{24}H_{20}ClN_3O_4$, ([M + H]$^+$): 450.1215, found: 450.1211. HPLC t_R = 22.90 min (98.94% purity).

4.2.39. N-hydroxy-4-((4-(4-methylbenzyl)-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl) benzamide (39)

The title compound was synthesized from compound **29** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 55%, mp 211–213 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.21 (s, 1H), 9.01 (s, 1H), 7.70–7.66 (m, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.49–7.43 (m, 2H), 7.42–7.35 (m, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 4.32 (q, *J* = 15.8 Hz, 2H), 3.50 (d, *J* = 13.5 Hz, 1H), 3.00 (d, *J* = 13.6 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO) *δ* 174.01, 164.45, 155.55, 139.74, 139.52, 136.65, 131.95, 131.74, 130.81, 129.15, 129.05, 128.59, 127.30, 127.02, 126.11, 68.11, 43.80, 41.18, 21.27. HRMS (AP-ESI) *m/z*, calculated for $C_{25}H_{23}N_3O_4$, ([M + H]$^+$): 430.1761, found: 430.1759. HPLC t_R = 23.07 min (96.80% purity).

4.2.40. N-hydroxy-4-((4-(4-methoxybenzyl)-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl) benzamide (40)

The title compound was synthesized from compound **30** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 56%, mp 215–217 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 9.16 (s, 1H), 9.00 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 4.33 (q, *J* = 15.9 Hz, 2H), 3.74 (s, 3H), 3.49 (d, *J* = 13.7 Hz, 1H), 2.99 (d, *J* = 13.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 174.07, 164.59, 158.93, 155.67, 139.67, 139.55, 132.09, 132.01, 129.09, 128.63, 127.33, 126.96, 126.66, 126.08, 113.98, 68.22, 55.37, 43.45, 41.19. HRMS (AP-ESI) *m/z*, calculated for $C_{25}H_{23}N_3O_5$, ([M + H]$^+$): 446.1711, found: 446.1709. HPLC t_R = 30.37 min (99.53% purity).

4.2.41. 4-((4-(4-(tert-butyl)benzyl)-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl) -N-hydroxybenzamide (41)

The title compound was synthesized from compound **31** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 65%, mp 200–202 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.13 (s, 1H), 9.17 (s, 1H), 8.99 (s, 1H), 7.70–7.65 (m, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.51–7.42 (m, 2H), 7.41–7.36 (m, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 4.34 (d, *J* = 15.6 Hz, 2H), 3.53 (d, *J* = 13.6 Hz, 1H), 3.02 (d, *J* = 13.7 Hz, 1H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, DMSO) *δ* 174.21, 164.38, 155.59, 149.84, 139.78, 139.57, 132.10, 131.88, 130.64, 129.10, 128.63, 127.41, 127.13, 126.03, 125.32, 67.98, 43.79, 41.29, 34.65, 31.65. HRMS (AP-ESI) *m/z*, calculated for $C_{28}H_{29}N_3O_4$, ([M + H]$^+$): 472.2231, found: 472.2230. HPLC t_R = 29.40 min (98.75% purity).

4.2.42. 4-((2,5-dioxo-4-phenethyl-4-phenylimidazolidin-1-yl) methyl)-N-hydroxybenzamide (42)

The title compound was synthesized from compound **32** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 56%, mp 132–134 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 9.27 (s, 1H), 9.01 (s, 1H), 7.75 (d, *J* = 1.8 Hz, 1H), 7.68 (dd, *J* = 8.3, 1.9 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.45–7.40 (m, 2H), 7.36 (dd, *J* = 8.0, 2.8 Hz, 1H), 7.25–7.29 (m, 4H), 7.19 (d, *J* = 7.0 Hz, 1H), 7.17–7.12 (m, 2H), 4.58 (s, 2H), 2.44 (q, *J* = 4.8, 4.1 Hz, 2H), 2.36 (dd, *J* = 10.2, 6.3 Hz, 1H), 2.33–2.21 (m, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 174.75, 164.40, 156.23, 140.87, 140.14, 138.90, 132.52, 129.15, 128.92, 128.60, 127.88, 127.75, 127.68, 126.56, 125.92, 66.94, 41.54, 35.37, 30.04. HRMS (AP-ESI) *m/z*, calculated for $C_{25}H_{23}N_3O_4$, ([M + H]$^+$): 430.1761, found: 430.1759. HPLC t_R = 9.15 min (99.21% purity).

4.2.43. N-hydroxy-4-((4-(naphthalen-1-ylmethyl)-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl) benzamide (43)

The title compound was synthesized from compound **33** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 67%, mp 162–164 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.13 (s, 1H), 9.20 (s, 1H), 9.00 (s, 1H), 8.25 (d, *J* = 7.8 Hz, 1H), 7.91 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.88 (s, 1H), 7.83–7.77 (m, 2H), 7.56–7.46 (m, 4H), 7.46–7.33 (m, 5H), 6.47 (d, *J* = 8.0 Hz, 2H), 4.29 (d, *J* = 15.9 Hz, 1H), 4.24–4.12 (m, 2H), 3.56 (d, *J* = 14.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 174.13, 164.39, 155.55, 139.75, 139.39, 133.92, 132.73, 131.93, 131.35, 129.61, 129.15, 128.81, 128.73, 128.40, 127.28, 126.64, 126.35, 126.28, 126.01, 125.55, 125.27, 68.35, 55.38, 41.14. HRMS (AP-ESI) *m/z*, calculated for $C_{28}H_{23}N_3O_4$, ([M + H]$^+$): 466.1761, found: 466.1761. HPLC t_R = 8.68 min (97.61% purity).

