Bioorganic Chemistry 87 (2019) 699–713

Contents lists available at ScienceDirect

Bioorganic Chemistry

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

Design and synthesis of parthenolide-SAHA hybrids for intervention of drug-resistant acute myeloid leukemia

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ARTICLE INFO

Keywords:
Parthenolide
SAHA
Hybrid
Histone deacetylase
Drug resistance

ABSTRACT

A series of parthenolide-SAHA hybrids were synthesized and evaluated for their anti-AML activities against HL-60 and HL-60/ADR cell lines. The most active compound **26** exhibited high activity against HL-60/ADR cell line with IC_{50} value of 0.15 μM, which demonstrated 16.8-fold improvement compared to that of the parent compound PTL (IC_{50} = 2.52 μM). Moreover, it was six times more potent than the reference drug SAHA (IC_{50} = 0.90 μM) and fifty-one times more potent than ADR (IC_{50} = 7.72 μM). The preliminary molecular mechanism of **26** indicated that compound **26** could significantly induce apoptosis of HL-60/ADR cells. The effect of compound **26** was mainly through mitochondria pathway. Further investigation revealed that the protein level of HDAC1 and HDAC6 were reduced after the treatment of compound **26** with a dose-dependent manner. Compound **26** could significantly decrease ABCC1 expression, which increased the accumulation of intracellular drug for overcoming the drug resistance. On the base of these results, compound **26** might be considered as a promising candidate for further evaluation as a potential anti-AML drug.

1. Introduction

Acute myeloid leukemia (AML) is a malignant disease characterized by an aberrant accumulation of immature myeloid hematopoietic cells [1,2]. Chemotherapy is one of the common treatments, and most patients can get longer survival interval through chemotherapy. But about 20 percent of patients will develop resistance after chemotherapy, more than half of those will relapse [3–5]. Many leukemia cells will not only develop resistance to specific drugs, but also cross-resistance to other types of drugs, this phenomenon is defined as multidrug resistance (MDR), therefore most of recurrent patients become insensitive to chemotherapeutic agents, eventually die of the disease [5,6]. Relapse has become a major problem in the treatment of leukemia, and drug resistance is an important cause of relapse [7–9]. The main cause of MDR is over-expression of the P-glycoprotein or multidrug resistance-associated proteins, which acts as drug efflux pump, lowering intracellular drug levels to sublethal concentrations [10–13]. Therefore, reversion of MDR is an effective strategy to effectively cure AML.

Histone deacetylases (HDACs) could remove acetyl groups from histones, maintained the dynamic equilibrium in acetylation levels of both nucleosomal histones and nonhistone proteins and played an important role in regulating cell proliferation and differentiation [14,15]. Especially, HDAC1 upregulation promoted multidrug resistance [16,17]. Hence, HDACs were considered to be effective targets for treatment of cancer. Histone deacetylase inhibitors (HDACi) have become a new class of anti-cancer drugs, HDACi could induce differentiation, cell cycle arrest and apoptosis in various transformed cell lines [18,19], and several HDACis were undergoing clinical trials for solid and hematological malignancies [20–22]. Recent reports suggested that HDACi may modulate the multidrug resistance-1 gene expression and reduce expression of P-glycoprotein [23–25]. Combination of HDACi and chemotherapy drugs could inhibit multidrug resistance-associated drug export. SAHA (Fig. 1), an orally bioavailable inhibitor of HDAC1 and HDAC6 [26], showed broad spectrum of anti-cancer effect. The combination of SAHA and flavopiridol effectively enhanced the killing activity against multidrug resistant neuroblastoma cell lines [27].

Parthenolide (PTL, Fig. 1), a prominent sesquiterpene lactone originally derived from Feverfew (*Tanacetum parthenium*), exhibited exceptional anti-cancer, anti-inflammatory and other properties [28]. PTL

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https://doi.org/10.1016/j.bioorg.2019.03.056
Received 22 August 2018; Received in revised form 15 January 2019; Accepted 19 March 2019

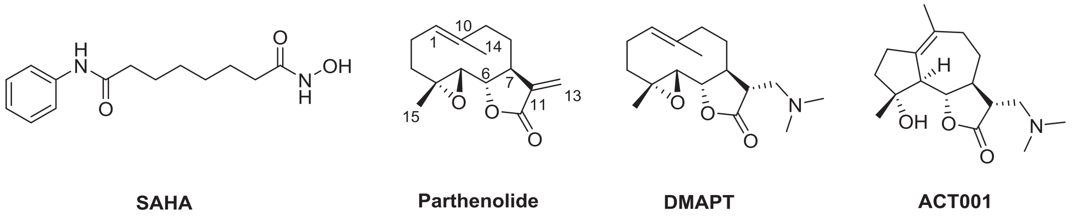


Fig. 1. Structures of SAHA, parthenolide, DMAPT and ACT001.

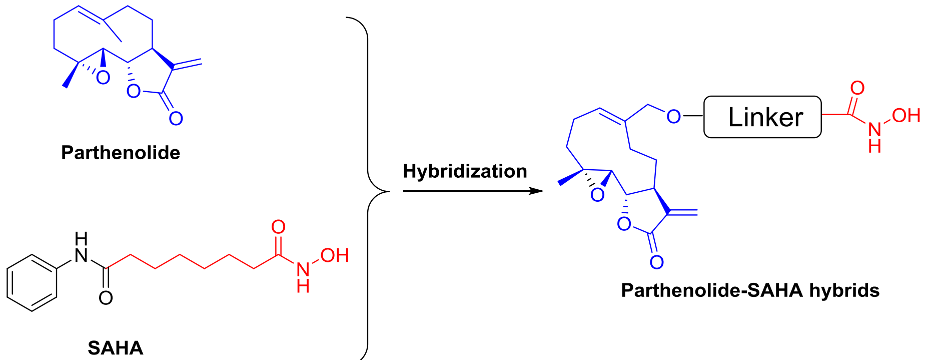


Fig. 2. Design of Parthenolide-SAHA hybrids.

could induce apoptosis of cancer cells, while have no effect on normal cells [29]. A prodrug of PTL, DMAPT, has been advanced into clinical trial for treatment of AML [30]. It was reported that PTL could reverse doxorubicin resistance in human lung carcinoma A549 cells by attenuating NF-κB activation and HSP70 up-regulation [31], and reverse resistance of multidrug-resistant hepatic carcinoma [32]. PTL exhibited its anti-cancer through targeting NF-κB, redox thiols or DNMT1 [29]. Moreover, PTL could specifically deplete HDAC1 protein without affecting other class I/II HDACs, through degradation of HDAC1 by ubiquitination/proteasomal [33].

Accordingly, herein, we reported the design (Fig. 2), synthesis of a series of PTL-SAHA hybrids, and evaluation of their anti-AML activities. The preliminary structure-activity relationship was revealed. Compound **26** showed high activity against adriamycin (ADR) resistant cell line HL-60/ADR cells. The most potent **26** could significantly induce apoptosis of HL-60/ADR cells. The preliminary molecular mechanism of **26** was also investigated.

2. Results and discussion

2.1. Chemistry

The hydroxamic acid moiety is the pharmacophore of SAHA, which is a zinc-binding group (ZBG). In order to incorporate both pharmacophores of PTL and SAHA activities into a single chemical entity, the hybrid molecules were designed as shown in Fig. 2. A series of hybrids were designed and synthesized by changing the connecting linker between PTL and hydroxamic acid units. The preparation of PTL-SAHA hybrids is illustrated in Schemes 1–5.

As show in Schemes 1 and 2, hybrids **5**, **8**, **14**, **17** were firstly designed. The intermediates **3** and **10** were readily obtained from suberic acid monomethyl ester and 7-bromoheptanoic acid, according to a reported procedure [34]. Methylparaben and intermediate **10** formed ether bonds under alkaline conditions to obtain compound **11**. Followed by ester hydrolysis, the intermediate acid **12** was obtained. Starting with the natural product PTL, melampomagnolide B (MMB) was synthesized according to the procedure previously reported by our group [35].

After all the key intermediates were in the hands, we posed to synthesize hybrids **5**, **8**, **14**, **17**. Direct esterification of MMB with intermediate **3**, followed by removal of Trt by TFA and Et_3SiH afforded **5**. MMB and *p*-aminobenzoic acid were reacted to obtain compound **6** by Mitsunobo reaction, followed by coupling with intermediate **3**, removal of protecting group Trt to obtain **8**. The acid **12** reacted with MMB, followed by removal of Trt group to generate **14**. Similarly, intermediate **15** was obtained by Mitsunobu reaction, followed by coupling with **10** and removal of Trt to yield **17**.

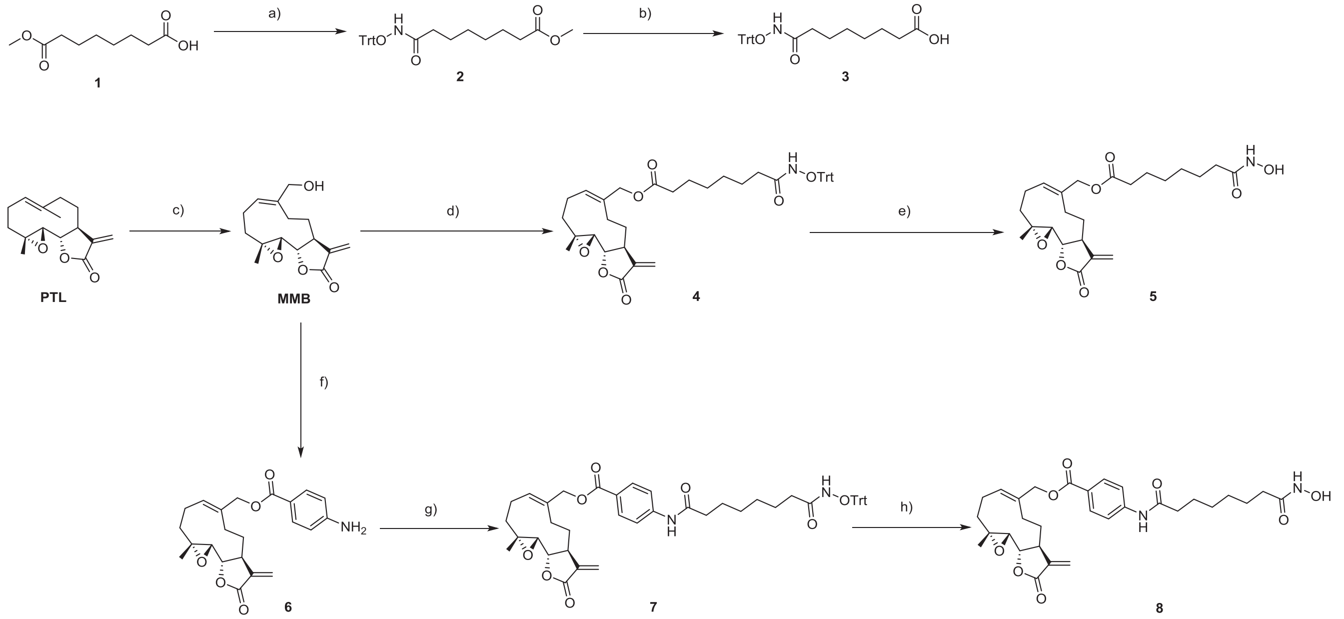
In order to explore the effect of chain length on the activity, we designed compounds **20a–20c**. Compounds **20a–20c** were prepared according to the procedure for synthesis of compound **17** by using different bromic acid as the starting materials (Scheme 3). Compounds **23a–23c** were designed and synthesized for investigating the effect of methoxy group(s) on the anti-AML activity. MMB reacted with different substituted cinnamic acids through Mitsunobu reaction to get intermediates **21a–21c** then followed by coupling with **10** and removal of Trt to generate compounds **23a–23c**.

We designed and synthesized compounds **26** and **29** to study the influence of substitution position of hydroxamic acid moiety on inhibitory activity. MMB reacted with *O*-coumaric acid and *trans*-3-coumaric acid to form intermediates **24** and **27** through the Mitunobu reaction, respectively. Intermediates **24** and **27** reacted with intermediate **10** to form **25** and **28**, then removal of protecting group Trt to obtain hybrids **26** and **29**, respectively.

In order to explore the effects of the PTL moiety on their anti-AML activities, we designed compound **32**, replacing PTL moiety with methyl group (Scheme 5). Coupling of **30** and **10** gave **31**, followed by removal of Trt to generate **32**. In order to explore the effect of α, β-unsaturated ester moiety on their anti-AML activities, we designed compound **36** with reduction of the double bond in γ-butyrolactone moiety. MMB was reduced by sodium borohydride to give compound **33**, followed the similar steps for preparation of **17** to generate compound **36**. Esterification of MMB and cinnamic acid gave compound **37** with trim of the hydroxamic acid moiety for study the importance of hydroxamic acid moiety.

