Bioorganic & Medicinal Chemistry 22 (2014) 1529–1538

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design, synthesis and preliminary bioactivity studies of 1,2-dihydrobenzo[*d*]isothiazol-3-one-1,1-dioxide hydroxamic acid derivatives as novel histone deacetylase inhibitors

Leiqiang Han [a], Lei Wang [a], Xuben Hou [a], Huansheng Fu [a], Weiguo Song [a], Weiping Tang [b], Hao Fang [a,*]

[a] Department of Medicinal Chemistry, Key Laboratory of Chemical Biology (Ministry of Education), School of Pharmacy, Shandong University, 44 West Wenhua Rd, Ji'nan 250012, PR China
[b] Division of Pharmaceutical Sciences, School of Pharmacy, University of Wisconsin, Madison 53705, USA

ARTICLE INFO

Article history:
Received 24 November 2013
Revised 22 January 2014
Accepted 23 January 2014
Available online 1 February 2014

Keywords:
1,2-Dihydrobenzo[*d*]isothiazol-3-one-1,1-dioxide
Histone deacetylase inhibitor
Antiproliferative

ABSTRACT

Histone deacetylase (HDAC) is a clinically validated target for antitumor therapy. In order to increase HDAC inhibition and efficiency, we developed a novel series of saccharin hydroxamic acids as potent HDAC inhibitors. Among them, compounds **11e**, **11m**, **11p** exhibited similar or better HDACs inhibitory activity compared with the approved drug SAHA. Further biological evaluation indicated that compound **11m** had potent antiproliferative activities against MDA-MB-231 and PC-3.

1. Introduction

Histone acetylation and deacetylation play important roles in the regulation of gene transcription and the modulation of chromatin structure. The levels of histone acetylation are determined by the activities of histone acetyltransferases and histone deacetylases (HDACs). HDAC is associated with a number of oncogenes and tumor suppressor genes and can be aberrantly expressed and/or inappropriately activated in cancer cells.[1] Presumably due to their involvement in repressing transcription, various HDAC isoforms are overexpressed in different cancers and as such are valid targets for cancer treatment.[2] HDAC inhibitors (HDACi) have therefore recently emerged as novel antitumor agents against malignancies. They regulate gene expression by enhancing the acetylation of histones and non-histone proteins, which include transcription factors, transcription regulators, signal transduction mediators, and DNA repair enzymes.[1] The cumulative result of these activities is the inhibition of tumor growth.

To date, two histone deacetylase inhibitors (Fig. 1), Vorinostat **1** (SAHA) and Romidepsin **2** (FK228) are approved for the treatment of cutaneous T-cell lymphoma (CTCL).[3] The common pharmacophore of HDACi consists of three domains: a zinc-binding group (ZBG) that chelates the active site Zn^{2+} ion, a saturated or unsaturated linker and a surface recognition cap group that interacts with the amino acid residues at the surface of the HDAC (Fig. 2). Extensive reports have aimed to improve the HDAC inhibition profile by manipulating the surface recognition cap group and linker region while retaining the hydroxamic acid as ZBG.[4]

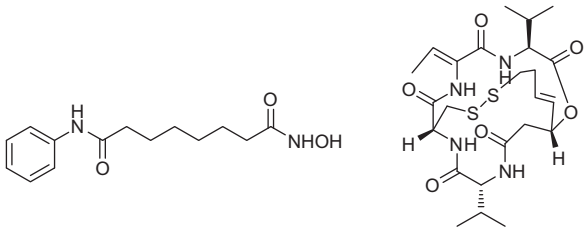


Figure 1. Approved drugs of HDACIs.

In our previous studies, we developed *N*-hydroxybenzamide,[5] 1,3,4-thiadiazole,[6] and tetrahydroisoquinoline[7–9] derivatives as novel HDAC inhibitors. Especially, tetrahydroisoquinoline derivatives show good inhibitory activities against HDAC and possess better antiproliferative activities in the xenograft models. In our on-going studies, the 1,2-dihydrobenzo[*d*]isothiazol-3-one-1,1-dioxide (saccharin) was chosen as a cap group of HDAC inhibitors because it was structurally similar to tetrahydroisoquinoline and it was also

* Corresponding author. Tel./fax: +86 531 88382731.
E-mail address: haofangcn@sdu.edu.cn (H. Fang).

http://dx.doi.org/10.1016/j.bmc.2014.01.045
0968-0896/

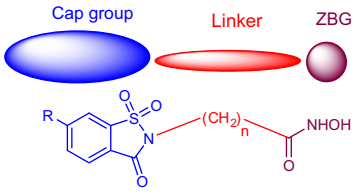


Figure 2. HDACi pharmacophore model and our saccharin-based hydroxamic acid derivative.

found in many clinically used agents.[10–12] Although the parent compound (R = H, Fig. 2) was mentioned in a patent,[13] variation of R group for the structure in Figure 2 and related SAR were not reported. Herein we report the synthesis, enzyme inhibition and antiproliferative activities against tumor cell lines of saccharin hydroxamic acid derivatives with various R groups.

2. Chemistry

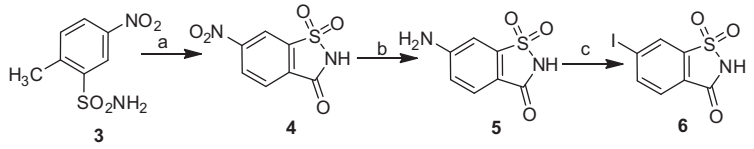
In order to develop the saccharin hydroxamates, we first synthesized key intermediate **4** in Scheme 1 following reported procedures.[14] Aryl iodide **6** was then prepared from intermediate **4** by hydrogenation and Sandmeyer reaction.

The preparation of various saccharin hydroxamic acid derivatives with the general structure shown in Figure 2 are described in Schemes 2 and 3. When the sodium salts of saccharin or **4** were heated with ω-bromoalkylcarboxylic ester in DMF at 100 °C, the N-alkylation products were obtained. Hydrolysis of the esters by hot concentrated HCl provided the target acids **7a**–**7h**. Acids **7i**, **7j**, **7k** were synthesized by direct alkylation under condition a. Final hydroxamic acids **8a**–**8k** were prepared by a mixed anhydride approach according to literature procedures.[5]

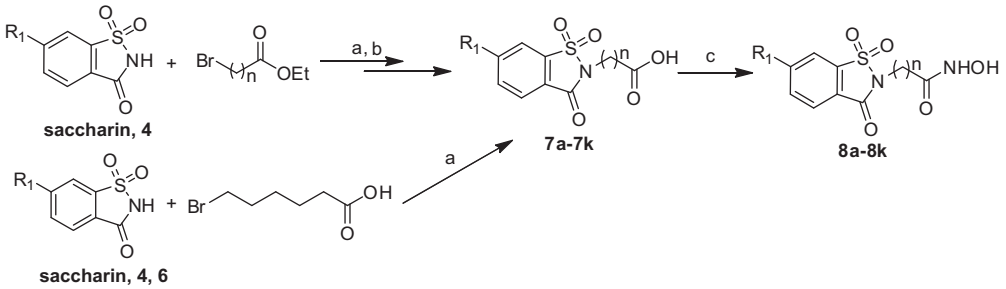
To gain more diversity, carboxylic acids **10a**–**10p** were synthesized from **7d**, **7h**, and **7j** by hydrogenation and amide formation as shown in Scheme 3. Final products **11a**–**11p** were obtained from **10a**–**10p** following the same method shown in Scheme 2.

3. Results and discussion

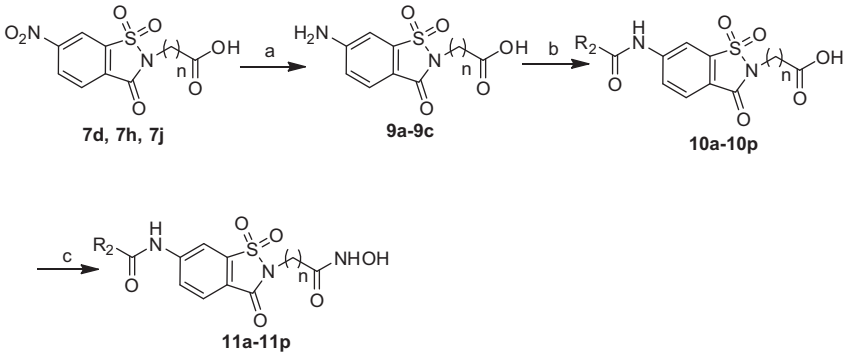
HDAC inhibitory activities of the saccharin hydroxamates were evaluated by the Color de Lys assay and the results were tabulated as IC_{50} values in Table 1. According to the data in Table 1, both the linkers and the substituents on saccharin have significant impacts on the inhibitory activities against HDAC. For example, the compounds with shorter linker (n = 1–4), such as **8a**–**8h**, showed poor inhibition on HDAC. When the length of linker reached to five methylene units, the compounds (e.g. **8i** and **8j**) had good inhibitory activities with IC_{50} value in the micromolar range. This result suggested that the length of the linker was crucial to binding affinities. Moreover, activities of compounds **11a**–**11e** also confirmed this hypothesis.



Scheme 1. Synthesis of intermediate **4**, **6**. Reagents: (a) CrO_3, H_2SO_4, H_2O; (b) H_2, Pd/C, THF; (c) CH_3COOH, HCl, $NaNO_2$, KI, H_2O.