4.2.44. N-hydroxy-4-((4-(naphthalen-2-ylmethyl)-2,5-dioxo-4-phenylimidazolidin-1-yl)methyl) benzamide (44)

The title compound was synthesized from compound **34** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 69%, mp 248–250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.30 (s, 1H), 8.97 (s, 1H), 7.88 (s, 1H), 7.82–7.70 (m, 5H), 7.56–7.44 (m, 4H), 7.43–7.31 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.58 (d, *J* = 8.0 Hz, 2H), 4.28 (dd, *J* = 8.3, 1.7 Hz, 2H), 3.75 (d, *J* = 13.5 Hz, 1H), 3.25 (d, *J* = 13.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 174.07, 164.47, 155.59, 139.61, 139.30, 133.20, 132.62, 132.58, 132.11, 129.71, 129.51, 129.15, 128.95, 128.72, 128.09, 127.99, 127.21, 126.75, 126.64, 126.42, 126.12, 68.14, 44.33, 41.23. HRMS (AP-ESI) *m/z*, calculated for $C_{28}H_{23}N_3O_4$, ([M + H]$^+$): 466.1761, found:466.1760. HPLC t_R = 7.24 min (99.63% purity).

4.2.45. Methyl 4-((3-(1-methoxy-1-oxo-3-phenylpropan-2-yl) ureido)methyl)benzoate (45)

The title compound was synthesized from methyl phenylalaninate and *methyl 4-(aminomethyl)benzoate* in a manner similar to that described for the preparation of compound **22**. White solid, yield: 71%, mp 132–134 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.36–7.22 (m, 5H), 7.21–7.14 (m, 2H), 6.65 (t, *J* = 6.1 Hz, 1H), 6.40 (d, *J* = 8.3 Hz, 1H), 4.44 (td, *J* = 8.2, 5.4 Hz, 1H), 4.25 (d, *J* = 6.1 Hz, 2H), 3.84 (s, 3H), 3.61 (s, 3H), 3.00 (dd, *J* = 13.7, 5.5 Hz, 1H), 2.90 (dd, *J* = 13.7, 6.3 Hz, 1H).

4.2.46. Methyl 4-((4-benzyl-2,5-dioxoimidazolidin-1-yl)methyl) benzoate (46)

The solution of compound **45** (66.67 g, 180 mmol) in CH_2Cl_2 was mixed with CH_3ONa (19.45 g, 360 mmol) for 30 min. Filter and wash the filtrate with 1 M HCl. Dry the organic solvent over with anhydrous magnesium sulfate and then it was removed under

reduced pressure to give a white solid, yield: 88%, mp 136–138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.26 (dd, J = 5.0, 1.9 Hz, 3H), 7.21–7.13 (m, 2H), 6.85 (d, J = 8.2 Hz, 2H), 4.58–4.46 (m, 2H), 4.38 (d, J = 16.1 Hz, 1H), 3.84 (s, 3H), 3.01 (dd, J = 4.7, 2.4 Hz, 2H).

4.2.47. Methyl 4-((4-benzyl-3-methyl-2,5-dioxoimidazolidin-1-yl) methyl)benzoate (47)

The title compound was synthesized from compound **46** and iodomethane in a manner similar to that described for the preparation of compound **4**. White solid, yield: 93%, mp 62–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.8, 2.5 Hz, 2H), 7.23–7.14 (m, 3H), 7.05 (J = 8.1 Hz, 2H), 7.00 (J = 8.2 Hz, 2H), 4.58 (d, J = 15.1 Hz, 1H), 4.48 (d, J = 15.1 Hz, 1H), 4.16 (t, J = 4.4 Hz, 1H), 3.91 (s, 3H), 3.18 (d, J = 4.4 Hz, 2H), 2.99 (s, 3H).

4.2.48. Methyl 4-((4-benzyl-2,5-dioxo-3-propylimidazolidin-1-yl) methyl)benzoate (48)

The title compound was synthesized from compound **46** and 1-iodopropane in a manner similar to that described for the preparation of compound **4**. Colorless oil, yield: 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.8 Hz, 2H), 7.22–7.12 (m, 3H), 7.05 (d, J = 4.4 Hz, 2H), 6.99 (d, J = 8.2 Hz, 2H), 4.58 (d, J = 15.0 Hz, 1H), 4.47 (d, J = 15.1 Hz, 1H), 4.27 (t, J = 4.3 Hz, 1H), 3.91 (s, 3H), 3.77 (ddd, J = 14.1, 8.8, 7.3 Hz, 1H), 3.16 (d, J = 4.4 Hz, 2H), 3.04 (ddd, J = 13.9, 8.5, 5.1 Hz, 1H), 1.62–1.48 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H).

4.2.49. Methyl 4-((3,4-dibenzyl-2,5-dioxoimidazolidin-1-yl) methyl)benzoate (49)

The title compound was synthesized from compound **46** and (bromomethyl)benzene in a manner similar to that described for the preparation of compound **4**. Colorless oil, yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.37–7.31 (m, 3H), 7.24–7.21 (m, 1H), 7.20–7.13 (m, 4H), 7.07–7.00 (m, 4H), 5.17 (d, J = 15.1 Hz, 1H), 4.64 (d, J = 15.0 Hz, 1H), 4.53 (d, J = 15.0 Hz, 1H), 4.08–3.99 (m, 2H), 3.92 (s, 3H), 3.20–3.07 (m, 2H).

4.2.50. Methyl 4-((4-benzyl-3-(4-chlorobenzyl)-2,5-dioxoimidazolidin-1-yl)methyl)benzoate (50)

The title compound was synthesized from compound **46** and 1-(bromomethyl)-4-chlorobenzene in a manner similar to that described for the preparation of compound **4**. Colorless oil, yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.25–7.22 (m, 1H), 7.18 (dd, J = 8.2, 6.4 Hz, 2H), 7.04 (td, J = 8.2, 1.8 Hz, 6H), 5.09 (d, J = 15.2 Hz, 1H), 4.64 (d, J = 15.1 Hz, 1H), 4.54 (d, J = 14.9 Hz, 1H), 4.07–3.95 (m, 2H), 3.92 (s, 3H), 3.13 (qd, J = 14.5, 4.6 Hz, 2H).