2.2. Inhibitory activity of PTL-SAHA hybrids against AML cell lines

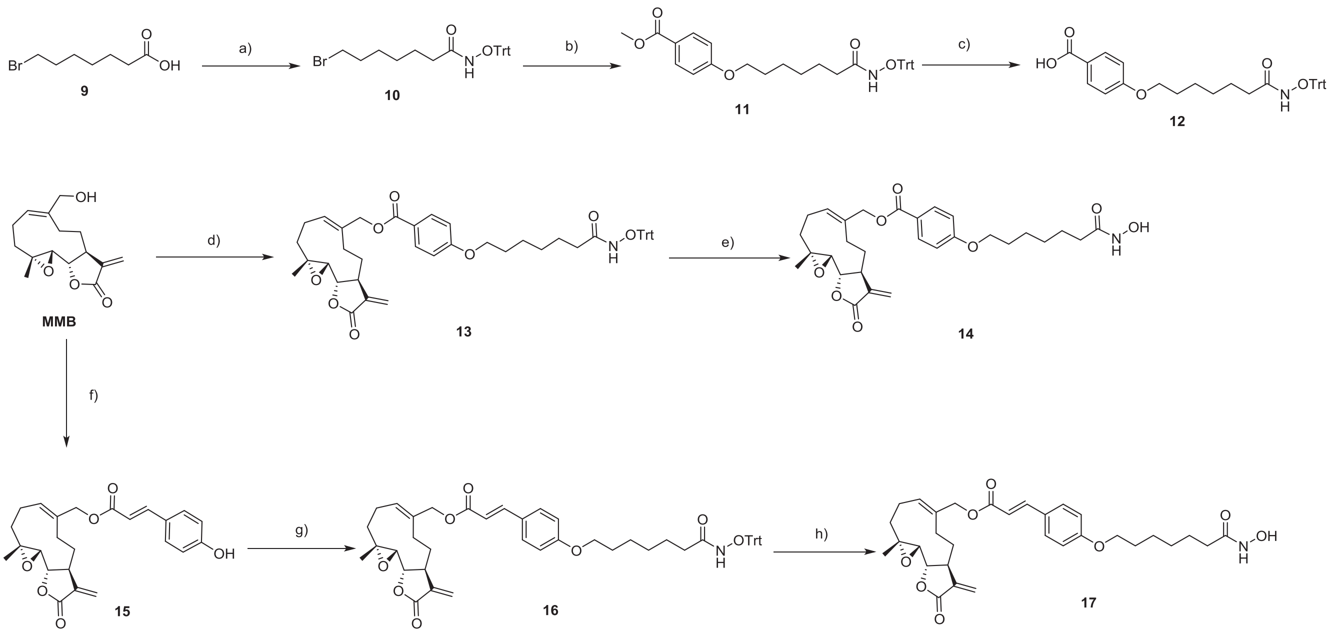
To evaluate the anti-cancer activity of the synthesized PTL-SAHA hybrids, all of hybrids (**5**, **8**, **14**, **17**, **20a–20c**, **23a–23c**, **26**, **29**, **32**, **36** and **37**) were tested for their activities against human AML cell line HL-



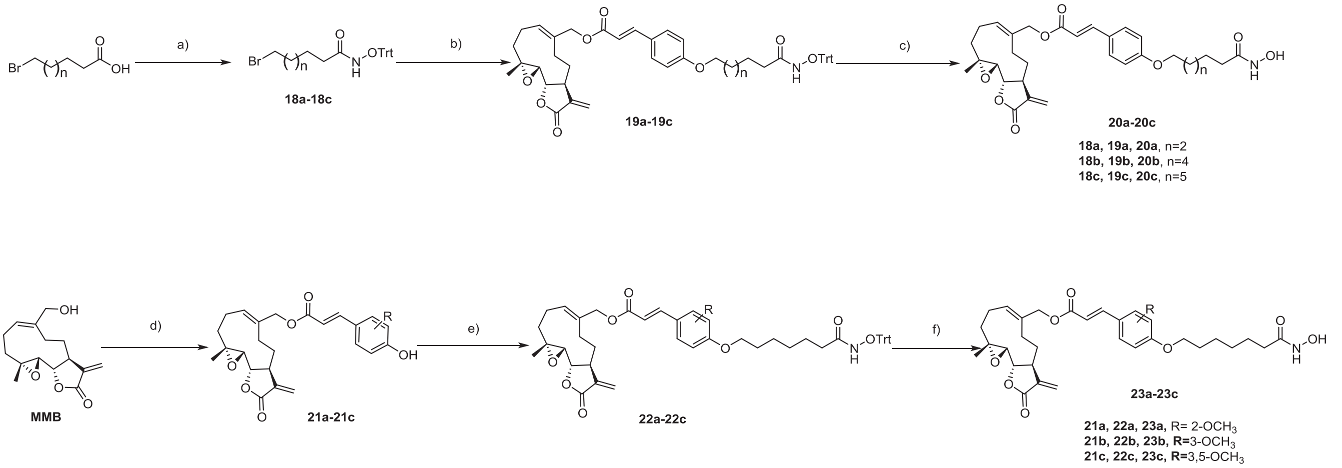
Scheme 1. Synthesis of compounds **5** and **8**. Reagents and conditions: (a) *O*-Tritylhydroxylamine, *N*-methylmorpholine, isobutylchloroformate, THF; (b) LiOH, H_2O, THF, two steps for 61%; (c) SeO_2, *t*-BuOOH, CH_2Cl_2, 70%; (d) Compound **3**, EDCI, DMAP, TEA, DCM, 71%; (e) TFA, Et_3SiH, DCM, 0 °C, 72%; (f) 4-Aminobenzoic acid, PPh_3, DIAD, 95%; (g) Compound **3**, HATU, DIPEA, DCM, 50 °C, 78%; (h) TFA, Et_3SiH, DCM, 0 °C, 80%.

60 and ADR resistant cell line HL-60/ADR with clinically used anticancer drugs ADR and SAHA as references. PTL and MMB were also included for comparison. The results were summarized in Tables 1 and 2. The anti-AML activity of each compound was expressed as the concentration of compound that achieved 50% inhibition (IC_{50}) of HL-60 and HL-60/ADR cells. The sensitivity ratio (SR) was determined as the ratio of IC_{50} value for HL-60 cells to IC_{50} value for HL-60/ADR cells for evaluation of the sensitivity of HL-60/ADR cells comparing to HL-60 cells. The bioactivity of each compound was evaluated by the combination of its IC_{50} and SR.

As shown in Table 1, PTL and SAHA showed moderate activity against HL-60 and HL-60/ADR cell lines. The SR values of PTL and SAHA were 1.40 and 1.68. The combination of PTL and SAHA did not increase the activity and the values of SR. MMB, a derivative of PTL, was less potent than PTL for both HL-60 and HL-60/ADR cell lines. Primarily designed hybrids **5** and **8** that combined PTL and hydroxamic acid moiety with different linkers exhibited comparable anti-AML activity against HL-60 cell line with PTL, MMB, and SAHA. However, for the HL-60/ADR cell line, the activities of both compounds were decreased, especially compound **8**. When we connected the PTL and hydroxamic acid moiety by ether bond, etc. compounds **14** ($IC_{50} = 1.22 \pm 0.63\,\mu M$) and **17** ($IC_{50} = 1.05 \pm 0.65\,\mu M$), they displayed improved anti-AML activity against HL-60/ADR cell line compared with PTL (($IC_{50} = 2.52 \pm 1.90\,\mu M$), and increased the values of



Scheme 2. Synthesis of compounds **14** and **17**. Reagents and conditions: (a) *O*-Tritylhydroxylamine, *N*-methylmorpholine, isobutylchloroformate, THF, 95%; (b) Methyl 4-hydroxybenzoate, K_2CO_3, dry DMF, 88%; (c) LiOH, H_2O, THF, 72%; (d) Compound **12**, DIC, DMAP, DCM, 61%; (e) TFA, Et_3SiH, DCM, 0 °C, 89%; (f) *p*-Coumalic acid, PPh_3, DIAD, 69%; (g) Compound **10**, K_2CO_3, dry DMF, 71%; (h) TFA, Et_3SiH, DCM, 0 °C, 82%.



Scheme 3. Synthesis of compounds **20a–20c** and **23a–23c**. Reagents and conditions: (a) *O*-Tritylhydroxylamine, *N*-methylmorpholine, isobutylchloroformate, THF, 87–95%; (b) Compound **15**, K_2CO_3, dry DMF, 77–86%; (c) TFA, Et_3SiH, DCM, 0 °C, 82–87%; (d) PPh_3, DIAD, different cinnamic acid, 54–63%; (e) Compound **10**, K_2CO_3, dry DMF, 44–69%; (f) TFA, Et_3SiH, DCM, 0 °C, 69–83%.

SR. The SR value of compound **17** was 2.77. Therefore, we chose compound **17** as a lead compound for further modification.

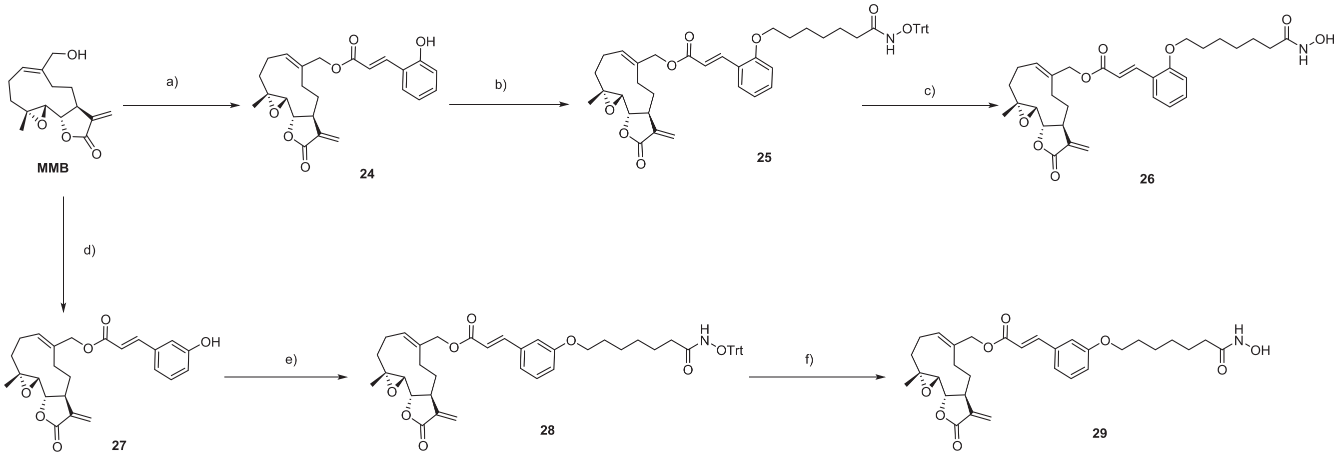
As show in Table 2, for subseries **20a–20c**, as the chain length increased, the anti-AML activity decreased and the SR values increased. Introduction of methyloxy group at the ortho-position (**23a**) of the benzene ring led to decrease of the activity against HL-60/ADR cells, but when introduction of methyloxy group at the meta-position (**23b**) of the benzene ring, which improved anti-AML potency to HL-60 and HL-60/ADR cells. Introduction of dimethyloxy groups (**23c**) at the meta-position of the benzene ring further increased the activity against HL-60 and HL-60/ADR cells with IC_{50} values of 0.39 ± 0.04 μM and 0.29 ± 0.11 μM, respectively. Then we studied the influence of different substitution position of the hydroxamic acid moiety on benzene ring. When the hydroxamic acid moiety was introduced at the meta-position of the benzene ring, etc. compound **29** with IC_{50} values of 0.37 ± 0.08 μM and 0.29 ± 0.11 μM for HL-60 and HL-60/ADR cell lines, respectively, the anti-AML activity against HL-60 and HL-60/ADR cells was greatly improved comparing to PTL and SAHA. To our surprise, the activity for HL-60/ADR cells was further improved when the hydroxamic acid moiety was introduced to ortho-position of the benzene ring, etc. compound **26** with IC_{50} value of 0.15 ± 0.05 μM for HL-60/ADR cell lines, which was 16.8-fold improvement compared to the parent compound PTL (IC_{50} = 2.52 μM). It is worth to note that it was six times more potent than the reference drug SAHA (IC_{50} = 0.90 μM) and fifty-one times more potent than ADR (IC_{50} = 7.72 μM).

Removal of the PTL moiety (**32**) or reduction of the double bond in γ-butyrolactone moiety (**36**) led to complete loss of anti-cancer activity (IC_{50} > 20 μM). Compound **37** (IC_{50} = 0.85 μM) with trim of the hydroxamic acid moiety was less potent than compound **26** (IC_{50} = 0.15 μM), and it had no selectivity for the HL-60/ADR cell line (SR = 0.63).