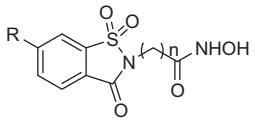


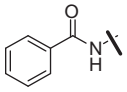
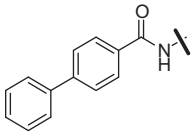
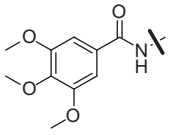
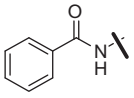
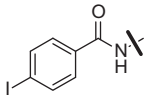
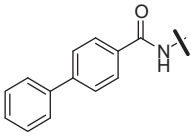
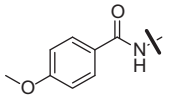
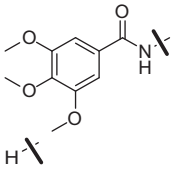
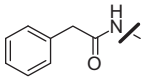
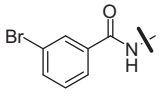
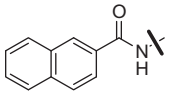
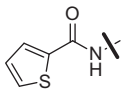
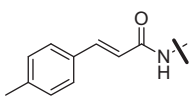
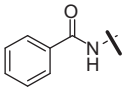
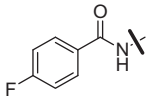
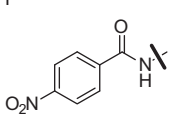
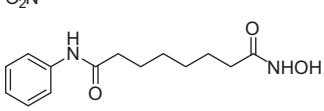
Scheme 2. Synthesis of compounds **8a**–**8k**. Reagents: (a) $NaHCO_3$, DMF; (b) HCl (concd); (c) *i*$BuCO_2Cl$, Et_3N, NH_2OH, THF.



Scheme 3. Synthesis of compounds **11a**–**11p**. Reagents: (a) H_2, Pd/C, THF; (b) (i) R_2CO_2H, $SOCl_2$; (ii) $NaHCO_3$, THF; (c) *i*$BuCO_2Cl$, Et_3N, NH_2OH, THF.

Table 1
In vitro HDAC activity



Compd	R	*n*	IC_{50} of HDAC[a] (μM)	Compd	R	*n*	IC_{50} of HDAC[a] (μM)
8a		1	>5	**8k**		5	0.155 ± 0.015
8b		1	>5	**11e**		5	0.152 ± 0.032
8c		2	>5	**11f**		5	>5
8d		2	>5	**11g**		5	0.353 ± 0.091
11a		2	>5	**11h**		5	0.170 ± 0.068
11b		2	>5	**11i**		5	0.156 ± 0.027
11c		2	>5	**11j**		5	0.244 ± 0.055
8e		3	>5	**11k**		5	0.438 ± 0.019
8f		3	>5	**11l**		5	0.592 ± 0.067
8g		4	>5	**11m**		5	0.113 ± 0.023
8h		4	>5	**11n**		5	1.25 ± 0.388
11d		4	0.417 ± 0.088	**11o**		5	0.170 ± 0.023
8i		5	4.39 ± 0.051	**11p**		5	0.096 ± 0.014
8j		5	3.41 ± 0.042	SAHA			0.135 ± 0.014

[a] All of the compounds were assayed three times, and their inhibition results are means of the three independent assays and expressed with standard deviations.

Table 2
Antiproliferative activities of representative compounds[a]

	IC_{50} (μM)			
	MDA-MB-231	PC-3	KG1	K562
SAHA	4.61 ± 0.80	9.79 ± 3.28	1.15 ± 0.01	3.77 ± 0.13
11e	5.15 ± 1.61	12.63 ± 3.81	2.21 ± 0.01	4.17 ± 0.81
11m	4.34 ± 0.41	9.28 ± 2.17	1.66 ± 0.32	6.02 ± 0.82
11p	7.72 ± 1.44	12.45 ± 2.16	2.64 ± 0.44	8.90 ± 1.61

[a] Each value was reproduced in three independent assays and expressed with standard deviations.

In addition, the substituents on saccharin also affected the inhibitory activities. For example, the minor differences in compounds **8i**–**8k** are the substituents on saccharin ring and they led to the change of IC_{50} values from 4.4 μM to 0.15 μM. The iodo substituent (**8k**, IC_{50} = 0.16 μM) showed similar inhibitory activity with positive control SAHA (IC_{50} = 0.13 μM). But the nitro substituent (**8j**, IC_{50} = 3.41 μM) did not exhibit improvement for the binding affinities compared with **8i** (IC_{50} = 4.4 μM), which did not have any substituent. These results indicated that the substituent on the 6-position of saccharin might be necessary for surface recognition and could be investigated further.

To test this hypothesis, **11e**–**11p** were designed and synthesized. Our preliminary biological evaluations suggested that most of these compounds had similar or even better HDACs inhibitory activities compared with SAHA. But **11f**, **11n** bearing biphenyl and styrene showed poor inhibition, which suggested a large substituent on this position was unfavorable for the interaction between the inhibitor and the narrow channel of HDAC binding pocket. In addition, compound **11l** with slightly poor inhibition activity may be also due to the steric effect derived from the naphathyl fragment. Other compounds, such as **11e**, **11m** and **11p**, possessed similar and even better HDAC inhibitory activity compared with the approved drug SAHA.

To further examine the saccharin hydroxamic acid HDAC inhibitors at the cellular level, active compounds **11e**, **11m** and **11p** were chosen as the representatives to evaluate their antiproliferative activities against the growth of cancer cells. Four tumor cell lines, MDA-MB-231 (breast cancer cell), PC-3 (prostatic cancer cell), KG1 and K562 (myelogenous leukemia cell) were tested using MTT assay. The IC_{50} values were summarized in Table 2. According to the inhibition data, human myelogenous leukemia cells (KG1) was the most sensitive to our saccharin HDACIs. It appeared that all of these compounds possessed better growth inhibition towards blood cancer than solid tumor cell. Among them, **11m** had the most similar inhibition profile and showed higher inhibitory potency on MDA-MB-231and PC-3 compared with SAHA.

In order to understand the interaction between these inhibitors and HDAC, we docked compound **11p** and SAHA in the active site of HDAC2 (PDB code: 3MAX) using AutoDock4.2[15] (Fig. 3). The result suggested that **11p** possessed a similar binding mode to SAHA in the active site of HDAC2. The hydroxamic acid moiety of **11p** and SAHA could chelate Zn^{2+} ion as well as form hydrogen bonds with Glu154 and Tyr308 in the HDAC2 active site. In addition, the nitrogen atom in amide group of **11p** could form another hydrogen bond with Leu267.

4. Conclusions

In conclusion, we have designed and synthesized a novel series of saccharin-based hydroxamic acid HDAC inhibitors, which have different linkers and substitutions in saccharin ring as the surface recognition motifs. The strong enzymatic inhibition of compounds **8k**, **11e**, **11h**–**11j**, **11m**, **11o** and **11p** indicate that the linker with five carbon units between the ZBG and the saccharin ring bearing a suitable substituent is optimal for potency. These results suggest that saccharin-based hydroxamate derivatives could be used as lead compounds to develop novel anticancer agents.

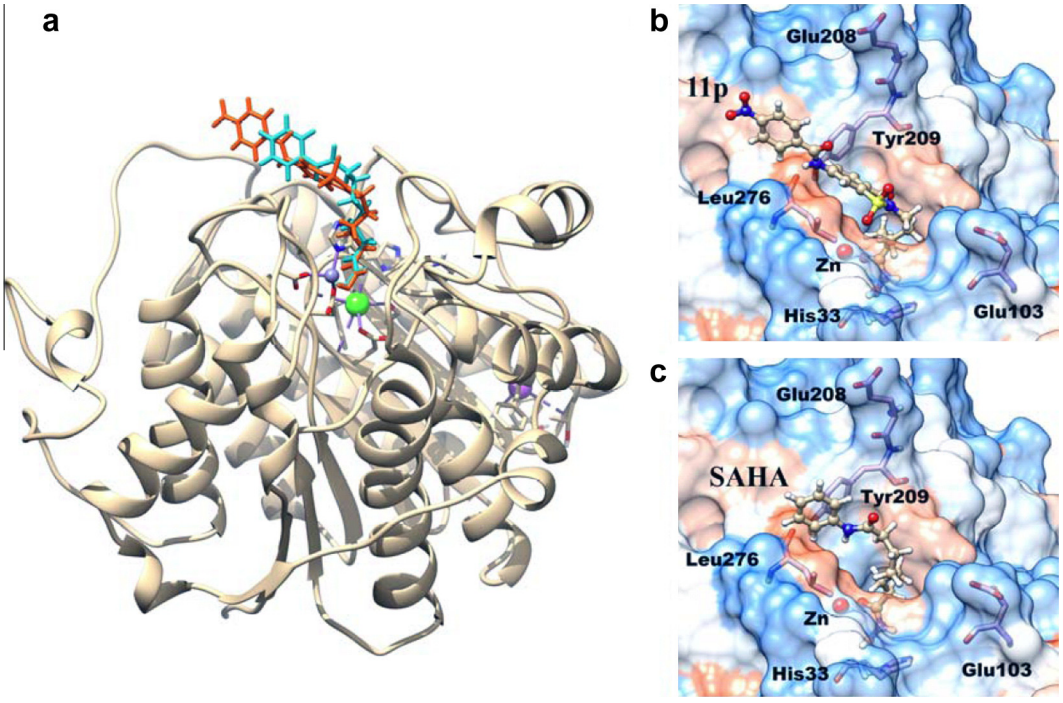


Figure 3. (a) The docking modes of compound **11p** (depicted in orange) and SAHA (depicted in cyan) in the active site of HDAC2; (b) Proposed binding preference of compound **11p**; (c) Proposed binding preference of SAHA. The pictures were produced using UCSF chimera software.[16]

5. Experimental section

5.1. Chemistry: general procedures

All materials and reagents used in this work are analytical reagents without further purification. All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. All reactions were monitored by thin-layer chromatography on 0.25 mm silica gel plates (60GF-254) and visualized with UV light, chloride ferric or iodine vapor. Melting points were determined on an electrothermal melting point apparatus without correction. ESI-MS was determined on an API 4000 spectrometer. NMR spectra were obtained on a Bruker DRX spectrometer (600 MHz) and a Bruker Avance spectrometer (300 MHz). The chemical shifts are defined as δ values (parts per million) relative to TMS internal standard. Significant ^{1}H NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) number of protons. HRMS spectrums were conducted on an Agilent 6510 Quadrupole Time-of-Flight LC/MS deliver. All reported yields are for purified products.