4.2.51. Methyl 4-((4-benzyl-3-(4-methylbenzyl)-2,5-dioxoimidazolidin-1-yl)methyl) benzoate (51)

The title compound was synthesized from compound **46** and 1-(bromomethyl)-4-methylbenzene in a manner similar to that described for the preparation of compound **4**. Colorless oil, yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.3 Hz, 2H), 7.30–7.20 (m, 1H), 7.20–7.11 (m, 5H), 7.03 (ddd, J = 13.7, 8.1, 2.8 Hz, 5H), 5.14 (d, J = 15.0 Hz, 1H), 4.62 (d, J = 14.8 Hz, 1H), 4.51 (d, J = 15.0 Hz, 1H), 4.10–3.95 (m, 2H), 3.91 (s, 3H), 3.22–3.05 (m, 2H), 2.34 (s, 3H).

4.2.52. Methyl 4-((4-benzyl-3-(4-methoxybenzyl)-2,5-dioxoimidazolidin-1-yl)methyl) benzoate (52)

The title compound was synthesized from compound **46** and *1-(bromomethyl)-4-methoxybenzene* in a manner similar to that described for the preparation of compound **4**. Colorless oil, yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.3 Hz, 2H), 7.24–7.21 (m, 1H), 7.20–7.14 (m, 2H), 7.11–6.98 (m, 6H), 6.86 (d, J = 8.6 Hz, 2H), 5.11 (d, J = 15.0 Hz, 1H), 4.62 (d, J = 15.1 Hz, 1H), 4.51 (d, J = 15.1 Hz, 1H), 4.03 (s, 1H), 3.96 (d, J = 15.0 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.20–3.07 (m, 2H).

4.2.53. Methyl 4-((4-benzyl-3-(4-(tert-butyl)benzyl)-2,5-dioxoimidazolidin-1-yl)methyl) benzoate (53)

The title compound was synthesized from compound **46** and *1-(bromomethyl)-4-(tert-butyl)benzene* in a manner similar to that described for the preparation of compound **4**. Colorless oil, yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.24–7.20 (m, 1H), 7.19–7.13 (m, 2H), 7.11 (d, J = 8.2 Hz, 2H), 7.02 (dd, J = 10.2, 7.7 Hz, 4H), 5.14 (d, J = 15.0 Hz, 1H), 4.62 (d, J = 15.1 Hz, 1H), 4.51 (d, J = 15.0 Hz, 1H), 4.06 (t, J = 4.4 Hz, 1H), 4.01 (d, J = 15.1 Hz, 1H), 3.92 (s, 3H), 3.20–3.07 (m, 2H), 1.32 (s, 9H).

4.2.54. Methyl 4-((4-benzyl-2,5-dioxo-3-phenethylimidazolidin-1-yl)methyl)benzoate (54)

The title compound was synthesized from compound **46** and *(2-bromoethyl)benzene* in a manner similar to that described for the preparation of compound **4**. Colorless oil, yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 2.3 Hz, 2H), 7.17 (q, J = 6.9 Hz, 4H), 7.12–7.08 (m, 2H), 7.05–6.98 (m, 4H), 4.56 (d, J = 15.0 Hz, 1H), 4.48 (d, J = 15.0 Hz, 1H), 4.03–4.10 (m, 1H), 3.92 (s, 3H), 3.30–3.15 (m, 2H), 3.07 (qd, J = 14.5, 4.5 Hz, 2H), 2.97–2.77 (m, 2H).

4.2.55. Methyl 4-((4-benzyl-3-(naphthalen-1-ylmethyl)-2,5-dioxoimidazolidin-1-yl) methyl)benzoate (55)

The title compound was synthesized from compound **46** and *1-(bromomethyl)naphthalene* in a manner similar to that described for the preparation of compound **4**. White solid, yield: 88%, mp 62–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.01 (m, 1H), 7.95–7.84 (m, 4H), 7.52 (ddt, J = 9.9, 7.4, 3.6 Hz, 3H), 7.43 (dd, J = 8.2, 7.0 Hz, 1H), 7.32 (d, J = 6.9 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 7.16 (dd, J = 8.4, 6.6 Hz, 2H), 7.03 (dd, J = 7.6, 5.1 Hz, 3H), 5.72 (d, J = 14.9 Hz, 1H), 4.67–4.49 (m, 3H), 3.93 (s, 3H), 3.78 (t, J = 4.3 Hz, 1H), 3.22–3.04 (m, 2H).

4.2.56. Methyl 4-((4-benzyl-3-(naphthalen-2-ylmethyl)-2,5-dioxoimidazolidin-1-yl) methyl)benzoate (56)

The title compound was synthesized from compound **46** and *2-(bromomethyl)naphthalene* in a manner similar to that described for the preparation of compound **4**. White solid, yield: 65%, mp 76–77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2 Hz, 2H), 7.82 (dd, J = 9.0, 5.3 Hz, 3H), 7.78–7.74 (m, 1H), 7.50 (ddd, J = 9.9, 5.2, 2.8 Hz, 3H), 7.28 (d, J = 1.8 Hz, 1H), 7.19 (dd, J = 8.3, 6.6 Hz, 2H), 7.11–7.03 (m, 4H), 5.33 (d, J = 15.1 Hz, 1H), 4.66 (d, J = 15.0 Hz, 1H), 4.56 (d, J = 15.0 Hz, 1H), 4.17 (d, J = 15.1 Hz, 1H), 4.05 (t, J = 4.6 Hz, 1H), 3.92 (s, 3H), 3.21 (dd, J = 14.5, 4.2 Hz, 1H), 3.10 (dd, J = 14.5, 5.0 Hz, 1H).