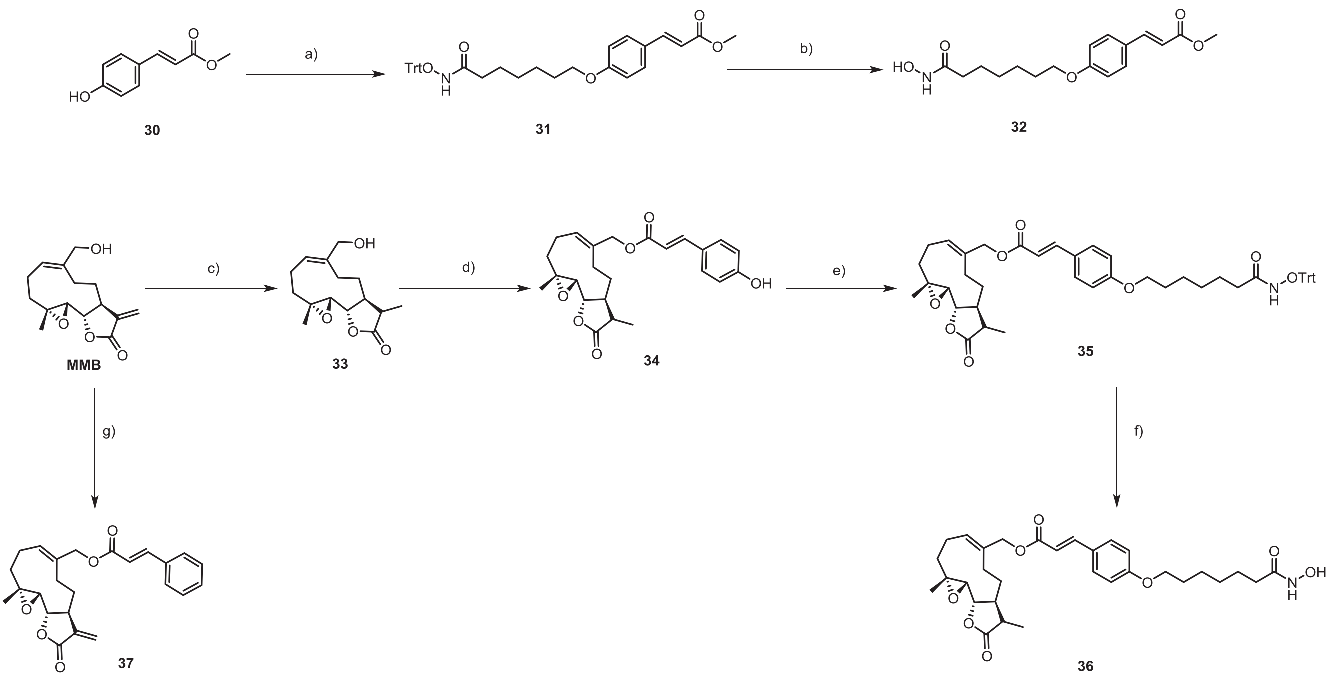
The most potent compound **26** was selected for study of its preliminary mechanism.

2.3. Preliminary mechanism study of compound 26

In order to study whether the effect of compound **26** was led by inducing apoptosis, cell apoptosis was detected by flow cytometry. As shown in Fig. 3, the percentage of apoptosis were 3.8 ± 0.2%, 6.53 ± 0.40%, 13.27 ± 0.67 and 20.97 ± 1.03% after the treatment of compound **26** at different concentrations of 0, 0.2 μM, 0.5 μM and 1 μM, respectively, for 48 h. The result demonstrated that compound **26**

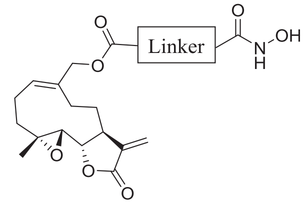


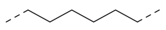
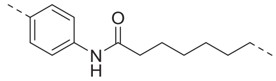
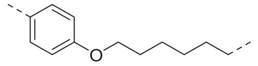
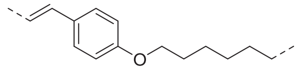
Scheme 4. Synthesis of compounds **26** and **29**. Reagents and conditions: (a) PPh_3, DIAD, *trans*-2-hydroxycinnamic acid, 68%; (b) compound **10**, K_2CO_3, dry DMF, 76%; (c) TFA, Et_3SiH, DCM, 0 °C, 63%; (d) PPh_3, DIAD, *trans*-3-hydroxycinnamic acid, 65%; (e) Compound **10**, K_2CO_3, dry DMF, 62%; (f) TFA, Et_3SiH, DCM, 0 °C, 82%.



Scheme 5. Synthesis of compounds **32**, **36** and **37**. Reagents and conditions: (a) Compound **10**, K_2CO_3, dry DMF, 93%; (b) TFA, Et_3SiH, DCM, 0 °C, 70%; (c) $NaBH_4$, EtOH, 0 °C, 74%; (d) Coumalic acid, PPh_3, DIAD, 71%; (e) Compound **10**, K_2CO_3, dry DMF, 73%; (f) TFA, Et_3SiH, DCM, 0 °C, 53%; (g) EDCI, DMAP, TEA, cinnamic acid, 86%.

Table 1
Antileukemic activity of compounds **5**, **8**, **14** and **17**.



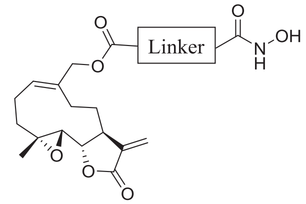
Compound	Linker	IC_{50}[a](μM)		SR[b] ($IC_{50\ HL\text{-}60}/IC_{50\ HL\text{-}60/ADR}$)
		HL-60	HL-60/ADR	
5		2.69 ± 1.16	3.56 ± 1.46	0.76
8		2.57 ± 1.03	8.94 ± 3.30	0.29
14		2.54 ± 0.86	1.22 ± 0.63	2.08
17		2.91 ± 0.39	1.05 ± 0.65	2.77
PTL	–	3.54 ± 0.44	2.52 ± 1.90	1.40
MMB	–	5.58 ± 3.43	4.80 ± 3.86	1.16
SAHA	–	1.52 ± 0.07	0.90 ± 0.22	1.68
SAHA + PTL	–	1.40 ± 0.35	0.94 ± 0.29	1.48
ADR[c]	–	0.097 ± 0.01	7.72 ± 4.90	0.013

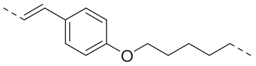
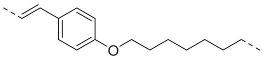
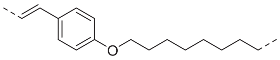
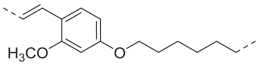
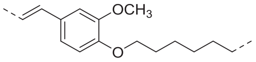
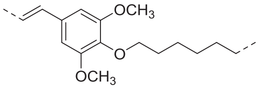
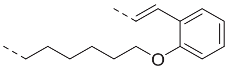
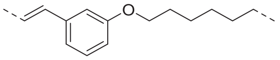
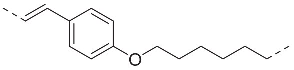
[a] All values are the mean of three independent experiments.
[b] SR: Sensitivity Ratio = $IC_{50\ HL\text{-}60}/IC_{50\ HL\text{-}60/ADR}$.
[c] ADR: Adriamycin, clinically used drug, was used as a positive control.

played its anti-AML effect mainly by inducing apoptosis.

To investigate the mechanism of compound **26** induced apoptosis of HL60/ADR cells, the mitochondrial signal pathway related protein level of Bax, Bcl-2, Cytochrome *C*, Caspase 3, Caspase 9 and PARP were detected. From the result in Fig. 4, the pro-apoptotic protein Bax was clearly increased, while the anti- apoptotic protein Bcl-2 was significantly decreased. The release of cytochrome *C* was increased with a dose-dependent manner after the treatment of compound **26**. The released cytochrome *C* activated the cleavage of caspases to induce apoptosis. From the result, the cleavage of caspase 3, caspase 9 and

Table 2
Antileukemic activities of derivative **20a-20c, 23a-23c, 26, 29, 32, 36** and **37**.



Compound	Linker	IC_{50}[a](μM)		SR[b]($IC_{50\ HL\text{-}60}/IC_{50\ HL\text{-}60/ADR}$)
		HL-60	HL-60/ADR	
20a		0.83 ± 0.13	0.48 ± 0.08	1.72
20b		3.25 ± 0.83	0.7 ± 0.14	4.64
20c		> 20	5.28 ± 1.50	N.D[c]
23a		2.99 ± 0.6	3.45 ± 0.84	0.87
23b		1.17 ± 0.13	0.54 ± 0.25	2.16
23c		0.39 ± 0.04	0.29 ± 0.11	1.34
26		0.32 ± 0.01	0.15 ± 0.05	2.13
29		0.37 ± 0.08	0.29 ± 0.11	1.28
17		2.91 ± 0.39	1.05 ± 0.65	2.77
32	–	> 20	> 20	N.D[c]
36	–	> 20	> 20	N.D[c]
37	–	0.53 ± 0.20	0.85 ± 0.41	0.63
PTL	–	3.54 ± 0.44	2.52 ± 1.90	1.40
SAHA	–	1.52 ± 0.07	0.90 ± 0.22	1.68
ADR	–	0.097 ± 0.01	7.72 ± 4.90	0.013

[a] All values are the mean of three independent experiments. SAHA used as a positive control.

[b] SR: Sensitivity Ratio = $IC_{50\ HL\text{-}60}/IC_{50\ HL\text{-}60/ADR}$.

[c] N.D = Not Detect.

PARP were prominently increased.

To further reveal the mechanism of compound **26**, western blot assay was performed. As compound **26** was modified based on the structure of HDAC inhibitor (SAHA), the protein expression of HDAC1 and HDAC6 were detected. From the result in Fig. 5, the protein level of HDAC1 and HDAC6 were significantly decreased after the treatment of compound **26** with a dose-dependent manner. The MTT assay showed that compound **26** was more sensitive to HL60/ADR than HL60 cells, which was just opposite to ADR, a clinically used drug for treatment of AML. It has been reported that ATP binding cassette subfamily is the major cause for drug resistance in HL60/ADR cells. ABC transporters, as multidrug efflux pumps could pump the intracellular drugs out which lead to multidrug resistance. From the result in Fig. 6A, the protein expression of ATP binding cassette subfamily C member 1 (ABCC1) was higher in HL60/ADR than that in HL60 cells. Moreover, it was reported that HDAC could increase the protein level of ABCC1. Therefore, we speculated that compound **26** would inhibit the expression of ABCC1 to overcome multidrug resistance. To verify this hypothesis, the protein expression of ABCC1 was detected by western blot assay. As shown in Fig. 6B, compound **26** could significantly decrease ABCC1 expression, which increased the accumulation of intracellular drug.

3. Conclusion

In conclusion, a series of fourteen parthenolide-SAHA hybrids was synthesized and evaluated for their anti-AML activities against HL-60 and HL-60/ADR cell lines. The most active compound **26** showed high activity against HL-60/ADR cell line with IC_{50} value of 0.15 μM, which demonstrated 16.8-fold improvement compared to that of the parent compound PTL (IC_{50} = 2.52 μM). Moreover, it was six times more potent than the reference drug SAHA (IC_{50} = 0.90 μM) and fifty-one times more potent than ADR (IC_{50} = 7.72 μM). The preliminary molecular mechanism of **26** indicated that compound **26** could significantly induce apoptosis of HL-60/ADR cells. The effect of compound **26** was mainly through mitochondria pathway. Further investigation revealed that the protein level of HDAC1 and HDAC6 were reduced after the treatment of compound **26** with a dose-dependent manner. Compound **26** could significantly decrease ABCC1 expression, which increased the

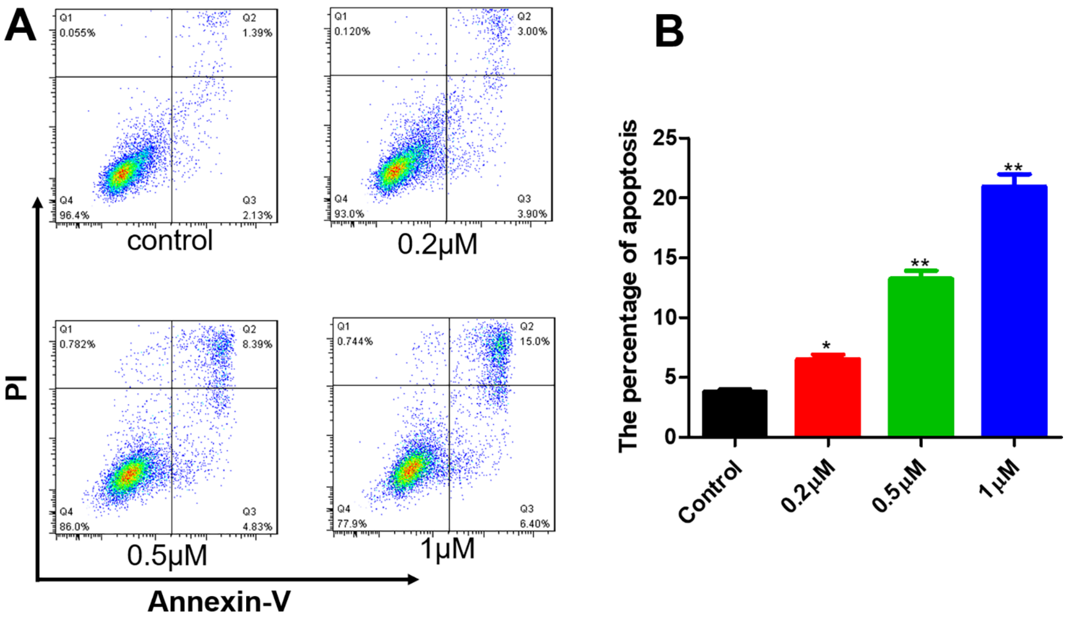


Fig. 3. Compound **26** induced cell apoptosis by flow cytometry assay. (A) The representative images of cell apoptosis by flow cytometry after the treatment of compound **26** for 48 h. (B) The statistical results of cell apoptosis assay. $^{*}P < 0.05$, $^{*}P < 0.01$.