5.1.1. 6-Nitrobenzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (4)

To a solution of chromium trioxide (9.0 g, 900 mmol) in water (67 ml), concentrated sulfuric acid (83.5 ml) was added gradually. The mixture was added 2-methyl-5-nitrobenzenesulfonamide **3** (4.32 g, 20 mmol) and then stirred at room temperature for 24 h. Crude product was obtained by filtration and then washed with water. The filter cake was stirred in 10% sodium bicarbonate solution and the insoluble residue was removed by filtration. The filtrate was acidified with 5% hydrochloric acid solution to generate the purified product with 55% yield, mp: 203–205 °C. ^{1}H NMR (DMSO-d_6) δ 7.91 (d, J = 8.4 Hz, 1H), 8.47 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 8.54 (s, 1H). MS (ESI) m/z: 227.1 $[M-H]^-$.

5.1.2. General procedure for the synthesis of 5 and 9a–9c

5.1.2.1. 6-Aminobenzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (5). To a solution of **4** (6.17 g) in 350 ml THF, 10% Pd/C was added. Then **4** was reduced by hydrogen at atmospheric pressure for 4 h and the catalyst was removed by filtration. The filtrate was evaporated to afford a slightly yellow powder in 95% yield with no more purification, mp: 263–265 °C.

Compounds **9a–9c** were synthesized following the procedure described above.

5.1.2.2. 3-(6-Amino-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)propanoic acid (9a). Yield: 88%, mp: 196–199 °C. ^{1}H NMR (DMSO-d_6) δ 2.64 (t, J = 7.2 Hz, 2H), 3.82 (t, J = 7.2 Hz, 2H), 6.88 (s, 2H), 6.93 (dd, J = 9.0 Hz 2.4 Hz, 1H), 7.04 (d, J = 1.8 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 12.49 (s, 1H). ^{13}C NMR (DMSO-d_6): 32.97, 34.02, 103.10, 111.38, 117.96, 126.49, 139.59, 155.57, 158.72, 171.60. HRMS (AP-ESI) m/z Calcd for $C_{10}H_{10}N_2O_5S$ $[M+H]^+$ 271.0383. Found: 271.0381.

5.1.2.3. 5-(6-Amino-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)pentanoic acid (9b). Yield: 92%, mp: 117–119 °C. ^{1}H NMR (DMSO-d_6) δ 1.53 (m, J = 7.2 Hz, 2H), 1.67 (m, J = 7.2 Hz, 2H), 2.24 (t, J = 7.2 Hz, 1H), 2.32 (t, J = 7.2 Hz, 1H), 3.59 (t, J = 7.2 Hz, 2H), 6.85 (s, 2H), 6.92 (dd, J = 9.0 Hz 1.8 Hz, 1H), 7.04 (d, J = 1.2 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 12.04 (s, 1H). ^{13}C NMR (DMSO-d_6): 21.59, 27.46, 32.77, 37.75, 103.08, 111.44, 117.91, 126.41, 139.56, 155.51, 158.99, 174.15. HRMS (AP-ESI) m/z Calcd for $C_{12}H_{14}N_2O_5S$ $[M+H]^+$ 299.0696. Found: 299.0688.

5.1.2.4. 6-(6-Amino-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (9c). Yield: 89%, mp: 168–170 °C. ^{1}H NMR (DMSO-d_6) δ 1.31 (m, J = 7.2 Hz, 2H), 1.49 (m, J = 7.2 Hz, 2H), 1.65 (m, J = 7.2 Hz, 2H), 2.18 (t, J = 7.2 Hz, 2H), 3.57 (t, J = 7.2 Hz, 2H), 6.85 (s, 2H), 6.92 (d, J = 7.8 Hz, 1H), 7.03 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 12.00 (s, 1H). ^{13}C NMR (DMSO-d_6): 23.89, 25.58, 27.84, 33.40, 37.97, 103.08, 111.50, 117.90, 126.39, 139.57, 155.48, 158.98, 174.33. HRMS (AP-ESI) m/z Calcd for $C_{13}H_{16}N_2O_5S$ $[M+H]^+$ 313.0853. Found: 313.0862.

5.1.3. 6-Iodobenzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (6)

Compound **6** was synthesized according to literature procedures.[17] Yield: 95%, mp: 224–226 °C. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.26 (s, 1H). MS (ESI) m/z: 308.2 $[M-H]^-$.

5.1.4. General procedure for the synthesis of 7a–7h

Saccharin or **4** (6.6 mmol) was added to a solution of sodium bicarbonate (1.1 g, 13.2 mmol) in 3 ml of DMF. The corresponding ester (7.9 mmol) was added slowly and the resulting solution was stirred for 4 h at 60–80 °C. The mixture was poured into 15 ml of water to give the crude product. It can be recrystallized from EtOH to give pure product.

The appropriate ester (1.00 mmol) was suspended in 3 ml of concentrated hydrochloric acid and heated under stirring at 100 °C until hydrolysis was completed (3–4 h, TLC analysis). After cooling to room temperature, the reaction mixture was diluted with water and the precipitated carboxylic acid product was collected and purified by recrystallization (*n*-hexane/ethyl acetate).

5.1.4.1. 2-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)acetic acid (7a). Yield: 67%, mp: 211–213 °C. ^{1}H NMR (DMSO-d_6) δ 4.49 (s, 2H), 8.02 (td, J = 7.8 Hz 1.2 Hz, 1H), 8.08 (td, J = 7.8 Hz 1.2 Hz, 1H), 8.15 (dd, J = 7.8 Hz 0.6 Hz, 1H), 8.35 (d, J = 7.8 Hz, 1H), 13.37 (s, 1H). MS (ESI) m/z: 240.2 $[M-H]^-$.

5.1.4.2. 2-(6-Nitro-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3H)-yl)acetic acid (7b). Yield: 71%, mp: 267–269 °C. ^{1}H NMR (DMSO-d_6) δ 4.55 (s, 2H), 8.36 (d, J = 8.4 Hz, 1H), 8.73 (dd, J = 8.4 Hz 2.1 Hz, 1H), 9.31 (d, J = 2.1 Hz, 1H). MS (ESI) m/z: 285.1$[M-H]^-$.

5.1.4.3. 3-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)propanoic acid (7c). Yield: 67%, mp: 164–166 °C. ^{1}H NMR (DMSO-d_6) δ 2.71 (t, J = 7.2 Hz, 2H), 3.94 (t, J = 7.2 Hz, 2H), 7.99 (t, J = 7.8 Hz, 1H), 8.05 (t, J = 7.8 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 12.53 (s, 1H). MS (ESI) m/z: 254.2 $[M-H]^-$.

5.1.4.4. 3-(6-Nitro-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)propanoic acid (7d). Yield: 73%, mp: 208–210 °C. ^{1}H NMR (DMSO-d_6) δ 2.73 (t, J = 7.2 Hz, 2H), 3.98 (t, J = 7.2 Hz, 2H), 8.32 (d, J = 8.4 Hz, 1H), 8.71 (d, J = 7.8 Hz, 1H), 9.28 (s, 1H), 12.55 (s, 1H). MS (ESI) m/z: 299.4 $[M-H]^-$.

5.1.4.5. 4-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)butanoic acid (7e). Yield: 73%, mp: 110–112 °C. ^{1}H NMR (DMSO-d_6) δ 1.90 (m, J = 7.2 Hz 2H), 2.34 (t, J = 7.2 Hz, 2H), 3.74 (t, J = 7.2 Hz, 2H), 7.97 (m, 2H), 8.09 (d, J = 6.9 Hz, 1H), 8.29 (d, J = 6.9 Hz 0.9 Hz, 1H), 12.14 (s, 1H). MS (ESI) m/z: 268.2 $[M-H]^-$.

5.1.4.6. 4-(6-Nitro-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)butanoic acid (7f). Yield: 75%, mp: 164–166 °C. ^{1}H NMR (DMSO-d_6) δ 1.94 (m, J = 7.2 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H), 3.80 (t, J = 7.2 Hz, 2H), 8.31 (d, J = 8.4 Hz, 1H), 8.71 (d, J = 8.4 Hz, 1H), 9.27 (s, 1H), 12.15 (s, 1H). MS (ESI) m/z: 313.3 $[M-H]^-$.

5.1.4.7. 5-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)pentanoic acid (7g). Yield: 75%, mp: 86–89 °C. ^{1}H NMR (DMSO-d_6) δ 1.56 (m, J = 7.2 Hz, 2H), 1.73 (m, J = 7.2 Hz, 2H), 2.26 (t, J = 7.2 Hz,

2H), 3.71 (t, J = 7.2 Hz, 2H), 7.99 (t, J = 7.8 Hz, 1H), 8.04 (t, J = 7.2 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 12.06 (s, 1H). MS (ESI) m/z: 282.4 $[M-H]^-$.

5.1.4.8. 5-(6-Nitro-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)pentanoic acid (7h). Yield: 71%, mp: 151–153 °C. ^{1}H NMR (DMSO-d_6) δ 1.57 (m, J = 7.2 Hz, 2H), 1.74 (m, J = 7.2 Hz, 2H), 2.26 (t, J = 7.2 Hz, 2H), 3.75 (t, J = 7.2 Hz, 2H), 8.32 (d, J = 8.4 Hz, 1H), 8.71 (dd, J = 8.4 Hz 2.4 Hz, 1H), 9.27 (d, J = 1.8 Hz, 1H), 12.06 (s, 1H). MS (ESI) m/z: 327.3 $[M-H]^-$.