4.2.57. Methyl 4-((4-benzyl-2,5-dioxo-3-(pyridin-2-ylmethyl) imidazolidin-1-yl)methyl) benzoate (57)

The title compound was synthesized from compound **46** and *2-(bromomethyl)pyridine* in a manner similar to that described for the preparation of compound **4**. White solid, yield: 90%, mp 171–173 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 4.8 Hz, 1H), 7.86–7.73 (m, 2H), 7.46–7.19 (m, 6H), 7.14–7.09 (m, 2H), 6.87 (d, J = 8.3 Hz, 2H), 4.93 (d, J = 16.6 Hz, 1H), 4.66–4.55 (m, 3H), 4.46 (d, J = 16.3 Hz, 1H), 3.86 (s, 3H), 3.28 (dd, J = 14.4, 4.7 Hz, 1H), 3.09 (dd, J = 14.4, 4.0 Hz, 1H).

4.2.58. Methyl 4-((4-benzyl-2,5-dioxo-3-(pyridin-3-ylmethyl) imidazolidin-1-yl)methyl) benzoate (58)

The title compound was synthesized from compound **46** and *3-(bromomethyl)pyridine* in a manner similar to that described for the preparation of compound **4**. White solid, yield: 75%, mp 172–174 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62–8.49 (m, 2H), 7.79–7.72 (m, 2H), 7.45–7.37 (m, 1H), 7.31–7.15 (m, 4H), 7.07 (d, J = 7.8 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 4.87 (d, J = 15.8 Hz, 1H), 4.64–4.37 (m, 4H), 3.86 (s, 3H), 3.32 (dd, J = 14.5, 4.0 Hz, 1H), 3.09 (dd, J = 14.6, 3.9 Hz, 1H).

4.2.59. Methyl 4-((4-benzyl-2,5-dioxo-3-(pyridin-4-ylmethyl) imidazolidin-1-yl)methyl) benzoate (59)

The title compound was synthesized from compound **46** and *4-(bromomethyl)pyridine* in a manner similar to that described for the preparation of compound **4**. White solid, yield: 85%, mp 184–185 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58–8.53 (m, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.34–7.31 (m, 2H), 7.29–7.17 (m, 3H), 7.08 (d, J = 7.7 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 4.85 (d, J = 16.5 Hz, 1H), 4.59 (t, J = 15.9 Hz, 2H), 4.51 (t, J = 4.2 Hz, 1H), 4.45 (d, J = 16.1 Hz, 1H), 3.85 (s, 3H), 3.30 (dd, J = 14.5, 3.9 Hz, 1H), 3.08 (dd, J = 14.5, 4.0 Hz, 1H).

4.2.60. 4-((4-benzyl-3-methyl-2,5-dioxoimidazolidin-1-yl)methyl)-N-hydroxybenzamide (60)

The title compound was synthesized from compound **47** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 73%, mp 171–173 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 9.01 (s, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.34–7.19 (m, 3H), 7.09 (dt, J = 6.6, 1.6 Hz, 2H), 6.74 (d, J = 8.2 Hz, 2H), 4.50 (d, J = 15.9 Hz, 1H), 4.45 (t, J = 4.3 Hz, 1H), 4.34 (d, J = 15.9 Hz, 1H), 3.22 (dd, J = 14.4, 4.7 Hz, 1H), 3.09 (dd, J = 14.4, 3.9 Hz, 1H), 2.93 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.39, 164.40, 156.30, 139.67, 135.25, 132.01, 130.12, 128.76, 127.43, 127.34, 126.89, 62.35, 41.28, 33.76, 28.45. HRMS (AP-ESI) m/z, calculated for $C_{19}H_{19}N_3O_4$, ([M + H]$^+$): 354.1448, found: 354.1446. HPLC t_R = 17.85min (98.65% purity).

4.2.61. 4-((4-benzyl-2,5-dioxo-3-propylimidazolidin-1-yl)methyl)-N-hydroxybenzamide (61)

The title compound was synthesized from compound **48** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 71%, mp 86–88 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.01 (s, 1H), 7.58–7.53 (m, 2H), 7.24 (ddd, J = 14.2, 7.8, 6.0 Hz, 3H), 7.09 (d, J = 7.0 Hz, 2H), 6.76 (d, J = 8.0 Hz, 2H), 4.58 (t, J = 4.3 Hz, 1H), 4.51 (d, J = 15.8 Hz, 1H), 4.36 (d, J = 15.9 Hz, 1H), 3.54 (dt, J = 13.8, 8.0 Hz, 1H), 3.24 (dd, J = 14.5, 4.6 Hz, 1H), 3.16 (ddd, J = 13.8, 8.5, 4.9 Hz, 1H), 3.06 (dd, J = 14.5, 4.0 Hz, 1H), 1.73–1.42 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.45, 164.45, 156.02, 139.70, 135.20, 132.03, 130.10, 128.75, 127.43, 127.40, 126.94, 59.83, 42.42, 41.32, 33.78, 20.78, 11.53. HRMS (AP-ESI) m/z, calculated for $C_{21}H_{23}N_3O_4$, ([M + H]$^+$): 382.1761, found: 382.1762. HPLC t_R = 9.74 min (99.10% purity).