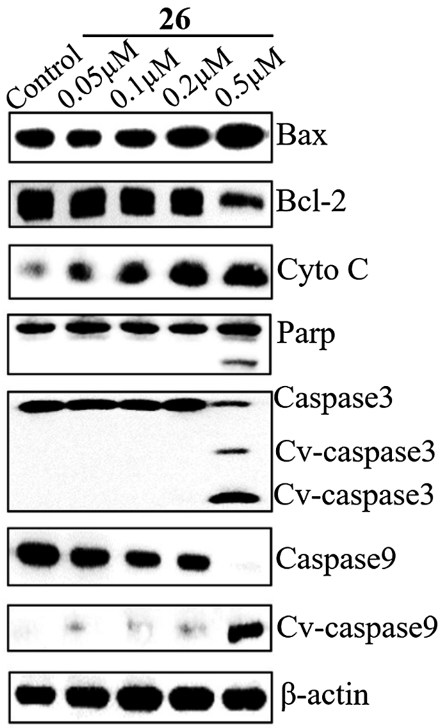


Fig. 4. The level of apoptosis related proteins of mitochondrial pathway after the treatment of compound **26** for 24 h.

accumulation of intracellular drug for overcoming the drug resistance.

On the base of these results, compound **26** might be considered as a promising candidate for further evaluation as a potential anti-AML drug.

4. Experimental

4.1. Chemistry

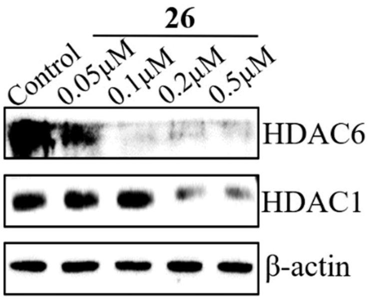


Fig. 5. The protein expression of HDAC1 and HDAC6 after the treatment of compound **26** for 24 h.

Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Tsingdao silica gel plates (60F-254). Visualization was achieved using UV light, phosphomolybdic acid in ethanol or potassium permanganate in water, each followed by heating. Tsingdao silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded with a 400 MHz (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants and integration.

*4.1.1. 8-Oxo-8-((trityloxy) amino) octanoic acid (**3**)*

Compound **3** was readily obtained from suberic acid monomethyl ester, according to a reported procedure [36]. ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.49–7.19 (m, 15H), 2.20 (t, J = 7.4 Hz, 2H), 1.85 (t, J = 7.3 Hz, 1H), 1.55–1.43 (m, 2H), 1.34–1.11 (m, 5H), 1.09–0.99 (m, 2H); ^{13}C NMR (100 MHz, MeOD-d_4) δ 177.6, 173.2, 143.6, 130.4, 129.0, 128.7, 94.4, 34.9, 33.5, 29.8, 29.7, 26.2, 25.8; HRMS (ESI) calcd for $C_{27}H_{29}NNaO_4$ $[M+Na]^+$ 454.1989, found 454.1986.

*4.1.2. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a, 10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl 8-oxo-8-((trityloxy)amino)octanoate (**4**)*

To a solution of MMB (80 mg, 0.3 mmol), EDCI (86.3 mg, 0.45 mmol), DMAP (1.2 mg, 0.01 mmol) and compound **3** (194.2 mg, 0.45 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (62.5 μL, 0.45 mmol) at

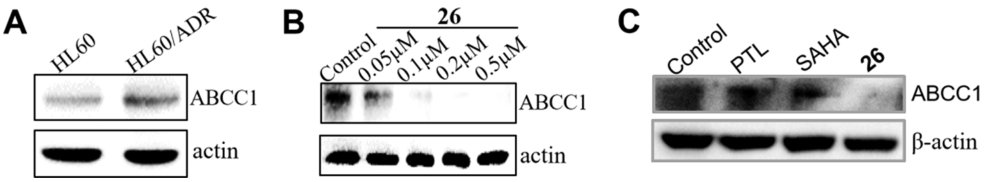


Fig. 6. Compound **26** inhibited the expression of ABCC1. (A) The protein expression of ABCC1 in HL60 and HL60/ADR cells. (B) The protein expression of ABCC1 after the treatment of compound **26** for 24 h at different concentrations. (C) The protein expression of ABCC1 after the treatment of PTL, SAHA and compound **26** for 24 h at 0.5 μM.

0 °C. The mixture was stirred for 8 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column to yield compound **4** (145 mg, yield: 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.28 (m, 16H), 6.25 (d, *J* = 3.0 Hz, 1H), 5.68 (t, *J* = 8.0 Hz, 1H), 5.54 (d, *J* = 2.7 Hz, 1H), 4.65 (d, *J* = 12.5 Hz, 1H), 4.44 (d, *J* = 12.5 Hz, 1H), 3.85 (t, *J* = 9.3 Hz, 1H), 2.87 (dd, *J* = 20.4, 10.5 Hz, 2H), 2.50–2.12 (m, 8H), 1.71–1.62 (m, 1H), 1.60 (s, 2H), 1.57–1.50 (m, 5H), 1.25 (s, 5H), 1.15–1.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 171.2, 169.5, 138.9, 135.1, 130.7, 129.2, 128.3, 120.4, 109.6, 100.1, 81.2, 66.6, 63.4, 60.1, 42.8, 36.8, 34.3, 32.1, 29.8, 28.9, 28.8, 25.9, 24.8, 24.6, 24.0, 18.1. HRMS (ESI) calcd for $C_{42}H_{47}NNaO_7$ $[M+Na]^+$ 700.3245, found 700.3250.

4.1.3. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl) methyl 8-(hydroxyamino)-8-oxooctanoate (5)

Compound **4** (86 mg, 0.13 mmol) was dissolved in dichloromethane (2 mL). The reaction mixture was then cooled in an ice bath and trifluoro acetic acid (TFA) and triethylsilane (Et_3SiH) were added alternately dropwise until the yellow color disappeared. Then the solvent was evaporated to give an oily crude product, which was purified by a silica gel column to yield a yellow oil (40 mg, yield: 72%). ^{1}H NMR (400 MHz, MeOD-*d4*) δ 6.17 (d, *J* = 3.2 Hz, 1H), 5.69 (d, *J* = 8.0 Hz, 1H), 5.65 (d, *J* = 2.8 Hz, 1H), 4.70 (d, *J* = 12.6 Hz, 1H), 4.51 (d, *J* = 12.6 Hz, 1H), 4.03 (t, *J* = 9.3 Hz, 1H), 3.05 (t, *J* = 8.7 Hz, 1H), 2.92 (d, *J* = 9.5 Hz, 1H), 2.59–2.06 (m, 10H), 1.62 (d, *J* = 5.5 Hz, 4H), 1.56 (s, 3H), 1.35 (s, 5H), 1.08 (t, *J* = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, MeOD-d_4) δ 175.1, 171.8, 141.0, 136.8, 131.2, 120.4, 82.9, 67.8, 64.8, 61.6, 43.9, 37.7, 35.0, 30.8, 30.8, 29.8, 29.8, 26.6, 26.5, 25.9, 25.5, 24.7, 18.1. HRMS (ESI) calcd for $C_{23}H_{33}NNaO_7$ $[M+Na]^+$ 458.2149, found 458.2154.

4.1.4. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl) methyl 4-aminobenzoate (6)

To a solution of **MMB** (65.0 mg, 0.25 mmol), PPh_3 (64.5 mg, 0.25 mmol) and 4-aminobenzoic acid (33.8 mg, 0.25 mmol) in dry THF (2.5 mL) were added DIAD (49 μL, 0.25 mmol) under an Ar atmosphere at 0 °C. The reaction mixture was stirred at room temperature for 8 h. Then, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:2] to give compound **6** as a yellow solid (90 mg, yield: 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.6 Hz, 2H), 6.57 (d, *J* = 8.6 Hz, 2H), 6.16 (d, *J* = 3.5 Hz, 1H), 5.69 (t, *J* = 8.3 Hz, 1H), 5.45 (d, *J* = 3.2 Hz, 1H), 4.77 (d, *J* = 12.6 Hz, 1H), 4.60 (d, *J* = 12.6 Hz, 1H), 4.05 (d, *J* = 7.0 Hz, 2H), 3.80 (t, *J* = 9.3 Hz, 1H), 2.92 (dd, *J* = 14.8, 5.8 Hz, 1H), 2.84 (d, *J* = 9.4 Hz, 1H), 2.50–2.05 (m, 6H), 1.62 (dd, *J* = 16.4, 8.8 Hz, 1H), 1.49 (s, 3H), 1.06 (t, *J* = 12.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 166.3, 151.2, 138.6, 135.4, 131.7, 130.2, 120.5, 119.1, 113.8, 81.1, 66.5, 63.3, 60.1, 42.8, 36.7, 25.9, 24.7, 23.9, 18.1. HRMS (ESI) calcd for $C_{22}H_{26}NO_5$ $[M+H]^+$ 384.1805, found 384.1807.

4.1.5. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl) methyl 4-(8-oxo-8-((trityloxy)amino)octanamido)benzoate (7)

Compound **3** (80.9 mg, 0.19 mmol) and HATU (95.1 mg, 0.25 mmol) was dissolved in dry DMF (4 mL), then DIPEA (44 μL, 0.25 mmol) was added. The mixture was stirred at 40 °C for 1 h, then compound **6** (48.0 mg, 0.13 mmol) was added. The reaction was stirred for 2 h at this temperature. Then, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 3:1–1:1] to give compound **7** as a yellow solid (81 mg, yield: 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.7 Hz, 2H),7.64 (d, *J* = 8.0 Hz, 2H), 7.52–7.27 (m, 16H), 6.20 (d, *J* = 3.5 Hz, 1H), 5.76 (t, *J* = 8.3 Hz, 1H), 5.51 (d, *J* = 3.1 Hz, 1H), 4.87 (d, *J* = 12.5 Hz, 1H), 4.70 (d, *J* = 12.6 Hz, 1H), 3.86 (t, *J* = 9.3 Hz, 1H), 3.03–2.92 (m, 1H), 2.89 (d, *J* = 9.4 Hz, 1H), 2.51–2.12 (m, 8H), 1.89 (s, 1H), 1.63 (dd, *J* = 14.7, 7.3 Hz, 3H), 1.55 (s, 3H), 1.25 (s, 7H), 1.12 (t, *J* = 12.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 172.2, 169.6, 166.0, 138.7, 135.2, 130.9, 130.6, 129.1, 128.3, 128.1, 128.1, 128.0, 120.6, 119.0, 81.2, 67.0, 63.4, 60.2, 42.9, 36.8, 29.8, 28.5, 25.9, 25.1, 24.7, 24.0, 18.1. HRMS (ESI) calcd for $C_{49}H_{53}N_2O_8$ $[M+H]^+$ 797.3796, found 797.3781.

4.1.6. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl) methyl 4-(8-(hydroxyamino)-8-oxooctanamido)benzoate (8)

Compound **4** (81 mg, 0.10 mmol) was dissolved in dichloromethane (2 mL). The reaction mixture was then cooled in an ice bath. TFA and Et_3SiH were added alternately dropwise until the yellow color disappeared. Then the solvent was evaporated to give an oily crude product, which was purified by a silica gel column to yield a yellow oil (45 mg, yield: 80%). ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.00 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 6.18 (d, *J* = 3.4 Hz, 1H), 5.81 (t, *J* = 8.3 Hz, 1H), 5.66 (d, *J* = 3.1 Hz, 1H), 4.95 (d, *J* = 12.7 Hz, 1H), 4.79 (d, *J* = 12.7 Hz, 1H), 4.07 (t, *J* = 9.3 Hz, 1H), 3.19–3.07 (m, 1H), 2.99 (d, *J* = 9.5 Hz, 1H), 2.65–2.37 (m, 6H), 2.30–2.10 (m, 4H), 1.83–1.63 (m, 5H), 1.60 (s, 3H), 1.44 (d, *J* = 2.9 Hz, 4H), 1.13 (t, *J* = 13.0 Hz, 1H). ^{13}C NMR (100 MHz, MeOD-d_4) δ 174.9, 171.8, 167.4, 144.8, 140.8, 136.8, 131.6, 131.3, 126.1, 120.6, 120.2, 82.9, 68.2, 64.8, 61.6, 43.9, 38.0, 37.7, 33.6, 30.7, 29.9, 29.8, 26.6, 26.5, 25.6, 24.7, 18.1. HRMS (ESI) calcd for $C_{30}H_{39}N_2O_8$ $[M+H]^+$ 555.2701, found 555.2703.