5.1.5. General procedure for the synthesis of 7i–7k

Saccharin, 4 or **6** (13.2 mmol) and sodium bicarbonate (1.1 g, 13.2 mmol) were added to 5 ml of DMF. 6-Bromohexanoic acid (14.0 mmol) was added slowly and the resulting solution was stirred for 4 h at 60–80 °C. The mixture was poured into 25 ml water to give the crude product. It can be recrystallized from ethanol or water to give pure product.

5.1.5.1. 6-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (7i). Yield: 81%, mp: 83–85 °C. ^{1}H NMR (DMSO-d_6) δ 1.35(m, J = 7.2 Hz, 2H), 1.51 (m, J = 7.2 Hz, 2H), 1.71 (m, J = 7.2 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 3.69 (t, J = 7.2 Hz, 2H), 7.99 (t, J = 7.2 Hz, 1H), 8.04 (t, J = 7.2 Hz, 1H), 8.10 (d, J = 7.2 Hz, 1H), 8.30 (d, J = 7.2 Hz, 1H), 12.00 (s, 1H). MS (ESI) m/z: 296.4 $[M-H]^-$.

5.1.5.2. 6-(6-Nitro-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (7j). Yield: 87%, mp: 165–167 °C. ^{1}H NMR (DMSO-d_6) δ 1.36 (m, J = 7.2 Hz, 2H), 1.52 (m, J = 7.2 Hz, 2H), 1.74 (m, J = 7.2 Hz, 2H), 2.20 (t, J = 7.2 Hz, 2H), 3.74 (t, J = 7.2 Hz, 2H), 8.31 (d, J = 8.4 Hz, 1H), 8.71 (dd, J = 7.8 Hz 1.8 Hz, 1H), 9.27 (s, 1H), 12.01 (s, 1H). MS (ESI) m/z: 341.3 $[M-H]^-$.

5.1.5.3. 6-(6-Iodo-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (7k). Yield: 84%, mp: 153–155 °C. ^{1}H NMR (DMSO-d_6) δ 1.32 (m, J = 7.2 Hz, 2H), 1.49 (m, J = 7.2 Hz, 2H), 1.69 (m, J = 7.2 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 3.98 (t, J = 7.2 Hz, 2H), 7.81 (d, J = 7.2 Hz, 1H), 8.35 (d, J = 7.8 Hz, 1H), 8.82 (s, 1H), 12.01 (s, 1H). MS (ESI) m/z: 422.2 $[M-H]^-$.

5.1.6. General procedure for the synthesis of 10a–10p

The carboxylic acid (6.5 mmol) was dissolved in excess thionyl chloride (10 ml) and two drops of DMF. The mixture was kept 60 °C for 2 h and excess thionyl chloride was evaporated. The freshly prepared acyl chloride was then dissolved in 15 ml of THF and the resulting solution was added to the mixture of **9a**, **9b** or **9c** (5.5 mmol) and sodium bicarbonate (13.5 mmol).The resulting mixture was stirred for 8 h at room temperature. After removing the solvent, the mixture was acidified with 1 M HCl and the final product was purified by recrystallization in water/ethanol.

5.1.6.1. 3-(6-Benzamido-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)propanoic acid (10a). Yield: 75%, mp: 182–185 °C. ^{1}H NMR (DMSO-d_6) δ 2.71 (t, J = 7.2 Hz, 2H), 3.93 (t, J = 7.2 Hz, 2H), 7.58 (t, J = 7.8 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 8.00 (d, J = 7.2 Hz, 2H), 8.12 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.65 (s, 1H), 11.04 (s, 1H), 12.54 (s, 1H). MS (ESI) m/z: 373.2 $[M-H]^-$.

5.1.6.2. 3-(6-([1,1′-Biphenyl]-4-ylcarboxamido)-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)propanoic acid (10b). Yield: 55%, mp: 267–269 °C. ^{1}H NMR (DMSO-d_6) δ 2.72 (t, J = 7.2 Hz, 2H), 3.95 (t, J = 7.2 Hz, 2H), 7.45 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.78 (d, J = 7.2 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 9.0 Hz, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.26 (dd, J = 8.4 Hz 1.2 Hz, 1H), 8.67 (d, J = 1.2 Hz, 1H), 11.08 (s, 1H), 12.54 (s, 1H). MS (ESI) m/z: 449.4 $[M-H]^-$.

5.1.6.3. 3-(1,1-Dioxido-3-oxo-6-(3,4,5-trimethoxybenzamido)benzo[*d*]isothiazol-2(3*H*)-yl)propanoic acid (10c). Yield: 47%, mp: 252–255 °C. ^{1}H NMR (DMSO-d_6) δ 2.71 (t, J = 7.2 Hz, 2H), 3.75 (s, 3H), 3.89 (s, 6H), 3.93 (t, J = 7.2 Hz, 2H), 7.32 (s, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.23 (dd, J = 9.0 Hz 1.8 Hz, 1H), 8.58 (d, J = 1.2 Hz, 1H), 10.86 (s, 1H), 12.53 (s, 1H). MS (ESI) m/z: 463.4 $[M-H]^-$.

5.1.6.4. 5-(6-Benzamido-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)pentanoic acid (10d). Yield: 67%, mp: 162–165 °C. ^{1}H NMR (DMSO-d_6) δ 1.54 (m, J = 7.2 Hz, 2H), 1.71 (m, J = 7.2 Hz, 2H), 2.25 (t, J = 7.2 Hz, 2H), 3.69 (t, J = 7.2 Hz, 2H), 7.56 (t, J = 7.5 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.99 (d, J = 7.8 Hz, 2H), 8.10 (d, J = 8.4 Hz, 1H), 8.23 (dd, J = 8.7 Hz 1.8 Hz, 1H), 8.64 (d, J = 1.8 Hz, 1H), 11.02 (s, 1H), 12.04 (s, 1H). MS (ESI) m/z: 401.3 $[M-H]^-$.

5.1.6.5. 6-(6-Benzamido-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10e). Yield: 67%, mp: 147–150 °C. ^{1}H NMR (DMSO-d_6) δ 1.34 (m, J = 7.2 Hz, 2H), 1.52 (m, J = 7.2 Hz, 2H), 1.71 (m, J = 7.2 Hz, 2H), 2.21 (t, J = 7.2 Hz, 2H), 3.69 (t, J = 7.2 Hz, 2H), 7.58 (t, J = 7.2 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 8.01 (d, J = 7.8 Hz, 2H), 8.10 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.67 (s, 1H), 11.08 (s, 1H), 12.02 (s, 1H). MS (ESI) m/z: 415.4 $[M-H]^-$.

5.1.6.6. 6-(6-([1,1′-Biphenyl]-4-ylcarboxamido)-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10f). Yield: 42%, mp: 205–207 °C. ^{1}H NMR (DMSO-d_6) δ 1.36 (m, J = 7.2 Hz, 2H), 1.53 (m, J = 7.2 Hz, 2H), 1.71 (m, J = 7.2 Hz, 2H), 2.20 (t, J = 7.2 Hz, 2H), 3.69 (t, J = 7.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.2 Hz, 2H), 7.78 (d, J = 7.8 Hz, 2H), 7.90 (d, J = 7.8 Hz, 2H), 8.11 (d, J = 8.4 Hz, 2H), 8.12 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.67 (s, 1H), 11.07 (s, 1H), 12.03 (s, 1H). MS (ESI) m/z: 491.4 $[M-H]^-$.

5.1.6.7. 6-(1,1-Dioxido-3-oxo-6-(3,4,5-trimethoxybenzamido)benzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10g). Yield: 57%, mp: 202–204 °C. ^{1}H NMR (DMSO-d_6) δ 1.35 (m, J = 7.2 Hz, 2H), 1.53 (m, J = 7.2 Hz, 2H), 1.72 (m, J = 7.2 Hz, 2H), 2.20 (t, J = 7.2 Hz, 2H), 3.69 (t, J = 7.2 Hz, 2H), 3.75 (s, 3H), 3.89 (s, 6H), 7.32 (s, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.23 (dd, J = 9.0 Hz 1.8 Hz, 1H), 8.59 (d, J = 1.2 Hz, 1H), 10.86 (s, 1H), 12.01 (s, 1H). MS (ESI) m/z: 505.4 $[M-H]^-$.

5.1.6.8. 6-(6-(4-Iodobenzamido)-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10h). Yield: 77%, mp: 209–211 °C. ^{1}H NMR (DMSO-d_6) δ 1.34 (m, J = 7.2 Hz, 2H), 1.52 (m, J = 7.2 Hz, 2H), 1.71 (m, J = 7.2 Hz, 2H), 2.20 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.62 (s, 1H), 11.04 (s, 1H), 12.01 (s, 1H). MS (ESI) m/z: 541.3 $[M-H]^-$.

5.1.6.9. 6-(6-(4-Methoxybenzamido)-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10i). Yield: 74%, mp: 135–138 °C. ^{1}H NMR (DMSO-d_6) δ 1.34 (m, J = 7.2 Hz, 2H), 1.52 (m, J = 7.2 Hz, 2H), 1.71 (m, J = 7.2 Hz, 2H), 2.20 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 3.83 (s, 3H), 7.11 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 9.0 Hz, 1H), 8.22 (dd, J = 8.4 Hz 1.8 Hz, 1H), 8.64 (d, J = 1.2 Hz, 1H), 10.85 (s, 1H), 12.07 (s, 1H). MS (ESI) m/z: 445.5 $[M-H]^-$.

5.1.6.10. 6-(1,1-Dioxido-3-oxo-6-(2-phenylacetamido)benzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10j). Yield: 67%, mp: 98–100 °C. ^{1}H NMR (DMSO-d_6) δ 1.32 (m, J = 7.2 Hz, 2H), 1.48 (m, J = 7.2 Hz, 2H), 1.66 (m, J = 7.2 Hz, 2H), 2.18 (t, J = 7.2 Hz, 2H), 3.65 (t, J = 7.2 Hz, 2H), 3.76 (s, 2H), 7.24 (m, 5H), 7.92 (dd,

J = 8.7 Hz 1.8 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 8.48 (d, J = 1.8 Hz, 1H), 11.03 (s, 1H), 11.98 (s, 1H). MS (ESI) m/z: 429.5 $[M-H]^-$.