4.2.62. 4-((3,4-dibenzyl-2,5-dioxoimidazolidin-1-yl)methyl)-N-hydroxybenzamide (62)

The title compound was synthesized from compound **49** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 70%, mp 144–146 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.03 (s, 1H), 7.55 (dd, J = 8.3, 2.4 Hz, 2H), 7.44–7.17 (m, 8H), 7.12–7.01 (d, J = 7.8 Hz, 2H), 6.74 (d, J = 8.0 Hz, 2H), 4.86 (d, J = 15.5 Hz, 1H), 4.55 (d, J = 15.9 Hz, 1H), 4.42 (dd, J = 20.5, 15.7 Hz, 2H), 4.33 (t, J = 4.2 Hz, 1H), 3.27 (dd, J = 14.5, 4.6 Hz, 1H), 3.07 (dd, J = 14.4, 3.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 172.10, 164.39, 156.41, 139.57, 136.82, 134.98, 132.08, 130.23, 129.17, 128.77, 128.56, 128.13, 127.50, 127.44, 126.93, 60.26, 44.66, 41.51, 33.66. HRMS (AP-ESI) m/z, calculated for $C_{25}H_{23}N_3O_4$, ([M + H]$^+$): 430.1761, found: 430.1759. HPLC t_R = 27.15 min (99.72% purity).

4.2.63. 4-((4-benzyl-3-(4-chlorobenzyl)-2,5-dioxoimidazolidin-1-yl)methyl)-N- hydroxybenzamide (63)

The title compound was synthesized from compound **50** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 76%, mp 171–173 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 9.03 (s, 1H), 7.64–7.53 (m, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 7.21 (t, J = 7.3 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 6.75 (d, J = 8.3, 2H), 4.83 (dd, J = 15.7, 1.7 Hz, 1H), 4.65–4.40 (m, 3H), 4.38 (t, J = 4.2 Hz, 1H), 3.28 (dd, J = 14.5, 4.6 Hz, 1H), 3.07 (dd, J = 14.5, 3.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 172.10, 164.42, 156.41, 139.54, 135.90, 134.99, 132.78, 132.08, 130.44, 130.18, 129.07, 128.77, 127.50, 127.44, 126.94, 60.30, 43.95, 41.53, 33.67. HRMS (AP-ESI) m/z, calculated for $C_{25}H_{22}ClN_3O_4$, ([M + H]$^+$): 464.1372, found: 464.1371. HPLC t_R = 14.02min (97.32% purity).

4.2.64. 4-((4-benzyl-3-(4-methylbenzyl)-2,5-dioxoimidazolidin-1-yl)methyl)-N- hydroxybenzamide (64)

The title compound was synthesized from compound **51** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 72%, mp 170–172 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.02 (s, 1H), 7.55 (dd, J = 8.3, 1.9 Hz, 2H), 7.34–7.14 (m, 7H), 7.06 (d, J = 7.1 Hz, 2H), 6.74 (d, J = 8.0 Hz, 2H), 4.83 (d, J = 15.4 Hz, 1H), 4.54 (d, J = 15.9 Hz, 1H), 4.38 (dd, J = 15.7, 7.5 Hz, 2H), 4.28 (t, J = 4.2 Hz, 1H), 3.25 (dd, J = 14.4, 4.7 Hz, 1H), 3.06 (dd, J = 14.4, 3.9 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.08, 164.43, 156.33, 139.57, 137.37, 135.01, 133.70, 132.08, 130.23, 129.73, 128.76, 128.60, 127.49, 127.43, 126.91, 60.05, 44.36, 41.48, 33.63, 21.19. HRMS (AP-ESI) m/z, calculated for $C_{26}H_{25}N_3O_4$, ([M + H]$^+$): 444.1918, found: 444.1916. HPLC t_R = 15.41 min (98.93% purity).

4.2.65. 4-((4-benzyl-3-(4-methoxybenzyl)-2,5-dioxoimidazolidin-1-yl)methyl)-N- hydroxybenzamide (65)

The title compound was synthesized from compound **52** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 67%, mp 166–168 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.02 (s, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.35–7.19 (m, 5H), 7.06 (d, J = 7.1 Hz, 2H), 6.93 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 8.0 Hz, 2H), 4.81 (d, J = 15.2 Hz, 1H), 4.53 (d, J = 15.9 Hz, 1H), 4.36 (dd, J = 15.6, 13.1 Hz, 2H), 4.27 (t, J = 4.2 Hz, 1H), 3.75 (s, 3H), 3.26 (dd, J = 14.4, 4.6 Hz, 1H), 3.06 (dd, J = 14.4, 3.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 172.10, 164.29, 159.31, 156.32, 139.57, 135.02, 132.06, 130.24, 130.08, 128.75, 128.63, 127.49, 127.42, 126.89, 114.56, 59.98, 55.57, 44.10, 41.45, 33.63. HRMS (AP-ESI) m/z, calculated for $C_{26}H_{25}N_3O_5$, ([M + H]$^+$): 460.1867, found: 460.1875. HPLC t_R = 29.74 min (96.87% purity).

4.2.66. 4-((4-benzyl-3-(4-(tert-butyl)benzyl)-2,5-dioxoimidazolidin-1-yl)methyl)-N- hydroxybenzamide (66)

The title compound was synthesized from compound **53** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 63%, mp 151–153 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 9.02 (s, 1H), 7.55 (dd, J = 8.3, 2.6 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.31–7.24 (m, 3H), 7.20 (t, J = 7.5 Hz, 2H), 7.03 (d, J = 6.9 Hz, 2H), 6.74 (d, J = 8.3 Hz, 2H), 4.90–4.77 (m, 1H), 4.54 (d, J = 15.9 Hz, 1H), 4.40 (dd, J = 15.7, 10.3 Hz, 2H), 4.32 (t, J = 4.1 Hz, 1H), 3.27 (dd, J = 14.4, 4.6 Hz, 1H), 3.07 (dd, J = 14.5, 3.8 Hz, 1H), 1.28 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 172.09, 164.42, 156.35, 150.55, 139.56, 134.95, 133.87, 132.07, 130.24, 128.73, 128.37,

127.48, 127.43, 126.91, 125.91, 60.26, 44.30, 41.48, 34.70, 33.63, 31.59. HRMS (AP-ESI) *m/z*, calculated for $C_{29}H_{31}N_3O_4$, ([M + H]$^+$): 486.2387, found: 486.2384. HPLC t_R = 19.20 min (99.46% purity).