4.1.7. 7-Bromo-N-(trityloxy)heptanamide (10)

Compound **9** (500 mg, 2.39 mmol) was dissolved in 20 mL dry tetrahydrofuran, followed by the addition of *N*-methylmorpholine (289 μL, 2.63 mmol). The solution was then cooled to 10 °C and isobutyl chloroformate (341 μL, 2.63 mmol) was added. After stirring for 5 min, O-(triphenylmethyl) hydroxylamine (658 mg, 2.39 mmol) was added and the reaction mixture was stirred overnight. The precipitate formed was filtered and the solvent evaporated under reduced pressure. The obtained product was dissolved in ethyl acetate and extracted with saturated solution of $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography using a mixture of PE/EA = 5:1–4:1 to yield a white solid (1.07 g, yield: 95%). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.34–7.48 (m, 15H), 3.35 (t, J = 5.8 Hz, 2H), 1.75–1.86 (m 3H), 1.61 (s, 1H), 1.44 (s, 1H), 1.27 (s, 3H), 1.07 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 141.2, 129.1, 128.2, 93.4, 33.9, 32.5, 31.1, 29.8, 28.2, 27.8, 23.3. HRMS (ESI) calcd for $C_{26}H_{28}BrNNaO_2$ $[M+Na]^+$ 488.1196, found 488.1201.

*4.1.8. Methyl 4-((7-oxo-7-((trityloxy) amino) heptyl) oxy) benzoate (**11**)*

To a solution of compound **10** (1.63 g, 3.5 mmol) and methyl 4-hydroxybenzoate (152 mg, 1 mmol) in dry DMF 15 mL, K_2CO_3 (552 mg, 4 mmol) was added. The mixture was stirred at 40 °C for 4 h. The reaction was quenched with saturated aqueous NaCl and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 3:1–1:1] to give compound **11** as a yellow solid (473 mg, yield: 88%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.7 Hz, 2H), 7.40 (d, J = 55.4 Hz, 16H), 6.88 (d, J = 8.0 Hz, 2H), 3.95 (t, J = 6.0 Hz, 2H), 3.88 (s, 3H), 1.77–1.54 (m, 5H), 1.31 (d, J = 17.6 Hz, 3H), 1.10 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 167.1, 163.0, 141.2, 131.7, 129.2, 128.3, 122.5, 114.2, 100.1, 68.1, 52.0, 31.2, 29.8, 29.0, 28.9, 25.8, 23.5. HRMS (ESI) calcd for $C_{34}H_{35}NNaO_5$ $[M+Na]^+$ 560.2407, found 560.2412.

*4.1.9. 4-((7-Oxo-7-((trityloxy)amino)heptyl)oxy)Benzoic acid (**12**)*

Compound **11** (509 mg, 0.95 mmol) was dissolved in 9.4 mL THF-H_2O (1:1), followed by the addition of $LiOH{\cdot}H_2O$ (795 mg, 1.89 mmol). The reaction mixture was stirred at room temperature overnight. Upon completion, 2 N HCl was added to acidify the reaction, and the solution was extracted with ethyl acetate three times. The collected organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography using a mixture of DCM: MeOH = 60:1 to yield a white solid (355 mg, yield: 72%). ^1H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 10.16 (s, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 9.3 Hz, 15H), 6.98 (d, J = 8.8 Hz, 2H), 3.97 (t, J = 6.4 Hz, 2H), 1.78 (t, J = 6.6 Hz, 1H), 1.67–1.55 (m, 2H), 1.24 (q, J = 16.2 Hz, 5H), 1.02 (d, J = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 142.5, 131.3, 128.9, 127.5, 127.4, 122.9, 114.2, 91.7, 67.6, 31.9, 28.9, 28.3, 28.0, 25.1, 24.6. HRMS (ESI) calcd for $C_{33}H_{32}NO_5$ $[M-H]^-$ 522.2286, found 522.2283.

*4.1.10. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl 4-((7-oxo-7-((trityloxy)amino)heptyl)oxy)benzoate (**13**)*

To a solution of MMB (28.5 mg, 0.11 mmol), DIC (33 mg, 0.16 mmol), DMAP (1.3 mg, 0.01 mmol) in dry DCM (1 mL), the compound **12** (56.5 mg, 0.11 mmol) was added at 0 °C. The mixture was stirred for 8 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with DCM (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column to yield compound **13** (50.8 mg, yield: 61%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.8 Hz, 2H), 7.81–7.27 (m, 16H), 6.88 (d, J = 8.8 Hz, 2H), 6.23 (d, J = 3.4 Hz, 1H), 5.77 (t, J = 8.3 Hz, 1H), 5.52 (d, J = 3.1 Hz, 1H), 4.87 (d, J = 12.6 Hz, 1H), 4.70 (d, J = 12.6 Hz, 1H), 3.95 (t, J = 6.4 Hz, 2H), 3.86 (t, J = 9.3 Hz, 1H), 2.98 (t, J = 9.0 Hz, 1H), 2.90 (d, J = 9.4 Hz, 1H), 2.52–2.14 (m, 6H), 1.76–1.67 (m, 3H), 1.61 (s, 3H), 1.56 (s, 3H), 1.25 (s, 4H), 1.15 (d, J = 12.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 169.5, 166.2, 163.3, 141.2, 138.8, 135.3, 131.8, 130.5, 129.2, 128.3, 122.0, 120.6, 114.3, 81.2, 68.2, 66.8, 63.5, 60.1, 42.9, 36.8, 29.8, 29.5, 29.0, 28.9, 28.8, 26.0, 25.8, 24.7, 24.0, 18.2. HRMS (ESI) calcd for $C_{48}H_{50}NO_8$ $[M-H]^-$ 768.3542, found 768.3538.

*4.1.11. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl 4-((7-(hydroxyamino)-7-oxoheptyl)oxy)benzoate (**14**)*

Compound **13** (50 mg, 0.066 mmol) was dissolved in dichloromethane (2 mL). The reaction mixture was then cooled in an ice bath. TFA and Et_3SiH were added alternately dropwise until the yellow color disappeared. Then the solvent was evaporated to give an oily crude product, which was purified by a silica gel column to yield a colorless oil compound **14** (31 mg, yield: 89%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.3 Hz, 2H), 6.20 (d, J = 2.9 Hz, 1H), 5.78 (t, J = 8.3 Hz, 1H), 5.49 (d, J = 2.5 Hz, 1H), 4.86 (d, J = 12.6 Hz, 1H), 4.71 (d, J = 12.6 Hz, 1H), 4.00 (s, 2H), 3.87 (t, J = 9.2 Hz, 1H), 3.00 (t, J = 9.7 Hz, 1H), 2.90 (d, J = 9.4 Hz, 1H), 2.53–2.28 (m, 4H), 2.27–2.13 (m, 3H), 1.79 (s, 2H), 1.75–1.63 (m, 3H), 1.56 (s, 3H), 1.25 (s, 5H), 1.13 (t, J = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 166.2, 163.3, 138.8, 135.3, 131.8, 130.9, 122.1, 120.6, 114.4, 81.2, 68.1, 67.0, 63.4, 60.2, 43.0, 36.8, 32.9, 32.1, 29.8, 28.9, 28.8, 26.0, 25.8, 25.0, 24.0, 18.2. HRMS (ESI) calcd for $C_{29}H_{37}NNaO_8$ $[M+Na]^+$ 550.2411, found 550.2414.

*4.1.12. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-hydroxyphenyl)acrylate (**15**)*

To a solution of MMB (264 mg, 1.0 mmol), PPh_3 (393 mg, 1.5 mmol) and coumalic acid (210 mg, 1.5 mmol) in dry THF (10 mL) were added DIAD (0.3 mL, 1.5 mmol) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 4 h. Then, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:2] to give compound **15** (285 mg, yield: 69%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 15.9 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.13–6.99 (m, 1H), 6.87 (d, J = 8.4 Hz, 2H), 6.26 (d, J = 8.9 Hz, 1H), 6.23 (d, J = 3.6 Hz, 1H), 5.72 (t, J = 7.9 Hz, 1H), 5.57 (d, J = 3.3 Hz, 1H), 4.76 (d, J = 12.5 Hz, 1H), 4.59 (d, J = 12.5 Hz, 1H), 3.89 (t, J = 9.3 Hz, 1H), 2.98 (t, J = 9.1 Hz, 1H), 2.91 (d, J = 9.4 Hz, 1H), 2.51–2.11 (m, 6H), 1.73–1.64 (m, 1H), 1.55 (s, 3H), 1.12 (t, J = 12.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 167.3, 158.6, 145.7, 138.5, 134.9, 130.6, 130.1, 126.3, 120.8, 116.0, 114.1, 81.2, 66.8, 63.3, 60.3, 42.6, 36.5, 25.8, 24.5, 23.8, 17.9. HRMS (ESI) calcd for $C_{24}H_{30}NO_6$ $[M+NH_4]^+$ 428.2068, found 428.2067.

*4.1.13. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl) methyl (E)-3-(4-((7-oxo-7-((trityloxy)amino)heptyl)oxy)phenyl)acrylate (**16**)*

To a solution of compound **10** (517 mg, 1.11 mmol) and compound **15** (130 mg, 0.32 mmol) in dry DMF 15 mL, K_2CO_3 (177 mg, 1.28 mmol) was added. The mixture was stirred at 40 °C for 4 h. The reaction was quenched with saturated brine and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:1] to give compound **16** as a yellow solid (181 mg, yield: 71%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79–7.58 (m, 2H), 7.54–7.27 (m, 17H), 6.88 (d, J = 7.8 Hz, 2H), 6.27 (d, J = 16.4 Hz, 2H), 5.74 (t, J = 7.6 Hz, 1H), 5.56 (s, 1H), 4.78 (d, J = 12.5 Hz, 1H), 4.59 (d, J = 12.5 Hz, 1H), 3.93 (s, 2H), 3.87 (t, J = 9.3 Hz, 1H), 2.99 (t, J = 9.6 Hz, 1H), 2.90 (d, J = 9.3 Hz, 1H), 2.56–2.30 (m, 4H), 2.30–2.13 (m, 2H), 1.77–1.59 (m, 5H), 1.56 (s, 3H), 1.31 (d, J = 17.5 Hz, 3H), 1.26 (s, 2H), 1.18–1.09 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 167.0, 161.2, 145.4, 141.1, 138.8, 135.2, 130.6, 129.9, 129.0, 128.1, 126.7, 120.3, 114.9, 114.6, 114.0, 81.1, 68.0, 66.7, 63.3, 60.0, 42.8, 36.7, 29.7, 28.9, 28.7, 25.9, 25.6, 24.7, 23.9, 18.0. HRMS (ESI) calcd for $C_{50}H_{52}NO_8$ $[M-H]^-$ 794.3693, found 794.3695.

*4.1.14. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-((7-(hydroxyamino)-7-oxoheptyl)oxy)phenyl)acrylate(**17**)*

Compound **16** (106 mg, 0.13 mmol) was dissolved in dichloromethane (2 mL). The reaction mixture was then cooled in an ice bath. TFA and Et_3SiH were added alternately dropwise until the yellow color disappeared. Then the solvent was evaporated to give an oily crude product, which was purified by a silica gel column to yield a colorless oil compound **17** (60 mg, yield: 82%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.63 (d, J = 16.0 Hz, 1H), 7.43 (d, J = 7.5 Hz, 2H), 6.87 (d, J = 7.8 Hz, 2H), 6.26 (d, J = 14.9 Hz, 2H), 5.74 (t, J = 8.2 Hz, 1H), 5.56 (s, 1H), 4.76 (d, J = 12.5 Hz, 1H), 4.59 (d, J = 12.6 Hz, 1H), 3.96 (s, 2H), 3.87 (t, J = 9.3 Hz, 1H), 3.01 (t, J = 10.3 Hz, 1H), 2.90 (d, J = 9.4 Hz, 1H), 2.50–2.15 (m, 8H), 1.77 (s, 2H), 1.72–1.64 (m, 3H), 1.56 (s, 3H), 1.46 (s, 2H), 1.42–1.36 (m, 2H), 1.17–1.09 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ169.7 (2C), 167.2, 161.3, 145.5, 138.9, 135.3, 130.9, 130.0, 126.8, 120.6, 115.1, 114.7, 81.3, 68.1, 67.0, 63.5, 60.2, 42.9, 36.8, 32.1, 29.8, 29.0, 28.9, 26.1, 25.8, 24.9, 24.0, 18.2. HRMS (ESI) calcd for $C_{31}H_{38}NO_8$ $[M-H]^-$ 552.2603, found 552.2600.

*4.1.15. General procedure for the synthesis of compounds **18a–18c***

Different acid (2.0 mmol, 1 eq) was dissolved in 40 mL dry tetrahydrofuran, followed by the addition of *N*-methylmorpholine (2.2 mmol, 1.1 eq). The solution was then cooled to 10 °C and isobutyl chloroformate (2.2 mmol, 1.1 eq) was added. After stirring for 5 min, O-(triphenylmethyl) hydroxylamine (2.2 mmol, 1.1 eq) was added and the reaction mixture was stirred overnight. The precipitate formed was filtered and the solvent evaporated under reduced pressure. The obtained product was dissolved in ethyl acetate and extracted with saturated solution of $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography using a mixture of PE/EA = 5:1–4:1 to yield a white solid **18a–18c**.

*4.1.15.1. 6-Bromo-N-(trityloxy)hexanamide (**18a**).* White amorphous solid (yield: 90%). ^1H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 7.33 (s, 15H), 3.41 (t, J = 6.4 Hz, 2H), 1.79 (s, 2H), 1.70–1.59 (m, 2H), 1.26–1.16 (m, 2H), 1.09 (d, J = 6.1 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 142.4, 128.9, 127.5, 127.4, 91.7, 34.8, 31.9, 31.7, 26.9, 23.8. HRMS (ESI) calcd for $C_{25}H_{26}BrNNaO_2$ $[M+Na]^+$ 474.1039, found 474.1042.