5.1.6.11. 6-(6-(3-Bromobenzamido)-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10k). Yield: 75%, mp: 142–144 °C. ^{1}H NMR (DMSO-d_6) δ 1.31 (m, J = 7.2 Hz, 2H), 1.50 (m, J = 7.2 Hz, 2H), 1.69 (m, J = 7.2 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 7.53 (t, J = 8.1 Hz, 1H), 7.85 (m, J = 8.1 Hz 1.2 Hz, 1H), 7.98 (dt, J = 8.4 Hz 1.2 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.19 (t, J = 1.8 Hz, 1H), 8.21 (dd, J = 8.4 Hz 1.8 Hz, 1H), 8.60 (d, J = 1.8 Hz, 1H), 11.08 (s, 1H), 11.99 (s, 1H). MS (ESI) m/z: 493.3/495.2 $[M-H]^-$.

5.1.6.12. 6-(6-(2-Naphthamido)-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10l). Yield: 65%, mp: 156–159 °C. ^{1}H NMR (DMSO-d_6) δ 1.32 (m, J = 7.2 Hz, 2H), 1.51 (m, J = 7.2 Hz, 2H), 1.70 (m, J = 7.2 Hz, 2H), 2.18 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 7.64 (m, 2H), 8.03 (m, 5H), 8.28 (dd, J = 8.4 Hz 1.5 Hz, 1H), 8.66 (s, 1H), 8.68 (d, J = 1.8 Hz, 1H), 11.20 (s, 1H), 12.00 (s, 1H). MS (ESI) m/z: 465.5 $[M-H]^-$.

5.1.6.13. 6-(1,1-Dioxido-3-oxo-6-(thiophene-2-carboxamido)benzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10m). Yield: 67%, mp: 201–203 °C. ^{1}H NMR (DMSO-d_6) δ 1.31 (m, J = 7.2 Hz, 2H), 1.47 (m, J = 7.2 Hz, 2H), 1.68 (m, J = 7.2 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 7.28 (m, 1H), 7.97 (dd, J = 5.1 Hz 0.9 Hz, 1H), 8.10 (m, 2H), 8.18 (dd, J = 8.4 Hz 1.8 Hz, 1H), 8.58 (d, J = 1.8 Hz, 1H), 10.96 (s, 1H), 12.00 (s, 1H). MS (ESI) m/z: 421.3 $[M-H]^-$.

5.1.6.14. (*E*)-6-(1,1-Dioxido-3-oxo-6-(3-(*p*-tolyl)acrylamido)benzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10n). Yield: 75%, mp: 249–251 °C. ^{1}H NMR (DMSO-d_6) δ 1.32 (m, J = 7.2 Hz, 2H), 1.49 (m, J = 7.2 Hz, 2H), 1.67 (m, J = 7.2 Hz, 2H), 2.18 (t, J = 7.2 Hz, 2H), 2.35 (s, 3H), 3.66 (t, J = 7.2 Hz, 2H), 6.76 (d, J = 15.9 Hz, 1H), 7.27 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.65 (d, J = 15.6 Hz, 1H), 7.96 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H), 8.61 (d, J = 1.5 Hz, 1H), 11.04 (s, 1H), 12.01 (s, 1H). MS (ESI) m/z: 455.4 $[M-H]^-$.

5.1.6.15. 6-(6-(4-Fluorobenzamido)-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10o). Yield: 73%, mp: 186–188 °C. ^{1}H NMR (DMSO-d_6) δ 1.29 (m, J = 7.2 Hz, 2H), 1.47 (m, J = 7.2 Hz, 2H), 1.68 (m, J = 7.2 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 7.41 (t, J = 9.0 Hz, 2H), 8.07 (m, 3H), 8.20 (dd, J = 8.7 Hz 1.8 Hz, 1H), 8.62 (d, J = 1.8 Hz, 1H), 11.03 (s, 1H), 12.01 (s, 1H). MS (ESI) m/z: 433.4 $[M-H]^-$.

5.1.6.16. 6-(6-(4-Nitrobenzamido)-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanoic acid (10p). Yield: 71%, mp: 218–220 °C. ^{1}H NMR (DMSO-d_6) δ 1.31 (m, J = 7.2 Hz, 2H), 1.50 (m, J = 7.2 Hz, 2H), 1.69 (m, J = 7.2 Hz, 2H), 2.19 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.21 (m, 3H), 8.41 (d, J = 8.7 Hz, 2H), 8.63 (d, J = 1.5 Hz, 1H), 11.32 (s, 1H), 12.02 (s, 1H). MS (ESI) m/z: 460.5 $[M-H]^-$.

5.1.7. General procedure for the synthesis of 8a–8k and 11a–1p

To a solution of the corresponding acid (3.3 mmol) in anhydrous THF (20 ml) was added Et_3N (0.33 ml, 3.3 mmol) and Isobutyl chloroformate (0.43 ml, 3.3 mmol) sequentially. The resulting solution was stirred for 10 min at 0 °C. A solution of $NH_2OH{\cdot}HCl$ (0.34 g, 5.0 mmol) and Et_3N (0.53 ml, 5.0 mmol) in anhydrous CH_3OH (1 ml) was added to the above mixture. The resulting solution was then stirred for 3–6 h at room temperature. After filtering the mixture, removing the solvents, the resulting residue was dissolved in ethyl acetate (50 ml), washed with HCl (1 M, 55 ml) and saturated sodium bicarbonate (50 ml) three times, respectively. The cured product can be purified by recrystallization with ethyl acetate or column chromatography (dichloromethane/methanol, 100:1).

5.1.7.1. 2-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)-*N*-hydroxyacetamide (8a). Yield: 42%, mp: 172–174 °C. ^{1}H NMR (DMSO-d_6) δ 4.26 (s, 2H), 8.01 (t, J = 7.2 Hz, 1H), 8.07 (t, J = 7.2 Hz, 1H), 8.13 (d, J = 7.2 Hz, 1H), 8.33 (d, J = 7.2 Hz, 1H), 9.08 (s, 1H), 10.83 (s, 1H). ^{13}C NMR (DMSO-d_6): 37.99, 121.60, 125.05, 126.48, 135.26, 135.79, 136.73, 158.54, 161.83. HRMS (AP-ESI) m/z Calcd for $C_9H_8N_2O_5S$ $[M+H]^+$ 257.0227. Found: 257.0220.

5.1.7.2. *N*-Hydroxy-2-(6-nitro-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)acetamide (8b). Yield: 31%, mp: 156–159 °C. ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 2H), 8.36 (d, J = 8.4 Hz, 1H), 8.73 (d, J = 8.4 Hz, 1H), 9.12 (s, 1H), 9.30 (s, 1H), 10.86 (s, 1H). ^{13}C NMR (DMSO-d_6): 38.54, 118.16, 126.73, 130.32, 131.03, 137.66, 151.85, 157.01, 161.45. HRMS (AP-ESI) m/z Calcd for $C_9H_7N_3O_7S$ $[M+H]^+$ 302.0077. Found: 302.0071.

5.1.7.3. 3-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)-*N*-hydroxypropanamide (8c). Yield: 27%, mp: 180–182 °C. ^{1}H NMR (DMSO-d_6) δ 2.47 (t, J = 7.2 Hz, 2H), 3.90 (t, J = 7.2 Hz, 2H), 7.99 (t, J = 7.2 Hz, 1H), 8.05 (t, J = 7.8 Hz, 1H), 8.11 (d, J = 7.2 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.85 (s, 1H), 10.57 (s, 1H). ^{13}C NMR (DMSO-d_6): 31.07, 34.86, 121.41, 125.02, 126.22, 135.25, 135.77, 136.62, 158.28, 165.81. HRMS (AP-ESI) m/z Calcd for $C_{10}H_{10}N_2O_5S$ $[M+H]^+$ 271.0383. Found: 271.0382.

5.1.7.4. *N*-Hydroxy-3-(6-nitro-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)propanamide (8d). Yield: 23% yield, mp: 191–193 °C. ^{1}H NMR (DMSO-d_6) δ 2.49 (t, J = 7.2 Hz, 2H), 3.95 (t, J = 7.2 Hz, 2H), 8.32 (d, J = 8.4 Hz, 1H), 8.71 (dd, J = 8.4 Hz 1.8 Hz, 1H), 8.85 (s, 1H), 9.28 (s, 1H), 10.58 (s, 1H). ^{13}C NMR (DMSO-d_6): 30.93, 35.42, 117.98, 126.73, 130.25, 130.97, 137.59, 151.78, 156.73, 165.56. HRMS (AP-ESI) m/z Calcd for $C_{10}H_9N_3O_7S$ $[M+H]^+$ 316.0234. Found: 316.0228.

5.1.7.5. 4-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)-*N*-hydroxybutanamide (8e). Yield: 33%, mp: 106–108 °C. ^{1}H NMR (DMSO-d_6) δ 1.94 (m, J = 7.2 Hz, 2H), 2.09 (t, J = 7.2 Hz, 2H), 3.73 (t, J = 7.2 Hz, 2H), 8.00 (t, J = 7.2 Hz, 1H), 8.05 (t, J = 7.2 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.78 (s, 1H), 10.42 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.12, 29.36, 38.26, 121.45, 125.01, 126.32, 135.19, 135.70, 136.69, 158.51, 168.15. HRMS (AP-ESI) m/z Calcd for $C_{11}H_{12}N_2O_5S$ $[M+H]^+$ 285.0540. Found: 285.0531.