4.2.67. 4-((4-benzyl-2,5-dioxo-3-phenethylimidazolidin-1-yl) methyl)-N-hydroxybenzamide (67)

The title compound was synthesized from compound **54** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 60%, mp 142–144 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 9.01 (s, 1H), 7.56 (dd, *J* = 8.3, 1.7 Hz, 2H), 7.40–7.20 (m, 8H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 4.57–4.42 (m, 2H), 4.33 (d, *J* = 15.9 Hz, 1H), 3.83 (ddd, *J* = 14.8, 8.7, 6.8 Hz, 1H), 3.40 (s, 1H), 3.27 (dd, *J* = 14.4, 4.6 Hz, 1H), 3.05 (d, *J* = 4.3 Hz, 1H), 2.90 (s, 1H), 2.83–2.71 (m, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 172.31, 164.43, 155.85, 139.63, 138.98, 135.28, 132.08, 130.09, 129.19, 128.92, 128.79, 126.97, 126.87, 60.09, 42.30, 41.29, 34.04, 33.53. HRMS (AP-ESI) *m/z*, calculated for $C_{26}H_{25}N_3O_4$, ([M + H]$^+$): 444.1918, found: 444.1917. HPLC t_R = 11.26 min (98.77% purity).

4.2.68. 4-((4-benzyl-3-(naphthalen-1-ylmethyl)-2,5-dioxoimidazolidin-1-yl)methyl)-N- hydroxybenzamide (68)

The title compound was synthesized from compound **55** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 53%, mp 153–154 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 9.04 (s, 1H), 8.18 (dd, *J* = 6.6, 3.2 Hz, 1H), 8.00 (dd, *J* = 6.4, 3.2 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.71–7.48 (m, 6H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 2H), 7.04 (d, *J* = 7.5 Hz, 2H), 6.79 (d, *J* = 8.3 Hz, 2H), 5.34 (s, 1H), 4.95 (d, *J* = 15.7 Hz, 1H), 4.55 (d, *J* = 15.9 Hz, 1H), 4.42 (d, *J* = 15.9 Hz, 1H), 4.20 (t, *J* = 4.1 Hz, 1H), 3.25 (dd, *J* = 14.4, 4.7 Hz, 1H), 3.05 (dd, *J* = 14.4, 3.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 172.06, 164.46, 156.28, 139.57, 134.82, 134.01, 132.12, 131.96, 131.44, 130.26, 129.21, 129.08, 128.72, 127.50, 127.45, 127.09, 126.96, 126.56, 125.95, 123.83, 60.44, 42.95, 41.53, 33.86. HRMS (AP-ESI) *m/z*, calculated for $C_{29}H_{25}N_3O_4$, ([M + H]$^+$): 480.1918, found: 480.1916. HPLC t_R = 6.93 min (99.67% purity).

4.2.69. 4-((4-benzyl-3-(naphthalen-2-ylmethyl)-2,5-dioxoimidazolidin-1-yl)methyl)-N- hydroxybenzamide (69)

The title compound was synthesized from compound **56** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 66%, mp 150–151 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 9.05 (s, 1H), 7.93 (dd, *J* = 8.6, 2.9 Hz, 3H), 7.83 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.56–7.50 (m, 2H), 7.46 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.29 (dd, *J* = 7.8, 2.0 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 7.0 Hz, 2H), 6.79 (d, *J* = 8.0 Hz, 2H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.60 (dd, *J* = 15.8, 10.6 Hz, 2H), 4.50–4.36 (m, 2H), 3.31 (dd, *J* = 14.5, 3.9 Hz, 1H), 3.09 (dd, *J* = 14.4, 3.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) *δ* 172.17, 164.53, 156.49, 139.64, 135.09, 134.34, 133.41, 132.93, 132.15, 130.70, 130.25, 128.92, 128.81, 128.47, 128.23, 128.08, 127.51, 127.23, 127.00, 126.84, 126.58, 60.32, 44.85, 41.59, 33.80. HRMS (AP-ESI) *m/z*, calculated for $C_{29}H_{25}N_3O_4$, ([M + H]$^+$): 480.1918, found: 480.1917. HPLC t_R = 9.26 min (95.71% purity).

4.2.70. 4-((4-benzyl-2,5-dioxo-3-(pyridin-2-ylmethyl) imidazolidin-1-yl)methyl)-N- hydroxybenzamide (70)

The title compound was synthesized from compound **57** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 63%, mp 156–158 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.01 (s, 1H), 8.53 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.79 (td, *J* = 7.7, 1.8 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.32 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.28–7.23 (m, 1H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.04–6.96 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 4.76 (q, *J* = 16.6 Hz, 2H), 4.54–4.34 (m, 3H), 3.34 (d, *J* = 13.7 Hz, 1H), 3.16 (d, *J* = 13.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 172.70, 164.39, 157.54, 155.24, 149.05, 139.33, 137.52, 133.96, 132.09, 130.43, 128.76, 127.64, 127.39, 126.95, 122.99, 122.49, 88.48, 55.37, 45.04, 41.16. HRMS (AP-ESI) *m/z*, calculated for $C_{24}H_{22}N_4O_4$, ([M + H]$^+$): 431.1714, found: 431.1712. HPLC t_R = 7.43 min (95.26% purity).