*4.1.15.2. 8-Bromo-N-(trityloxy)octanamide (**18b**).* White amorphous solid (yield: 87%). ^1H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 7.33 (s, 15H), 3.50 (t, J = 6.7 Hz, 2H), 1.83–1.70 (m, 3H), 1.35–1.22 (m, 3H), 1.22–1.03 (m, 4H), 0.97 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 142.5, 128.9, 127.7, 127.5, 127.4, 126.6, 91.7, 35.1, 32.1, 28.1, 27.7, 27.3. HRMS (ESI) calcd for $C_{27}H_{30}BrNNaO_2$ $[M+Na]^+$ 502.1352, found 502.1358.

*4.1.15.3. 9-Bromo-N-(trityloxy)nonanamide (**18c**).* White amorphous solid (yield: 95%). ^1H NMR (400 MHz, DMSO-d_6) δ 12.43 (s, 1H), 9.62 (s, 15H), 5.79 (t, J = 6.0 Hz, 2H), 4.06 (d, J = 5.8 Hz, 4H), 3.66–3.56 (m, 2H), 3.55–3.31 (m, 6H), 3.25 (d, J = 5.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 142.5, 128.9, 127.5, 127.4, 91.7, 35.2, 32.2, 32.0, 28.5, 28.2, 27.9, 27.4, 24.7. HRMS (ESI) calcd for $C_{28}H_{32}BrNNaO_2$ $[M+Na]^+$ 516.1509, found 516.1512.

*4.1.16. General procedure for the synthesis of compounds **19a–19c***

To a solution of compound **19a–19c** (0.85 mmol, 3.5 eq) and compound **15** (100 mg, 0.24 mmol, 1 eq) in dry DMF 15 mL, K_2CO_3 (132.7 mg, 0.96 mmol, 4 eq) was added. The mixture was stirred at 40 °C for 4 h. The reaction was quenched with saturated brine and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:1] to give compound **19a–19c** as a yellow solid.

*4.1.16.1. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-((6-oxo-6-((trityloxy)amino)hexyl)oxy)phenyl)acrylate (**19a**).* White amorphous solid (yield: 81%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 15.9 Hz, 1H), 7.44 (d, J = 8.5 Hz, 5H), 7.33 (s, 13H), 6.87 (d, J = 8.2 Hz, 2H), 6.27 (t, J = 9.5 Hz, 2H), 5.74 (t, J = 8.0 Hz, 1H), 5.56 (d, J = 2.9 Hz, 1H), 4.78 (d, J = 12.5 Hz, 1H), 4.59 (d, J = 12.6 Hz, 1H), 3.94–3.82 (m, 3H), 2.99 (t, J = 8.9 Hz, 1H), 2.89 (d, J = 9.4 Hz, 1H), 2.53–2.12 (m, 7H), 1.67 (s, 6H), 1.56 (s, 3H), 1.33 (s, 2H), 1.17–1.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 169.5, 167.1, 161.3, 145.5, 141.3, 138.9, 135.3, 130.7, 130.0, 129.2, 128.3, 126.8, 120.5, 115.0, 114.7, 114.1, 100.1, 81.2, 67.9, 66.9, 63.5, 60.1, 42.9, 36.8, 29.8, 29.8, 28.9, 26.0, 25.6, 24.8, 24.0, 18.1. HRMS (ESI) calcd for $C_{49}H_{51}NNaO_8$ $[M+Na]^+$ 804.3507, found 804.3510.

*4.1.16.2. ((1aR,7aR,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydroxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-((8-oxo-8((trityloxy)amino)octyl)oxy)phenyl)acrylate (**19b**).* White amorphous solid (yield: 77%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.65 (d, J = 15.8 Hz, 1H), 7.45 (d, J = 8.2 Hz, 4H), 7.33 (s, 13H), 6.88 (d, J = 7.9 Hz, 2H), 6.27 (d, J = 15.5 Hz, 2H), 5.74 (t, J = 8.0 Hz, 1H), 5.56 (s, 1H), 4.78 (d, J = 12.4 Hz, 1H), 4.59 (d, J = 12.5 Hz, 1H), 3.95 (t, J = 5.3 Hz, 2H), 3.87 (t, J = 9.2 Hz, 1H), 2.99 (t, J = 10.2 Hz, 1H), 2.90 (d, J = 9.3 Hz, 1H), 2.54–2.11 (m, 6H), 1.79–1.68 (m, 3H), 1.61 (d, J = 18.0 Hz, 3H), 1.56 (s, 3H), 1.43–1.32 (m, 3H), 1.25 (s, 3H), 1.17–1.09 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.1, 161.4, 145.5, 141.2, 138.9, 135.3, 130.8, 130.0, 129.9, 129.2, 128.2, 127.8, 126.8, 120.5, 115.0, 114.7, 81.2, 68.2, 66.9, 63.5, 60.1, 42.9, 36.8, 29.8, 29.2, 29.1, 26.0, 25.9, 24.8, 24.0, 18.2. HRMS (ESI) calcd for $C_{51}H_{54}NO_8$ $[M-H]^-$ 808.3855, found 808.3853.

*4.1.16.3. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-((9-oxo-9-((trityloxy)amino)nonyl)oxy)phenyl)acrylate (**19c**).* White amorphous solid (yield: 86%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 15.9 Hz, 1H), 7.54–7.27 (m, 18H), 6.89 (d, J = 8.3 Hz, 2H), 6.26 (t, J = 10.1 Hz, 2H), 5.74 (t, J = 8.0 Hz, 1H), 5.56 (d, J = 2.6 Hz, 1H), 4.78 (d, J = 12.5 Hz, 1H), 4.59 (d, J = 12.6 Hz, 1H), 3.96 (t, J = 6.4 Hz, 2H), 3.87 (t, J = 9.3 Hz, 1H), 2.98 (t, J = 9.0 Hz, 1H), 2.89 (d, J = 9.4 Hz, 1H), 2.52–2.12 (m, 6H), 1.74 (dd, J = 19.4, 11.9 Hz, 3H), 1.54 (d, J = 14.7 Hz, 4H), 1.39 (d, J = 7.0 Hz, 3H), 1.23 (d, J = 22.6 Hz, 6H), 1.17–1.08 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 169.5, 167.1, 161.3, 145.5, 141.2, 138.9, 135.3, 130.7, 129.9, 129.1, 128.2, 127.7, 127.4, 126.7, 120.4, 115.0, 114.6, 81.2, 68.2, 66.8, 63.4, 60.1, 42.8, 36.8, 29.8, 29.2, 29.1, 26.0, 24.7, 24.0, 18.1. HRMS (ESI) calcd for $C_{52}H_{56}NO_8$ $[M-H]^-$ 822.4011, found 822.4008.

*4.1.17. General procedure for the synthesis of compounds **20a–20c***

Compound **19a–19c** (85 mg) was dissolved in dichloromethane (2 mL). The reaction mixture was then cooled in an ice bath. TFA and Et_3SiH were added alternately dropwise until the yellow color disappeared. Then the solvent was evaporated to give an oily crude product, which was purified by a silica gel column to yield a colorless oil compound **20a–20c**.

*4.1.17.1. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-((6-(hydroxyamino)-6-oxohexyl)oxy)phenyl)acrylate (**20a**).* White amorphous solid (yield: 83%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.60 (d, J = 15.9 Hz, 1H), 7.40 (d, J = 8.5 Hz, 2H), 6.84

(d, *J* = 8.5 Hz, 2H), 6.29–6.17 (m, 2H), 5.71 (t, *J* = 8.0 Hz, 1H), 5.54 (d, *J* = 3.0 Hz, 1H), 4.74 (d, *J* = 12.5 Hz, 1H), 4.58 (d, *J* = 12.6 Hz, 1H), 3.96–3.81 (m, 3H), 3.00 (t, *J* = 8.8 Hz, 1H), 2.88 (d, *J* = 9.4 Hz, 1H), 2.47–2.12 (m, 8H), 1.82–1.71 (m, 2H), 1.68 (d, *J* = 7.4 Hz, 3H), 1.54 (s, 3H), 1.44 (s, 2H), 1.10 (t, *J* = 12.5 Hz, 1H).^{13}C NMR (100 MHz, CDCl$_3$) δ 169.8(2C), 167.1, 161.1, 145.4, 138.8, 135.1, 130.8, 130.0, 126.7, 120.6, 115.0, 114.7, 81.3, 67.8, 67.0, 63.4, 60.3, 42.8, 36.7, 32.7, 28.8, 26.0, 25.5, 25.1, 24.9, 23.9, 18.1. HRMS (ESI) calcd for $C_{30}H_{36}NO_8$ $[M-H]^-$ 538.2446, found 538.2442.

*4.1.17.2. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-((8-(hydroxyamino)-8-oxooctyl)oxy)phenyl)acrylate **(20b)**.* White amorphous solid (yield: 87%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 (t, *J* = 16.9 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.25 (d, *J* = 15.8 Hz, 2H), 5.72 (t, *J* = 8.1 Hz, 1H), 5.55 (d, *J* = 2.4 Hz, 1H), 4.73 (t, *J* = 15.5 Hz, 1H), 4.59 (d, *J* = 12.6 Hz, 1H), 3.94 (t, *J* = 6.1 Hz, 2H), 3.86 (t, *J* = 9.3 Hz, 1H), 3.00 (t, *J* = 8.8 Hz, 1H), 2.89 (d, *J* = 9.4 Hz, 1H), 2.51–2.11 (m, 8H), 1.78–1.65 (m, 3H), 1.63 (d, *J* = 11.4 Hz, 2H), 1.54 (s, 3H), 1.41 (d, *J* = 7.4 Hz, 2H), 1.33 (s, 4H), 1.11 (t, *J* = 12.7 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.7(2C), 167.1, 161.3, 145.4, 138.9, 135.2, 130.7, 130.0, 126.7, 120.5, 115.0, 114.7, 81.3, 68.2, 67.0, 63.4, 60.2, 42.9, 36.7, 29.8, 29.1, 29.0, 26.0, 25.9, 25.4, 24.9, 24.9, 24.0, 18.1. HRMS (ESI) calcd for $C_{32}H_{41}NNaO_8$ $[M+Na]^+$ 590.2724, found 590.2728.

*4.1.17.3. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-((9-(hydroxyamino)-9-oxononyl)oxy)phenyl)acrylate **(20c)**.* White amorphous solid (yield: 82%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.54 (s, 1H), 7.64 (d, *J* = 15.9 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.31–6.20 (m, 2H), 5.74 (t, *J* = 8.2 Hz, 1H), 5.56 (d, *J* = 3.1 Hz, 1H), 4.77 (d, *J* = 12.5 Hz, 1H), 4.59 (d, *J* = 12.5 Hz, 1H), 3.96 (t, *J* = 6.4 Hz, 2H), 3.87 (t, *J* = 9.3 Hz, 1H), 3.05–2.95 (m, 1H), 2.90 (d, *J* = 9.4 Hz, 1H), 2.50–2.11 (m, 8H), 1.82–1.72 (m, 2H), 1.69–1.59 (m, 3H), 1.56 (s, 3H), 1.43 (s, 2H), 1.32 (s, 6H), 1.13 (t, *J* = 12.6 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.7(2C), 167.2, 161.3, 145.5, 138.9, 135.2, 130.8, 130.0, 126.7, 120.6, 115.0, 114.6, 81.2, 68.2, 67.0, 63.5, 60.2, 42.9, 36.7, 33.1, 29.8, 29.3, 29.2, 29.2, 29.1, 26.0, 25.4, 24.8, 24.0, 18.2. HRMS (ESI) calcd for $C_{33}H_{43}NNaO_8$ $[M+Na]^+$ 604.2881, found 604.2885.

*4.1.18. General procedure for the synthesis of compounds **21a–21c***

To a solution of **2** (1.0 mmol), PPh$_3$ (1.5 mmol) and corresponding acid (1.5 mmol) in dry THF (10 mL) were added DIAD (1.5 mmol) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 8 h. Then, the reaction was quenched with saturated aqueous NH$_4$Cl and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na$_2$SO$_4$, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:1] to give compound **21a–21c** as a white solid.

*4.1.18.1. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-hydroxy-2-methoxyphenyl)acrylate **(21a)**.* White amorphous solid (yield: 63%) ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, *J* = 16.1 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 6.97 (s, 1H), 6.50–6.41 (m, 2H), 6.37 (d, *J* = 16.1 Hz, 1H), 6.22 (d, *J* = 3.5 Hz, 1H), 5.73 (t, *J* = 8.2 Hz, 1H), 5.55 (d, *J* = 3.1 Hz, 1H), 4.74 (d, *J* = 12.5 Hz, 1H), 4.60 (d, *J* = 12.5 Hz, 1H), 3.88 (t, *J* = 9.3 Hz, 1H), 3.81 (s, 3H), 3.11–2.99 (m, 1H), 2.92 (d, *J* = 9.4 Hz, 1H), 2.50–2.12 (m, 6H), 1,74–1.61 (m, 1H), 1.55 (s, 3H), 1.12 (t, *J* = 12.5 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.1, 168.2, 160.5, 160.2, 141.6, 138.7, 135.3, 131.0, 130.8, 120.9, 115.7, 114.5, 108.2, 99.3, 81.4, 67.0, 63.5, 60.4, 55.6, 42.9, 36.7, 26.1, 25.0, 24.0, 18.1. HRMS (ESI) calcd for $C_{25}H_{28}NaO_7$ $[M+Na]^+$ 463.1727, found 463.1730.