5.1.7.6. *N*-Hydroxy-4-(6-nitro-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)butanamide (8f). Yield: 53%, mp: 156–158 °C. ^{1}H NMR (DMSO-d_6) δ 1.95 (m, J = 7.2 Hz, 2H), 2.09 (t, J = 7.2 Hz, 2H), 3.77 (t, J = 7.2 Hz, 2H), 8.32 (d, J = 8.4 Hz, 1H), 8.71 (dd, J = 8.4 Hz 1.8 Hz, 1H), 9.03 (s, 1H), 9.28 (d, J = 1.2 Hz, 1H), 10.39 (s, 1H). ^{13}C NMR (DMSO-d_6): 23.99, 29.29, 38.82, 117.92, 126.73, 130.21, 131.03, 137.57, 151.75, 156.98, 168.11. HRMS (AP-ESI) m/z Calcd for $C_{11}H_{11}N_3O_7S$ $[M+H]^+$ 330.0390. Found: 330.0380.

5.1.7.7. 5-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)-*N*-hydroxypentanamide (8g). Yield: 35%, mp: 103–105 °C. ^{1}H NMR (DMSO-d_6) δ 1.56 (m, J = 7.2 Hz, 2H), 1.68 (m, J = 7.2 Hz, 2H), 1.99 (t, J = 7.2 Hz, 2H), 3.70 (t, J = 7.2 Hz, 2H), 7.99 (t, J = 7.8 Hz, 1H), 8.04 (t, J = 7.8 Hz, 1H), 8.10 (d, J = 7.2 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.70 (s, 1H), 10.37 (s, 1H). ^{13}C NMR (DMSO-d_6): 22.38, 27.47, 31.65, 38.39, 121.43, 124.98, 126.25, 135.18,

135.70, 136.70, 158.52, 168.69. HRMS (AP-ESI) *m*/*z* Calcd for $C_{12}H_{14}N_2O_5S$ $[M+H]^+$ 299.0696. Found: 299.0699.

5.1.7.8. *N*-Hydroxy-5-(6-nitro-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)pentanamide (8h). Yield: 31%, mp: 157–159 °C. ^{1}H NMR (DMSO-d_6) δ 1.57 (m, J = 7.2 Hz, 2H), 1.70 (m, J = 7.2 Hz, 2H), 1.99 (t, J = 7.2 Hz, 2H), 3.74 (t, J = 7.2 Hz, 2H), 8.31 (d, J = 8.4 Hz, 1H), 8.70 (s, 1H), 8.71 (dd, J = 8.4 Hz 1.8 Hz, 1H), 9.27 (d, J = 1.2 Hz, 1H), 10.37 (s, 1H). ^{13}C NMR (DMSO-d_6): 22.33, 27.35, 31.62, 38.99, 117.91, 126.74, 130.22, 130.94, 137.59, 151.75, 157.00, 168.64. HRMS (AP-ESI) *m*/*z* Calcd for $C_{12}H_{13}N_3O_7S$ $[M+H]^+$ 344.0547. Found: 344.0552.

5.1.7.9. 6-(1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)-*N*-hydroxyhexanamide (8i). Yield: 32%, mp: 139–141 °C. ^{1}H NMR (DMSO-d_6) δ 1.31 (m, J = 7.2 Hz, 2H), 1.50 (m, J = 7.2 Hz, 2H), 1.70 (m, J = 7.2 Hz, 2H), 1.93 (t, J = 7.2 Hz, 2H), 3.69 (t, J = 7.2 Hz, 2H), 7.99 (t, J = 7.2 Hz, 1H), 8.04 (t, J = 7.2 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H), 8.67 (s, 1H), 10.34 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.56, 25.66, 27.61, 32.02, 38.52, 121.42, 125.00, 126.27, 135.19, 135.70, 136.72, 158.51, 168.92. HRMS (AP-ESI) *m*/*z* Calcd for $C_{13}H_{16}N_2O_5S$ $[M+H]^+$ 313.0853. Found: 313.0858.

5.1.7.10. *N*-Hydroxy-6-(6-nitro-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanamide (8j). Yield: 27%, mp: 158–160 °C. ^{1}H NMR (DMSO-d_6) δ 1.33 (m, J = 7.2 Hz, 2H), 1.51 (m, J = 7.2 Hz, 2H), 1.73 (m, J = 7.2 Hz, 2H),1.94 (t, J = 7.2 Hz, 2H), 3.73 (t, J = 7.2 Hz, 2H), 8.31 (d, J = 8.4 Hz, 1H), 8.67 (s, 1H), 8.71 (dd, J = 8.4 Hz 1.2 Hz, 1H), 9.27 (d, J = 1.8 Hz, 1H), 10.34 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.54, 25.64, 27.50, 32.00, 38.62, 117.89, 126.74, 130.21, 130.94, 137.60, 151.75, 156.98, 168.90. HRMS (AP-ESI) *m*/*z* Calcd for $C_{13}H_{15}N_3O_7S$ $[M+H]^+$ 358.0703. Found: 358.0695.

5.1.7.11. *N*-Hydroxy-6-(6-iodo-1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(3*H*)-yl)hexanamide (8k). Yield: 34%, mp: 122–124 °C. ^{1}H NMR (DMSO-d_6) δ 1.31 (m, J = 7.2 Hz, 2H), 1.51 (m, J = 7.2 Hz, 2H), 1.69 (m, J = 7.2 Hz, 2H), 1.93 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 7.81 (d, J = 7.2 Hz, 1H), 8.35 (d, J = 7.8 Hz, 1H), 8.66 (s, 1H), 8.82 (s, 1H), 10.33 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.54, 25.64, 27.56, 32.01, 38.64, 103.79, 125.70, 126.25, 129.82, 137.76, 143.99, 158.20, 168.89. HRMS (AP-ESI) *m*/*z* Calcd for $C_{13}H_{15}IN_2O_5S$ $[M+H]^+$ 438.9819. Found: 438.9824.

5.1.7.12. *N*-(2-(3-(Hydroxyamino)-3-oxopropyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)benzamide (11a). Yield: 25%, mp: 239–241 °C. ^{1}H NMR (DMSO-d_6) δ 2.48 (t, J = 7.2 Hz, 2H), 3.90 (t, J = 7.2 Hz, 2H), 7.58 (t, J = 7.2 Hz, 2H), 7.66 (t, J = 7.2 Hz, 1H), 8.00 (d, J = 7.2 Hz, 2H), 8.12 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.65 (s, 1H), 8.86 (s, 1H), 10.59 (s, 1H), 11.05 (s, 1H). ^{13}C NMR (DMSO-d_6): 31.36, 35.10, 110.96, 120.52, 125.41, 126.33, 128.10, 128.73, 132.55, 133.97, 138.09, 145.87, 158.14, 165.84, 166.66. HRMS (AP-ESI) *m*/*z* Calcd for $C_{17}H_{15}N_3O_6S$ $[M+H]^+$ 390.0754. Found: 390.0762.

5.1.7.13. *N*-(2-(3-(Hydroxyamino)-3-oxopropyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)-[1,1′-biphenyl]-4-carboxamide (11b). Yield: 53%, mp: 230–232 °C. ^{1}H NMR (DMSO-d_6) δ 2.49 (t, J = 7.2 Hz, 2H), 3.91 (t, J = 7.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.78 (d, J = 7.2 Hz, 2H), 7.90 (d, J = 7.8 Hz, 2H), 8.11 (d, J = 7.8 Hz, 2H), 8.12 (d, J = 7.8 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.69 (s, 1H), 8.88 (s, 1H), 10.60 (s, 1H), 11.08 (s, 1H). ^{13}C NMR (DMSO-d_6): 31.21, 34.93, 110.79, 120.31, 125.22, 126.12, 126.70, 126.93, 128.29, 128.66, 129.04, 132.44, 137.91, 138.82, 143.85, 145.73, 157.97, 165.69, 166.06. HRMS (AP-ESI) *m*/*z* Calcd for $C_{23}H_{19}N_3O_6S$ $[M+H]^+$ 466.1067. Found: 466.1070.

5.1.7.14. *N*-(2-(3-(Hydroxyamino)-3-oxopropyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)-3,4,5-trimethoxybenzamide (11c). Yield: 43%, mp: 220–222 °C. ^{1}H NMR (DMSO-d_6) δ 2.48 (t, J = 7.2 Hz, 2H), 3.76 (s, 3H), 3.89 (s, 6H), 3.92 (t, J = 7.2 Hz, 2H), 7.32 (s, 2H), 8.13 (d, J = 9.0 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.60 (s, 1H), 8.86 (s, 1H), 10.59 (s, 1H), 10.87 (s, 1H). ^{13}C NMR (DMSO-d_6): 31.19, 34.92, 56.12, 60.13, 105.60, 110.98, 120.31, 125.29, 126.10, 128.82, 137.87, 140.94, 145.61, 152.68, 157.97, 165.69, 165.78. HRMS (AP-ESI) *m*/*z* Calcd for $C_{20}H_{21}N_3O_9S$ $[M+H]^+$ 480.1071. Found: 480.1061.

5.1.7.15. *N*-(2-(5-(Hydroxyamino)-5-oxopentyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)benzamide (11d). Yield: 53%, mp: 207–209 °C. ^{1}H NMR (DMSO-d_6) δ 1.53 (m, J = 7.2 Hz, 2H), 1.67 (m, J = 7.2 Hz, 2H), 1.98 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 7.56 (t, J = 7.5 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.99 (d, J = 7.2 Hz, 2H), 8.10 (d, J = 8.4 Hz, 1H), 8.22 (dd, J = 8.7 Hz 1.2 Hz, 1H), 8.65 (d, J = 1.5 Hz, 1H), 8.68 (d, J = 1.5 Hz, 1H), 10.36 (s, 1H), 11.02 (s, 1H). ^{13}C NMR (DMSO-d_6): 22.39, 27.56, 31.66, 38.42, 110.76, 120.32, 125.19, 126.10, 127.92, 128.54, 132.36, 133.80, 137.91, 145.67, 158.26, 166.47, 168.69. HRMS (AP-ESI) *m*/*z* Calcd for $C_{19}H_{19}N_3O_6S$ $[M+H]^+$ 418.1067. Found: 418.1076.