4.2.71. 4-((4-benzyl-2,5-dioxo-3-(pyridin-3-ylmethyl) imidazolidin-1-yl)methyl)-N- hydroxybenzamide (71)

The title compound was synthesized from compound **58** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 54%, mp 160–161 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 9.00 (s, 1H), 8.55 (d, *J* = 2.3 Hz, 1H), 8.52 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.73 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.38 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.31–7.17 (m, 3H), 7.06 (d, *J* = 7.1 Hz, 2H), 6.76 (d, *J* = 8.1 Hz, 2H), 4.84 (d, *J* = 15.8 Hz, 1H), 4.61–4.49 (m, 2H), 4.44 (t, *J* = 4.2 Hz, 1H), 4.39 (d, *J* = 16.0 Hz, 1H), 3.30 (dd, *J* = 14.4, 3.9 Hz, 1H), 3.08 (dd, *J* = 14.5, 3.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 172.13, 164.42, 156.47, 149.80, 149.27, 139.55, 136.32, 135.04, 132.61, 132.08, 130.14, 128.78, 127.49, 127.40, 126.95, 124.13, 60.49, 42.34, 41.53, 33.71. HRMS (AP-ESI) *m/z*, calculated for $C_{24}H_{22}N_4O_4$, ([M + H]$^+$): 431.1714, found: 431.1708. HPLC t_R = 10.22 min (97.35% purity).

4.2.72. 4-((4-benzyl-2,5-dioxo-3-(pyridin-4-ylmethyl) imidazolidin-1-yl)methyl)-N- hydroxybenzamide (72)

The title compound was synthesized from compound **59** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 56%, mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 9.00 (s, 1H), 8.55–8.52 (m, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.32–7.29 (m, 2H), 7.28–7.25 (m, 1H), 7.21 (t, *J* = 7.4 Hz, 2H), 7.09–7.04 (m, 2H), 6.78 (d, *J* = 8.0 Hz, 2H), 4.82 (d, *J* = 16.6 Hz, 1H), 4.63–4.52 (m, 2H), 4.49 (t, *J* = 4.3 Hz, 1H), 4.41 (d, *J* = 16.0 Hz, 1H), 3.29 (dd, *J* = 14.5, 4.0 Hz, 1H), 3.07 (dd, *J* = 14.5, 4.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 172.15, 164.40, 156.51, 150.25, 146.00, 139.53, 135.01, 132.09, 130.12, 128.79, 127.50, 127.41, 126.97, 123.10, 60.73, 43.64, 41.58, 33.71. HRMS (AP-ESI) *m/z*, calculated for $C_{24}H_{22}N_4O_4$, ([M + H]$^+$): 431.1714, found: 431.1713. HPLC t_R = 7.25 min (96.10% purity).

4.2.73. Methyl 4-((3-(1-methoxy-4-methyl-1-oxopentan-2-yl) ureido)methyl)benzoate (73)

The title compound was synthesized from methyl leucinate and *methyl 4-(aminomethyl)benzoate* in a manner similar to that described for the preparation of compound **22**. White solid, yield: 82%, mp 89–91 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.54 (t, *J* = 6.1 Hz, 1H), 6.44 (d, *J* = 8.3 Hz, 1H), 4.29 (dd, *J* = 6.2, 2.2 Hz, 2H), 4.19 (td, *J* = 8.4, 6.3 Hz, 1H), 3.84 (s, 3H), 3.62 (s, 3H), 1.64 (dq, *J* = 8.2, 6.4 Hz, 1H), 1.47 (ddd, *J* = 8.0, 5.9, 2.0 Hz, 2H), 0.88 (dd, *J* = 12.1, 6.6 Hz, 6H).

4.2.74. Methyl 4-((4-isobutyl-2,5-dioxoimidazolidin-1-yl)methyl) benzoate (74)

The title compound was synthesized from compound **73** in a manner similar to that described for the preparation of compound **46**. White solid, yield: 97%, mp 136–138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 4.60 (s, 2H), 4.24–4.13 (m, 1H), 3.84 (s, 3H), 1.79 (ddd, *J* = 9.1, 4.5, 1.9 Hz, 1H), 1.54 (ddd, *J* = 13.5, 9.1, 4.3 Hz, 1H), 1.43 (ddd, *J* = 14.1, 9.5, 5.2 Hz, 1H), 0.89 (dd, *J* = 6.6, 2.8 Hz, 6H).

4.2.75. Methyl 4-((4-isobutyl-3-methyl-2,5-dioxoimidazolidin-1-yl)methyl)benzoate (75)

The title compound was synthesized from compound **74** and iodomethane in a manner similar to that described for the preparation of compound **4**. Colorless oil, yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 4.69 (d,

J = 2.0 Hz, 2H), 3.90 (s, 3H), 3.87 (dd, J = 6.4, 5.1 Hz, 1H), 2.95 (s, 3H), 1.85 (dp, J = 13.3, 6.7 Hz, 1H), 1.78–1.68 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H).

4.2.76. Methyl 4-((4-isobutyl-2,5-dioxo-3-propylimidazolidin-1-yl) methyl)benzoate (76)

The title compound was synthesized from compound **74** and 1-iodopropane in a manner similar to that described for the preparation of compound **4**. Colorless oil, yield: 81%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 4.79–4.57 (m, 2H), 4.24 (t, J = 4.9 Hz, 1H), 3.84 (s, 3H), 3.48 (dt, J = 14.1, 7.9 Hz, 1H), 3.05 (ddd, J = 13.8, 8.2, 5.0 Hz, 1H), 1.84–1.72 (m, 1H), 1.65 (td, J = 5.6, 4.9, 1.9 Hz, 2H), 1.61–1.42 (m, 2H), 0.95–0.84 (m, 6H), 0.84–0.77 (m, 3H).