*4.1.18.2. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-hydroxy-3-methoxyphenyl)acrylate **(21b)**.* White amorphous solid (yield: 55%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, *J* = 15.9 Hz, 1H), 7.07 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.25 (dd, *J* = 9.7, 6.2 Hz, 2H), 5.88 (s, 1H), 5.75 (t, *J* = 8.3 Hz, 1H), 5.56 (d, *J* = 3.2 Hz, 1H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.60 (d, *J* = 12.5 Hz, 1H), 3.94 (s, 3H), 3.88 (t, *J* = 9.3 Hz, 1H), 3.09–2.98 (m, 1H), 2.91 (d, *J* = 9.4 Hz, 1H), 2.55–2.14 (m, 6H), 1.74–1.64 (m, 1H), 1.56 (s, 3H), 1.14 (t, *J* = 12.6 Hz, 1H).^{13}C NMR (100 MHz, CDCl$_3$) δ 169.4, 166.8, 148.2, 146.8, 145.6, 138.8, 135.0, 130.8, 126.6, 123.2, 120.3, 114.7, 114.6, 109.2, 81.0, 66.9, 63.3, 60.0, 55.9, 42.7, 36.6, 25.8, 24.7, 23.8, 18.0. HRMS (ESI) calcd for $C_{25}H_{29}O_7$ $[M+H]^+$ 441.1908, found 441.1910.

*4.1.18.3. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-hydroxy-3,5-dimethoxyphenyl)acrylate **(21c)**.* Yellow amorphous solid (yield: 54%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58 (d, *J* = 15.9 Hz, 1H), 6.74 (s, 2H), 6.30–6.21 (m, 2H), 5.80 (s, 1H), 5.75 (t, *J* = 8.2 Hz, 1H), 5.55 (d, *J* = 3.2 Hz, 1H), 4.77 (d, *J* = 12.5 Hz, 1H), 4.60 (d, *J* = 12.5 Hz, 1H), 3.92 (s, 6H), 3.88 (t, *J* = 9.3 Hz, 1H), 3.11–2.99 (m, 1H), 2.91 (d, *J* = 9.4 Hz, 1H), 2.53–2.13 (m, 6H), 1.73–1.66 (m, 1H), 1.56 (s, 3H), 1.14 (t, *J* = 12.7 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.5, 166.9, 147.4, 145.9, 139.1, 137.6, 135.3, 131.1, 125.7, 120.4, 115.2, 105.3, 81.2, 67.2, 63.5, 60.1, 56.5, 43.0, 36.8, 26.1, 25.0, 24.0, 18.2. HRMS (ESI) calcd for $C_{26}H_{30}NaO_8$ $[M+Na]^+$ 493.1833, found 493.1838.

*4.1.19. General procedure for the synthesis of compounds **22a–22c***

To a solution of compound **10** (350.0 mg, 0.75 mmol, 3.5 eq) and compound **21a–21c** (0.2 mmol, 1 eq) in dry DMF 15 mL, K$_2$CO$_3$ (110.5 mg, 0.8 mmol, 4 eq) was added. The mixture was stirred at 40 °C for 4 h. The reaction was quenched with saturated brine and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na$_2$SO$_4$, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:1] to give compound **22a–22c** as a yellow solid.

*4.1.19.1. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2-methoxy-4-((7-oxo-7-((trityloxy)amino)heptyl)oxy)phenyl)acrylate **(22a)**.* White amorphous solid (yield: 57%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90 (d, *J* = 16.0 Hz, 1H), 7.59–7.28 (m, 16H), 6.52–6.35 (m, 3H), 6.23 (d, *J* = 2.9 Hz, 1H), 5.74 (t, *J* = 8.1 Hz, 1H), 5.54 (s, 1H), 4.76 (d, *J* = 12.5 Hz, 1H), 4.59 (d, *J* = 12.5 Hz, 1H), 3.93 (t, *J* = 6.6 Hz, 2H), 3.90–3.79 (m, 4H), 3.05 (t, *J* = 9.8 Hz, 1H), 2.92 (d, *J* = 9.4 Hz, 1H), 2.52–2.12 (m, 6H), 1.76–1.66 (m, 3H), 1.61 (s, 4H), 1.56 (s, 3H), 1.28 (s, 3H), 1.18–1.09 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.6, 167.8, 162.7, 160.2, 141.3, 138.9, 135.5, 130.9, 130.8, 129.2, 128.3, 120.5, 116.2, 115.0, 106.0, 99.0, 81.2, 68.2, 67.0, 63.5, 60.1, 55.6, 42.9, 36.8, 29.8, 29.1, 26.2, 25.8, 25.0, 24.0, 18.2. HRMS (ESI) calcd for $C_{51}H_{54}NO_9$ $[M-H]^-$ 824.3804, found 824.3800.

*4.1.19.2. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3-methoxy-4-((7-oxo-7-((trityloxy)amino)heptyl)oxy)phenyl)acrylate **(22b)**.* White amorphous solid (yield: 69%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73 (s, 1H), 7.62 (d, *J* = 15.8 Hz, 1H), 7.46 (s, 2H), 7.33 (s, 13H), 7.06 (d, *J* = 8.2 Hz, 1H), 7.01 (s, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.27 (d, *J* = 14.9 Hz, 2H), 5.74 (t, *J* = 8.0 Hz, 1H), 5.56 (s, 1H), 4.78 (d, *J* = 12.6 Hz, 1H), 4.60 (d, *J* = 12.5 Hz, 1H), 3.99 (t, *J* = 6.3 Hz, 2H), 3.93–3.81 (m, 4H), 3.02 (t, *J* = 10.2 Hz, 1H), 2.95

(s, 1H), 2.90 (d, *J* = 9.5 Hz, 1H), 2.87 (s, 1H), 2.54–2.14 (m, 6H), 1.83-1.64 (m, 5H), 1.56 (s, 3H), 1.29 (s, 3H), 1.17–1.09 (m, 2H). ^{13}C NMR (100 MHz, CDCl3) δ 169.48, 167.00, 162.65, 151.16, 149.71, 145.70, 138.99, 135.28, 130.88, 129.15, 128.22, 127.02, 122.91, 120.38, 114.91, 112.50, 110.20, 81.20, 68.97, 66.99, 63.45, 60.06, 56.12, 42.89, 36.79, 28.92, 26.06, 25.72, 24.87, 24.01, 18.14. HRMS (ESI) calcd for $C_{51}H_{54}NO_9$ $[M-H]^-$ 824.3804, found 824.3802.

*4.1.19.3. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3,5-dimethoxy-4-((7-oxo-7-((trityloxy)amino)heptyl)oxy)phenyl)acrylate (**22c**)*. Yellow amorphous solid (yield: 44%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59 (d, *J* = 15.8 Hz, 1H), 7.46 (s, 2H), 7.32 (s, 14H), 6.71 (s, 2H), 6.31 (d, *J* = 15.9 Hz, 1H), 6.23 (s, 1H), 5.74 (t, *J* = 8.1 Hz, 1H), 5.55 (s, 1H), 4.78 (d, *J* = 12.5 Hz, 1H), 4.60 (d, *J* = 12.6 Hz, 1H), 3.95 (t, *J* = 6.5 Hz, 2H), 3.90–3.80 (m, 7H), 3.03 (t, *J* = 9.1 Hz, 1H), 2.90 (d, *J* = 9.4 Hz, 1H), 2.53–2.11 (m, 6H), 1.84 (d, *J* = 15.8 Hz, 2H), 1.70–1.62 (m, 3H), 1.55 (s, 3H), 1.30 (d, *J* = 19.8 Hz, 3H), 1.25 (s, 2H), 1.16–1.07 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 177.4, 169.4, 166.7, 153.8, 145.7, 141.2, 139.8, 139.0, 135.1, 131.0, 129.4, 129.2, 129.1, 128.2, 127.4, 126.8, 120.3, 116.4, 105.4, 93.4, 81.1, 73.5, 67.1, 63.4, 60.0, 56.2, 42.8, 36.7, 29.9, 29.7, 26.0, 25.5, 24.8, 23.9, 18.1. HRMS (ESI) calcd for $C_{52}H_{57}NNaO_{10}$ $[M+Na]^+$ 878.3875, found 878.3880.

*4.1.20. General procedure for the synthesis of compounds **23a–23c***

Compound **22a–22c** was dissolved in dichloromethane. The reaction mixture was then cooled in an ice bath. TFA and Et$_3$SiH were added alternately dropwise until the yellow color disappeared. Then the solvent was evaporated to give an oily crude product, which was purified by a silica gel column to yield a colorless oil compound **23a–23c**.

*4.1.20.1. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-((7-(hydroxyamino)-7-oxoheptyl)oxy)-2-methoxyphenyl)acrylate (**23a**)*. White amorphous solid (yield: 83%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, *J* = 16.0 Hz, 1H), 7.37 (s, 1H), 6.53–6.32 (m, 3H), 6.22 (s, 1H), 5.74 (t, *J* = 8.0 Hz, 1H), 5.54 (s, 1H), 4.74 (d, *J* = 12.4 Hz, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 3.97 (s, 2H), 3.90–3.74 (m, 4H), 3.07 (t, *J* = 9.3 Hz, 1H), 2.92 (d, *J* = 9.3 Hz, 1H), 2.50–2.12 (m, 8H), 1.78 (s, 2H), 1.72–1.61 (m, 3H), 1.56 (s, 3H), 1.52–1.37 (m, 4H), 1.13 (t, *J* = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.7, 167.8, 162.6, 160.2, 141.3, 138.9, 135.5, 131.0, 130.9, 120.5, 116.3, 115.1, 106.1, 99.1, 81.3, 68.1, 67.1, 63.5, 60.2, 55.7, 43.0, 36.8, 32.1, 29.8, 29.1, 28.9, 26.3, 25.8, 25.2, 24.1, 22.8, 18.2. HRMS (ESI) calcd for $C_{32}H_{40}NO_9$ $[M-H]^-$ 582.2709, found 582.2706.

*4.1.20.2. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl 4-((7-(hydroxyamino)-7-oxoheptyl)oxy)-3-methoxybenzoate (**23b**)*. White amorphous solid (yield: 72%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61 (d, *J* = 15.8 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.01 (s, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.32–6.17 (m, 2H), 5.74 (t, *J* = 8.2 Hz, 1H), 5.55 (d, *J* = 3.0 Hz, 1H), 4.77 (d, *J* = 12.5 Hz, 1H), 4.60 (d, *J* = 12.5 Hz, 1H), 4.03 (s, 2H), 3.95–3.81 (m, 4H), 3.03 (t, *J* = 8.9 Hz, 1H), 2.90 (d, *J* = 9.4 Hz, 1H), 2.54–2.12 (m, 8H), 1.83 (s, 2H), 1.74–1.63 (m, 3H), 1.56 (s, 3H), 1.50–1.40 (m, 3H), 1.13 (t, *J* = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.6, 167.0, 151.1, 149.7, 145.7, 139.0, 135.3, 131.0, 127.1, 123.0, 120.5, 115.0, 112.6, 110.3, 81.3, 68.8, 67.1, 63.5, 60.1, 56.2, 42.9, 36.8, 29.8, 28.8, 28.6, 26.1, 25.5, 25.0, 24.0, 18.2. HRMS (ESI) calcd for $C_{32}H_{41}NNaO_9$ $[M+Na]^+$ 606.2674, found 606.2675.

*4.1.20.3. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-((7-(hydroxyamino)-7-oxoheptyl)oxy)-3,5-dimethoxyphenyl)acrylate (**23c**)*. Yellow amorphous solid (yield: 69%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.02 (s, 1H), 7.56 (d, *J* = 15.9 Hz, 1H), 6.70 (s, 2H), 6.28 (d, *J* = 15.9 Hz, 1H), 6.22 (d, *J* = 3.3 Hz, 1H), 5.73 (t, *J* = 8.1 Hz, 1H), 5.54 (d, *J* = 3.0 Hz, 1H), 4.76 (d, *J* = 12.5 Hz, 1H), 4.59 (d, *J* = 12.5 Hz, 1H), 3.96 (t, *J* = 6.0 Hz, 2H), 3.91–3.78 (m, 7H), 3.04 (t, *J* = 8.9 Hz, 1H), 2.89 (d, *J* = 9.4 Hz, 1H), 2.54–2.09 (m, 8H), 1.68 (d, *J* = 3.2 Hz, 3H), 1.64 (d, *J* = 11.3 Hz, 2H), 1.54 (s, 3H), 1.44 (s, 2H), 1.37–1.30 (m, 2H), 1.11 (t, *J* = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.6, 166.7, 153.7, 145.6, 139.7, 139.0, 135.1, 131.1, 129.5, 120.4, 116.6, 105.6, 81.3, 73.5, 67.3, 63.4, 60.2, 56.3, 42.9, 36.7, 29.9, 29.8, 28.8, 26.0, 25.4, 25.3, 25.0, 24.0, 22.8, 18.1. HRMS (ESI) calcd for $C_{33}H_{42}NO_{10}$ $[M-H]^-$ 612.2814, found 612.2812.