5.1.7.16. *N*-(2-(6-(Hydroxyamino)-6-oxohexyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)benzamide (11e). Yield: 47%, mp: 188–190 °C. ^{1}H NMR (DMSO-d_6) δ 1.31 (m, J = 7.2 Hz, 2H), 1.51 (m, J = 7.2 Hz, 2H), 1.70 (m, J = 7.2 Hz, 2H), 1.94 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 7.58 (t, J = 7.2 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 8.00 (d, J = 7.2 Hz, 2H), 8.11 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.65 (s, 1H), 8.67 (s, 1H), 10.34 (s, 1H), 11.04 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.56, 25.67, 27.70, 32.03, 38.56, 110.77, 120.34, 125.22, 126.14, 127.93, 128.57, 132.38, 133.82, 137.93, 145.67, 158.26, 166.49, 168.90. HRMS (AP-ESI) *m*/*z* Calcd for $C_{20}H_{21}N_3O_6S$ $[M+H]^+$ 432.1224. Found: 432.1228.

5.1.7.17. *N*-(2-(6-(Hydroxyamino)-6-oxohexyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)-[1,1′-biphenyl]-4-carboxamide (11f). Yield: 52%, mp: 234–236 °C. ^{1}H NMR (DMSO-d_6) δ 1.32 (m, J = 7.2 Hz, 2H), 1.52 (m, J = 7.2 Hz, 2H), 1.71 (m, J = 7.2 Hz, 2H), 1.95 (t, J = 7.2 Hz, 2H), 3.69 (t, J = 7.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.2 Hz, 2H), 7.78 (d, J = 7.2 Hz, 2H), 7.90 (d, J = 7.8 Hz, 2H), 8.11 (d, J = 8.4 Hz, 2H), 8.12 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.68 (s, 1H), 8.69 (s, 1H), 10.36 (s, 1H), 11.07 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.57, 25.68, 27.71, 32.04, 38.56, 110.78, 120.32, 125.21, 126.13, 126.72, 126.94, 128.30, 128.65, 129.05, 132.47, 137.93, 138.84, 143.86, 145.69, 158.26, 166.06, 168.91. HRMS (AP-ESI) *m*/*z* Calcd for $C_{26}H_{25}N_3O_6S$ $[M+H]^+$ 508.1537. Found: 508.1537.

5.1.7.18. *N*-(2-(6-(Hydroxyamino)-6-oxohexyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)-3,4,5-trimethoxybenzamide (11g). Yield: 47%, mp: 148–150 °C. ^{1}H NMR (DMSO-d_6) δ 1.31 (m, J = 7.2 Hz, 2H), 1.51 (m, J = 7.2 Hz, 2H), 1.70 (m, J = 7.2 Hz, 2H), 1.94 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 3.75 (s, 3H), 3.89 (s, 6H), 7.32 (s, 2H), 8.12 (d, J = = 8.4 Hz, 1H), 8.23 (dd, J = 9.0 Hz 1.8 Hz, 1H), 8.59 (d, J = 1.2 Hz, 1H), 8.68 (s, 1H), 10.35 (s, 1H), 10.87 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.56, 25.68, 27.70, 32.02, 38.56, 56.14, 60.14, 105.61, 110.97, 120.33, 125.30, 126.13, 128.86, 137.90, 140.95, 145.59, 152.69, 158.26, 165.80, 168.90. HRMS (AP-ESI) *m*/*z* Calcd for $C_{23}H_{27}N_3O_9S$ $[M+H]^+$ 522.1541. Found: 522.1538.

5.1.7.19. *N*-(2-(6-(Hydroxyamino)-6-oxohexyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)-4-iodobenzamide (11h). Yield: 47%, mp: 193–195 °C. ^{1}H NMR (DMSO-d_6) δ 1.30 (m, J = 7.2 Hz, 2H), 1.51 (m, J = 7.2 Hz, 2H), 1.70 (m, J = 7.2 Hz, 2H), 1.94 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 7.8 Hz, 2H), 8.10 (d, J = 8.4 Hz, 1H), 8.21 (dd, J = 8.4 Hz 1.2 Hz, 1H), 8.62 (d, J = 1.2 Hz, 1H), 8.63 (s, 1H), 10.34 (s, 1H), 11.05 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.56, 25.67, 27.68, 32.03, 38.61, 100.42, 110.88, 120.47, 125.29, 126.12, 129.76, 133.09, 137.45, 137.88, 145.45, 158.22, 165.77, 168.93. HRMS (AP-ESI) m/z Calcd for $C_{20}H_{20}IN_3O_6S$ $[M+H]^+$ 558.0190. Found: 558.0185.

5.1.7.20. *N*-(2-(6-(Hydroxyamino)-6-oxohexyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)-4-methoxybenzamide (11i). Yield: 74%, mp: 116–118 °C. ^{1}H NMR (DMSO-d_6) δ 1.32 (m, J = 7.2 Hz, 2H), 1.51 (m, J = 7.2 Hz, 2H), 1.70 (m, J = 7.2 Hz, 2H), 1.94 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 3.86 (s, 3H), 7.11 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 9.6 Hz, 2H), 8.09 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.64 (d, J = 1.2 Hz, 1H), 8.67 (s, 1H), 10.34 (s, 1H), 10.86 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.56, 25.68, 27.70, 32.03, 38.53, 55.48, 110.62, 113.79, 120.02, 125.05, 125.67, 126.03, 130.01, 137.91, 145.91, 158.29, 162.53, 165.71, 168.93. HRMS (AP-ESI) m/z Calcd for $C_{21}H_{23}N_3O_7S$ $[M+H]^+$ 462.1329. Found: 462.1324.

5.1.7.21. 6-(1,1-Dioxido-3-oxo-6-(2-phenylacetamido)benzo[*d*]isothiazol-2(3*H*)-yl)-*N*-hydroxyhexanamide (11j). Yield: 67%, mp: 165–168 °C. ^{1}H NMR (DMSO-d_6) δ 1.26 (m, J = 7.2 Hz, 2H), 1.47 (m, J = 7.2 Hz, 2H), 1.66 (m, J = 7.2 Hz, 2H), 1.91 (t, J = 7.2 Hz, 2H), 3.64 (t, J = 7.2 Hz, 2H), 3.76 (s, 2H), 7.23 (m, 5H), 7.91 (dd, J = 8.4 Hz 1.8 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 8.49 (d, J = 1.5 Hz, 1H), 8.65 (s, 1H), 10.33 (s, 1H), 11.03 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.55, 25.65, 27.68, 32.00, 38.53, 43.25, 109.58, 120.05, 124.22, 126.30, 126.75, 128.36, 129.21, 134.98, 138.12, 145.47, 158.20, 168.84, 170.55. HRMS (AP-ESI) m/z Calcd for $C_{21}H_{23}N_3O_6S$ $[M+H]^+$ 446.1380. Found: 446.1382.

5.1.7.22. 3-Bromo-*N*-(2-(6-(hydroxyamino)-6-oxohexyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)benzamide (11k). Yield: 68%, mp: 198–201 °C. ^{1}H NMR (DMSO-d_6) δ 1.31 (m, J = 7.2 Hz, 2H), 1.49 (m, J = 7.2 Hz, 2H), 1.68 (m, J = 7.2 Hz, 2H), 1.91 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 7.53 (t, J = 8.1 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.98 (dt, J = 8.4 Hz 1.2 Hz, 1H), 8.11 (d, J = 8.7 Hz, 1H), 8.19 (t, J = 1.8 Hz, 1H), 8.21 (dd, J = 8.4 Hz 1.8 Hz, 1H), 8.61 (d, J = 1.8 Hz, 1H), 8.65 (s, 1H), 10.33 (s, 1H), 11.09 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.56, 25.67, 27.70, 32.03, 38.57, 110.95, 120.57, 121.75, 125.33, 126.14, 127.16, 130.46, 130.80, 135.04, 135.94, 137.86, 145.35, 158.21, 164.91, 168.90. HRMS (AP-ESI) m/z Calcd for $C_{20}H_{20}BrN_3O_6S$ $[M+H]^+$ 510.0329. Found: 510.0338/512.0399.

5.1.7.23. *N*-(2-(6-(Hydroxyamino)-6-oxohexyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)-2-naphthamide (11l). Yield: 75%, mp: 124–127 °C. ^{1}H NMR (DMSO-d_6) δ 1.31 (m, J = 7.2 Hz, 2H), 1.49 (m, J = 7.2 Hz, 2H), 1.69 (m, J = 7.2 Hz, 2H), 1.91 (t, J = 7.2 Hz, 2H), 3.68 (t, J = 7.2 Hz, 2H), 7.63 (m, 2H), 8.03 (m, 5H), 8.28 (dd, J = 8.7 Hz 1.8 Hz, 1H), 8.66 (m, 3H), 10.33 (s, 1H), 11.21 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.57, 25.68, 27.72, 32.03, 38.55, 110.78, 120.32, 124.31, 125.19, 126.14, 127.05, 127.71, 128.25, 128.66, 129.05, 131.05, 131.91, 134.55, 137.93, 145.74, 158.26, 166.50, 168.92, 170.30. HRMS (AP-ESI) m/z Calcd for $C_{24}H_{23}N_3O_6S$ $[M+H]^+$ 482.1380. Found: 482.1387.