4.2.77. Methyl 4-((3-benzyl-4-isobutyl-2,5-dioxoimidazolidin-1-yl) methyl)benzoate (77)

The title compound was synthesized from compound **74** and (bromomethyl)benzene in a manner similar to that described for the preparation of compound **4**. Colorless oil, yield: 89%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.39–7.27 (m, 5H), 4.72–4.66 (m, 2H), 4.03 (d, J = 4.7 Hz, 1H), 3.85 (s, 3H), 1.73–1.54 (m, 3H), 0.95–0.79 (m, 2H), 0.74 (d, J = 6.4 Hz, 3H), 0.67 (d, J = 6.3 Hz, 3H).

4.2.78. N-hydroxy-4-((4-isobutyl-3-methyl-2,5-dioxoimidazolidin-1-yl)methyl)benzamide (78)

The title compound was synthesized from compound **75** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 58%, mp 122–124 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.02 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 4.64–4.52 (m, 2H), 4.14 (t, J = 5.7 Hz, 1H), 2.86 (s, 3H), 1.82–1.72 (m, 1H), 1.64 (t, J = 6.3 Hz, 2H), 0.88 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.55, 164.39, 156.33, 140.11, 132.43, 127.84, 127.56, 59.93, 41.65, 37.66, 28.31, 24.30, 23.29, 22.88. HRMS (AP-ESI) m/z, calculated for $C_{16}H_{21}N_3O_4$, ([M + H]$^+$): 320.1605, found: 320.1612. HPLC t_R = 6.06 min (95.71% purity).

4.2.79. N-hydroxy-4-((4-isobutyl-2,5-dioxo-3-propylimidazolidin-1-yl)methyl)benzamide (79)

The title compound was synthesized from compound **76** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 66%, mp 89–91 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 9.02 (s, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 4.68–4.52 (m, 2H), 4.23 (t, J = 5.6 Hz, 1H), 3.46 (dt, J = 14.1, 7.9 Hz, 1H), 3.04 (ddd, J = 13.8, 8.3, 5.1 Hz, 1H), 1.76 (dt, J = 13.2, 6.6 Hz, 1H), 1.69–1.62 (m, 2H), 1.61–1.41 (m, 2H), 0.99–0.77 (m, 9H). ^{13}C NMR (101 MHz, DMSO) δ 173.53, 164.40, 156.10, 140.12, 132.42, 127.80, 127.59, 57.74, 42.48, 41.60, 37.65, 24.17, 23.50, 22.68, 21.10, 11.53. HRMS (AP-ESI) m/z, calculated for $C_{22}H_{19}N_3O_4$, ([M + H]$^+$): 348.1918, found: 348.1921. HPLC t_R = 13.41 min (98.96% purity).

4.2.80. 4-((3-benzyl-4-isobutyl-2,5-dioxoimidazolidin-1-yl) methyl)-N-hydroxybenzamide (80)

The title compound was synthesized from compound **77** in a manner similar to that described for the preparation of compound **13**. White solid, yield: 67%, mp 101–102 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 9.04 (s, 1H), 7.72 (d, J = 7.9 Hz, 2H), 7.43–7.25 (m, 7H), 4.70 (d, J = 15.5 Hz, 1H), 4.66–4.58 (m, 2H), 4.38 (d, J = 15.7 Hz, 1H), 4.02 (t, J = 5.5 Hz, 1H), 1.62 (tdd, J = 18.4, 13.9, 8.8 Hz, 3H), 0.74 (d, J = 6.4 Hz, 3H), 0.68 (d, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.32, 164.41, 156.61, 140.03, 137.05, 132.50, 129.10, 128.23, 128.01, 127.89, 127.67, 58.29, 44.98, 41.86, 37.72, 24.12, 23.33, 22.51. HRMS (AP-ESI) m/z, calculated for $C_{22}H_{19}N_3O_4$, ([M + H]$^+$): 396.1918, found: 396.1919. HPLC t_R = 22.08 min (99.32% purity).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

HL-60 cell	human promyelocytic leukemia cell line
HDACs	histone deacetylases
HATs	histone acetyltransferases
NOC-7	a HDAC6 inhibitor
SAHA	a pan-HDAC inhibitor
Bax	a pro-apoptotic protein of Bcl-2 family
TEA	triethylamine;
MF	N,N-Dimethylformamide;
THF	tetrahydrofuran
SAR	structure and activity relationship;
SEM	standard error of the mean
KG1 cell	human acute myeloid leukemia cell line;
NCI–H929 cell	human multiple myeloma cell line;
Jurkat cell	human acute T cell leukemia cell line;
HEL,	human erythroleukemia cell line;
HUVECs	human umbilical vein endothelial cells
GEC-1 cell	gastric epithelial cells
Tubastatin A	a HDAC6 selective inhibitor
TUNEL assay	terminal deoxynucleotidyl transferase (TdT) deoxyuridine triphosphate (dUTP) Nick-End labeling Assay
PI	propidium iodide;
MOMP	mitochondrial outer membrane permeabilization
TMRE	tetramethylrhodamine ethyl ester
TSA	Trichostatin A, a potent pan-HDAC inhibitor
FBS	fetal bovine serum
MTT	3-(4,5-Dimethyl-2-Thiazolyl)-2,5-Diphenyl Tetrazolium Bromide;
DMSO	Dimethyl sulfoxide;
RIPA	RIPA Lysis Buffer
PMSF	Phenylmethylsulfonyl fluoride, a protease inhibitor
SDS	Sodium dodecyl sulfate
PVDF	polyvinylidene fluoride;
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
TBST	Tris Buffered saline Tween
ECL,	electrochemiluminescence
PBS	phosphate buffer saline;
TLC	thin-layer chromatography
HRMS	High-resolution mass spectra
mp	melting point

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmech.2021.113526.

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