5.1.7.24. *N*-(2-(6-(Hydroxyamino)-6-oxohexyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)thiophene-2-carboxamide (11m). Yield: 49%, mp: 194–196 °C. ^{1}H NMR (DMSO-d_6) δ 1.28 (m, J = 7.2 Hz, 2H), 1.48 (m, J = 7.2 Hz, 2H), 1.67 (m, J = 7.2 Hz, 2H), 1.91 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 7.28 (m, 1H), 7.97 (dd, J = 4.8 Hz 0.9 Hz, 1H), 8.10 (m, 2H), 8.18 (dd, J = 8.4 Hz 1.8 Hz, 1H), 8.59 (d, J = 1.5 Hz, 1H), 8.67 (s, 1H), 10.35 (s, 1H), 10.98 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.56, 25.66, 27.69, 32.02, 38.54, 110.74, 120.32, 125.12, 126.17, 128.34, 130.55, 133.42, 137.90, 138.52, 145.30, 158.23, 160.62, 168.91. HRMS (AP-ESI) m/z Calcd for $C_{18}H_{19}N_3O_6S_2$ $[M+H]^+$ 438.0788. Found: 438.0782.

5.1.7.25. (*E*)-6-(1,1-Dioxido-3-oxo-6-(3-(*p*-tolyl)acrylamido)benzo[*d*]isothiazol-2(3*H*)-yl)-*N*-hydroxyhexanamide (11n). Yield: 45%, mp: 231–233 °C. ^{1}H NMR (DMSO-d_6) δ 1.27 (m, J = 7.2 Hz, 2H), 1.48 (m, J = 7.2 Hz, 2H), 1.67 (m, J = 7.2 Hz, 2H), 1.92 (t, J = 7.2 Hz, 2H), 2.35 (s, 3H), 3.66 (t, J = 7.2 Hz, 2H), 6.77 (d, J = 15.9 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 15.6 Hz, 1H), 7.96 (dd, J = 8.7 Hz 1.8 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.62 (d, J = 1.5 Hz, 1H), 8.67 (s, 1H), 10.34 (d, J = 1.2 Hz, 1H), 11.05 (s, 1H). ^{13}C NMR (DMSO-d_6): 20.98, 24.57, 25.67, 27.71, 32.03, 38.51, 109.60, 119.82, 119.92, 124.21, 126.21, 127.97, 129.61, 131.45, 138.10, 140.21, 142.14, 145.66, 158.19, 164.69, 168.93. HRMS (AP-ESI) m/z Calcd for $C_{23}H_{25}N_3O_6S$ $[M+H]^+$ 472.1537. Found: 472.1531.

5.1.7.26. 4-Fluoro-*N*-(2-(6-(hydroxyamino)-6-oxohexyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)benzamide (11o). Yield: 53%, mp: 202–204 °C. ^{1}H NMR (DMSO-d_6) δ 1.28 (m, J = 7.2 Hz, 2H), 1.48 (m, J = 7.2 Hz, 2H), 1.67 (m, J = 7.2 Hz, 2H), 1.92 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 7.41 (t, J = 8.4 Hz, 2H), 8.07 (m, 3H), 8.20 (dd, J = 8.7 Hz 1.8 Hz, 1H), 8.63 (d, J = 1.5 Hz, 1H), 8.67 (s, 1H), 10.34 (s, 1H), 11.04 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.56, 25.67, 27.69, 32.02, 38.55, 110.80, 115.43 (d, J = 21.8 Hz), 120.39, 125.24, 126.12, 130.22 (d, J = 2.3 Hz), 130.74 (d, J = 9.0 Hz), 137.89, 145.57, 158.23, 162.82 (d, J = 249.0 Hz), 165.32, 168.91. HRMS (AP-ESI) m/z Calcd for $C_{20}H_{20}FN_3O_6S$ $[M+H]^+$ 450.1130. Found: 450.1121.

5.1.7.27. *N*-(2-(6-(Hydroxyamino)-6-oxohexyl)-1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)-4-nitrobenzamide (11p). Yield: 51%, mp: 179–181 °C. ^{1}H NMR (DMSO-d_6) δ 1.28 (m, J = 7.2 Hz, 2H), 1.49 (m, J = 7.2 Hz, 2H), 1.68 (m, J = 7.2 Hz, 2H), 1.91 (t, J = 7.2 Hz, 2H), 3.67 (t, J = 7.2 Hz, 2H), 8.13 (d, J = 8.4 Hz, 1H), 8.22 (m, 3H), 8.41 (d, J = 8.7 Hz, 2H), 8.64 (d, J = 1.5 Hz, 1H), 8.68 (s, 1H), 10.35 (s, 1H), 11.35 (s, 1H). ^{13}C NMR (DMSO-d_6): 24.56, 25.67, 27.68, 32.02, 38.62, 111.09, 120.82, 123.62, 125.49, 126.18, 129.52, 137.86, 139.32, 145.16, 149.50, 158.17, 164.84, 168.92. HRMS (AP-ESI) m/z Calcd for $C_{20}H_{20}N_4O_8S$ $[M+H]^+$ 477.1075. Found: 477.1070.

5.2. In vitro HDAC assay

We performed assays according to the kit instruction. HDAC came from HeLa cell nucleus extracts, mainly including HDAC1 and HDAC2, and the substrate was an acetylated histone peptide. The tested compounds and the control drug SAHA were diluted to various concentrations. On the 96-well plate, HDAC (5 μL/well) were incubated at 37 °C with 10 μL of various concentrations of samples and 25 μL of substrate. After reacting for 30 min, the mixture (50 μL/well) of Color de Lys Developer and TSA was added. Then, after 30 min the ultraviolet absorption of the wells was measured on a microtiter-plate reader at 405 nm. The inhibition rates were calculated from the ultraviolet absorption readings of

inhibited wells related to those of control wells. Finally, the IC_{50} values were determined using a regression analysis of the concentration and inhibition data.

5.3. MTT assay

MDA-MB-231, PC-3, KG1 and K562 cells were respectively cultured in RPMI1640 medium containing 10% FBS at 37 °C in 5% CO_2 humidified incubator. Cell proliferation was determined by the MTT (3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyl-2*H*-tetrazolium bromide) assay. Briefly, cells were plated in a 96-well plate at 5000 cells per well, cultured for 8 h in complete growth medium, then treated with various concentrations of compounds for 48 h. 0.5% MTT solution was added to each well. After further incubation for 4 h, formazan formed from MTT was extracted by adding 150 μL DMSO and mixing for 10 min. Optical density was read with an microtiter-plate reader at 570 nm.

5.4. Docking study

AutoDock 4.2 was used for all docking calculations. One hundred runs were performed using Lamarckian Genetic Algorithm (LGA) with default parameters. The molecular structures were generated with Sybyl/Sketch module and optimized using semiempirical MOPAC/AM1 method and then assigned with AM1-BCC charges. Results differing less than 0.5 Å in positional root-mean-square deviation (RMSD) were clustered together. Conformations in first cluster with the most favorable free binding energy were selected as the best docking result.

Acknowledgments

This work was supported by National Natural Science Foundation China (Nos. 81373281, 21172133), Shandong Provincial Natural Science Foundation (No. ZR2010HM028), Shandong Natural Science Fund for Distinguished Young Scholars (No. JQ201319), the Program for New Century Excellent Talents in University (No. NCET-12-0337), and Independent Innovation Foundation of Shandong University, IIFSDU (No. 2012JC003).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2014.01.045. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Sato, A. *Onco. Targets Ther.* **2012**, *5*, 67.
2. Weichert, W. *Cancer Lett.* **2009**, *280*, 168.
3. Gryder, B. E.; Sodji, Q. H.; Oyelere, A. K. *Future Med. Chem.* **2012**, *4*, 505.
4. Patil, V.; Sodji, Q. H.; Kornacki, J. R.; Mrksich, M.; Oyelere, A. K. *J. Med. Chem.* **2013**, *56*, 3492.
5. Jiao, J.; Fang, H.; Wang, X.; Guan, P.; Yuan, Y.; Xu, W. *Eur. J. Med. Chem.* **2009**, *44*, 4470.
6. Guan, P.; Sun, F.; Hou, X.; Wang, F.; Yi, F.; Xu, W.; Fang, H. *Bioorg. Med. Chem.* **2012**, *20*, 3865.
7. Zhang, Y.; Feng, J.; Jia, Y.; Wang, X.; Zhang, L.; Liu, C.; Fang, H.; Xu, W. *J. Med. Chem.* **2011**, *54*, 2823.
8. Zhang, Y.; Fang, H.; Feng, J.; Jia, Y.; Wang, X.; Xu, W. *J. Med. Chem.* **2011**, *54*, 5532.
9. Zhang, Y.; Feng, J.; Liu, C.; Zhang, L.; Jiao, J.; Fang, H.; Su, L.; Zhang, X.; Zhang, J.; Li, M.; Wang, B.; Xu, W. *Bioorg. Med. Chem.* **2010**, *18*, 1761.
10. Sommermeyer, H.; Schreiber, R.; Greuel, J. M.; De Vry, J.; Glaser, T. *Eur. J. Pharmacol.* **1993**, *240*, 29.
11. Blanchet, J.; Macklin, T.; Ang, P.; Metallinos, C.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 3199.
12. Youdim, M. B.; Ashkenazi, R. *Eur. J. Pharmacol.* **1985**, *119*, 39.
13. Gomez, Vidal, J. A.; Dominguez, Seglar, J. F.; Tabraue, Chavez, M. PCT Int. Appl. WO/2008/003800 A1.
14. Hiroyoshi, K.; Shuji, Y.; Masato, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3824.
15. Morris, G. M.; Huey, R.; Lindstrom, W.; Sanner, M. F.; Belew, R. K.; Goodsell, D. S.; Olson, A. J. *J. Comput. Chem.* **2009**, *30*, 2785.
16. Pettersen, E. F.; Goddard, T. D.; Huang, C. C.; Couch, G. S.; Greenblatt, D. M.; Meng, E. C.; Ferrin, T. E. *J. Comput. Chem.* **2004**, *25*, 1605.
17. Li, Z.; Mu, X.; Fan, Z.; Li, Y.; Liu, B. CN 200510013913.