*4.1.21. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2-hydroxyphenyl)acrylate (**24**)*

To a solution of MMB (322 mg, 1.22 mmol), PPh$_3$ (479 mg, 1.83 mmol) and *trans*-2-hydroxycinnamic acid (300 mg, 1.83 mmol) in dry THF (10 mL) were added DIAD (0.36 mL, 1.83 mmol) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 4 h. Then, the reaction was quenched with saturated aqueous NH$_4$Cl and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na$_2$SO$_4$, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:1] to give compound **24** (344 mg, yield: 68%) as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96 (d, *J* = 16.1 Hz, 1H), 7.42 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.25–7.19 (m, 1H), 6.90 (t, *J* = 7.5 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.59 (d, *J* = 16.1 Hz, 1H), 6.22 (d, *J* = 3.5 Hz, 1H), 5.75 (t, *J* = 8.1 Hz, 1H), 5.55 (d, *J* = 3.2 Hz, 1H), 4.76 (d, *J* = 12.4 Hz, 1H), 4.62 (d, *J* = 12.4 Hz, 1H), 3.89 (t, *J* = 9.3 Hz, 1H), 3.16–3.02 (m, 1H), 2.93 (d, *J* = 9.4 Hz, 1H), 2.53–2.13 (m, 6H), 1.68 (t, *J* = 12.5 Hz, 1H), 1.56 (s, 3H), 1.13 (t, *J* = 12.5 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.2, 167.8, 155.8, 141.5, 138.8, 135.3, 131.8, 131.3, 129.7, 121.5, 120.8, 117.9, 116.6, 81.4, 67.5, 63.5, 60.3, 43.0, 36.7, 29.8, 26.2, 25.2, 24.0, 18.2. HRMS (ESI) calcd for $C_{24}H_{26}NaO_6$ $[M+Na]^+$ 433.1622, found 433.1625.

*4.1.22. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2-((7-oxo-7-((trityloxy)amino)heptyl)oxy)phenyl)acrylate (**25**)*

To a solution of compound **10** (341 mg, 0.73 mmol) and compound **24** (150 mg, 0.365 mmol) in dry DMF 3.6 mL, K$_2$CO$_3$ (151 mg, 1.10 mmol) was added. The mixture was stirred at 40 °C for 4 h. The reaction was quenched with saturated brine and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na$_2$SO$_4$, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:1] to give compound **25** as a yellow solid (220 mg, yield: 76%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, *J* = 15.8 Hz, 1H), 7.75 (s, 1H), 7.48 (d, *J* = 7.2 Hz, 4H), 7.33 (s, 14H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.23 (s, 1H), 5.72 (d, *J* = 7.5 Hz, 1H), 5.54 (s, 1H), 4.84–4.51 (m, 2H), 3.97 (d, *J* = 5.8 Hz, 2H), 3.86 (t, *J* = 9.0 Hz, 1H), 2.97 (s, 1H), 2.89 (d, *J* = 9.3 Hz, 1H), 2.53–2.11 (m, 6H), 1.76 (s, 2H), 1.70 (s, 2H), 1.55 (s, 3H), 1.31 (d, *J* = 21.6 Hz, 2H), 1.26 (s, 3H), 1.11 (t, *J* = 12.3 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.5(2C), 167.3, 158.0, 141.3, 138.8, 135.3, 131.9, 130.6, 129.3, 129.2, 129.1, 128.2, 127.4, 123.2, 120.7, 120.5, 117.7, 112.3, 81.2, 68.4, 66.8, 63.4, 60.1, 42.8, 36.8, 32.0, 29.8, 29.5, 28.9, 26.0, 25.8, 24.7, 24.0, 22.8, 18.1. HRMS (ESI) calcd for $C_{50}H_{52}NO_8$ $[M-H]^-$ 794.3698, found 794.3695.

*4.1.23. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(2-((7-(hydroxyamino)-7-oxoheptyl)oxy)phenyl)acrylate (**26**)*

Compound **25** (133 mg, 0.17 mmol) was dissolved in dichloromethane (2 mL). The reaction mixture was then cooled in an ice bath, TFA and Et$_3$SiH were added alternately dropwise until the yellow color disappeared. Then the solvent was evaporated to give an oily crude product, which was purified by a silica gel column to yield a colorless oil, compound **26** (60 mg, yield: 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.05 (d, J = 16.1 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.49 (d, J = 16.1 Hz, 1H), 6.22 (s, 1H), 5.74 (t, J = 7.8 Hz, 1H), 5.55 (s, 1H), 4.73 (d, J = 12.7 Hz, 1H), 4.67 (d, J = 12.7 Hz, 1H), 3.99 (t, J = 5.0 Hz, 2H), 3.87 (t, J = 9.3 Hz, 1H), 3.01 (t, J = 9.4 Hz, 1H), 2.90 (d, J = 9.4 Hz, 1H), 2.58–2.03 (m, 8H), 1.80 (s, 2H), 1.73–1.59 (m, 3H), 1.55 (s, 3H), 1.48 (s, 2H), 1.41 (d, J = 8.2 Hz, 2H), 1.12 (t, J = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8(2C), 167.9, 158.1, 141.6, 138.8, 135.0, 132.2, 130.7, 128.7, 123.0, 120.8, 120.7, 117.2, 112.3, 81.2, 68.6, 67.2, 63.5, 60.4, 42.8, 36.7, 29.8, 29.8, 29.0, 28.6, 26.0, 25.8, 24.9, 23.9, 18.1. HRMS (ESI) calcd for $C_{31}H_{39}NNaO_8$ $[M+Na]^+$ 576.2568, found 576.2573.

4.1.24. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3-hydroxyphenyl)acrylate (27)

To a solution of MMB (500 mg, 1.89 mmol), PPh_3 (745 mg, 2.84 mmol) and *trans*-3-hydroxycinnamic acid (466 mg, 2.84 mmol) in dry THF (18 mL) were added DIAD (0.56 mL, 2.84 mmol) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 4 h. Then, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:1] to give compound **27** (504 mg, yield: 65%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 16.0 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.11 (s, 1H), 7.01 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 16.0 Hz, 1H), 6.23 (d, J = 3.0 Hz, 1H), 5.71 (t, J = 8.1 Hz, 1H), 5.56 (d, J = 2.6 Hz, 1H), 4.74 (d, J = 12.5 Hz, 1H), 4.59 (d, J = 12.5 Hz, 1H), 3.89 (s, 1H), 3.00 (t, J = 9.4 Hz, 1H), 2.89 (d, J = 9.4 Hz, 1H), 2.49–2.09 (m, 6H), 1.67 (t, J = 10.8 Hz, 1H), 1.54 (s, 3H), 1.10 (t, J = 12.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 167.0, 156.7, 145.7, 138.7, 135.5, 134.9, 131.0, 130.2, 120.9, 120.6, 118.1, 117.5, 114.6, 81.5, 67.3, 63.4, 60.4, 42.8, 36.6, 25.9, 24.8, 23.9, 18.0. HRMS (ESI) calcd for $C_{24}H_{26}NaO_6$ $[M+Na]^+$ 433.1622, found 433.1625.

4.1.25. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3-((7-oxo-7-((trityloxy)amino)heptyl)oxy)phenyl)acrylate (28)

To a solution of compound **10** (341 mg, 0.73 mmol) and compound **27** (150 mg, 0.365 mmol) in dry DMF 3.6 mL, K_2CO_3 (151 mg, 1.10 mmol) was added. The mixture was stirred at 40 °C for 4 h. The reaction was quenched with saturated brine and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:1] to give compound **28** as a yellow solid (180 mg, yield: 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 15.9 Hz, 1H), 7.55–7.28 (m, 16H), 7.08 (d, J = 7.3 Hz, 1H), 7.00 (s, 1H), 6.92 (d, J = 7.9 Hz, 1H), 6.40 (d, J = 15.9 Hz, 1H), 6.25 (s, 1H), 5.74 (t, J = 8.0 Hz, 1H), 5.56 (s, 1H), 4.79 (d, J = 12.4 Hz, 1H), 4.61 (d, J = 12.4 Hz, 1H), 3.92 (t, J = 5.7 Hz, 2H), 3.86 (t, J = 9.4 Hz, 1H), 2.97 (t, J = 10.3 Hz, 1H), 2.89 (d, J = 9.2 Hz, 1H), 2.53–2.14 (m, 6H), 1.70 (d, J = 6.7 Hz, 6H), 1.56 (s, 3H), 1.38–1.28 (m, 5H), 1.16–1.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.5, 166.7, 159.6, 145.8, 138.9, 135.6, 135.2, 131.0, 130.9, 130.1, 129.2, 128.2, 120.8, 120.5, 117.7, 117.2, 113.7, 81.2, 68.1, 67.0, 63.5, 60.1, 42.9, 36.8, 32.1, 29.8, 29.1, 28.9, 26.0, 25.8, 24.7, 24.0, 22.8, 18.2. HRMS (ESI) calcd for $C_{50}H_{53}NNaO_8$ $[M+Na]^+$ 818.3663, found 818.3668.

4.1.26. ((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(3-((7-(hydroxyamino)-7-oxoheptyl)oxy)phenyl)acrylate (29)

Compound **28** (100 mg, 0.125 mmol) was dissolved in dichloromethane (2 mL). The reaction mixture was then cooled in an ice bath. TFA and Et_3SiH were added alternately dropwise until the yellow color disappeared. Then the solvent was evaporated to give an oily crude product, which was purified by a silica gel column to yield a colorless oil compound **29** (57 mg, yield: 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 15.6 Hz, 1H), 7.26 (s, 1H), 7.06 (d, J = 6.0 Hz, 1H), 6.98 (s, 1H), 6.90 (s, 1H), 6.37 (d, J = 15.6 Hz, 1H), 6.23 (s, 1H), 5.73 (s, 1H), 5.55 (s, 1H), 4.75 (d, J = 12.2 Hz, 1H), 4.61 (d, J = 12.4 Hz, 1H), 3.97–3.79 (m, 3H), 3.01 (s, 1H), 2.89 (d, J = 8.8 Hz, 1H), 2.54–2.10 (m, 8H), 1.83–1.61 (m, 5H), 1.54 (s, 3H), 1.49–1.34 (m, 4H), 1.11 (t, J = 12.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 166.7, 159.6, 145.7, 138.9, 135.5, 135.1, 131.1, 130.1, 121.0, 120.5, 117.7, 117.3, 113.5, 81.3, 68.0, 67.3, 63.4, 60.2, 42.9, 36.7, 32.9, 29.8, 29.0, 28.8, 26.0, 25.7, 25.3, 25.0, 24.0, 18.1. HRMS (ESI) calcd for $C_{31}H_{39}NNaO_8$ $[M+Na]^+$ 576.2568, found 576.2574.

4.1.27. Methyl (E)-3-(4-((7-oxo-7-((trityloxy)amino)heptyl)oxy)phenyl)acrylate (31)

To a solution of compound **10** (480 mg, 1.0 mmol) and compound **30** (100 mg, 0.51 mmol) in dry DMF 5 mL, K_2CO_3 (213 mg, 1.54 mmol) was added. The mixture was stirred at 40 °C for 4 h. The reaction was quenched with saturated brine and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:1] to give compound **31** as a yellow solid (269 mg, yield: 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 15.9 Hz, 1H), 7.46 (d, J = 8.1 Hz, 4H), 7.33 (s, 14H), 6.87 (d, J = 8.1 Hz, 2H), 6.30 (d, J = 16.0 Hz, 1H), 3.93 (t, J = 6.1 Hz, 2H), 3.79 (s, 3H), 1.75–1.66 (m, 2H), 1.61 (s, 4H), 1.29 (s, 3H), 1.10 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 161.1, 144.8, 129.9, 129.2, 128.3, 127.1, 115.2, 115.0, 68.1, 51.7, 29.8, 29.8, 29.0, 28.9, 25.8. HRMS (ESI) calcd for $C_{36}H_{37}NNaO_5$ $[M+Na]^+$ 586.2564, found 586.2568.

4.1.28. Methyl (E)-3-(4-((7-(hydroxyamino)-7-oxoheptyl)oxy)phenyl)acrylate (32)

Compound **31** (140 mg, 0.248 mmol) was dissolved in dichloromethane (2 mL). The reaction mixture was then cooled in an ice bath. TFA and Et_3SiH were added alternately dropwise until the yellow color disappeared. Then the solvent was evaporated to give an oily crude product, which was purified by a silica gel column to yield a colorless oil compound **32** (56 mg, yield: 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.64 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 16.1 Hz, 1H), 6.96 (d, J = 8.3 Hz, 2H), 6.47 (d, J = 16.0 Hz, 1H), 4.00 (t, J = 6.1 Hz, 2H), 3.70 (s, 3H), 1.95 (t, J = 7.1 Hz, 2H), 1.76–1.64 (m, 2H), 1.58–1.46 (m, 2H), 1.44–1.35 (m, 2H), 1.34–1.24 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 166.9, 160.6, 144.3, 130.1, 126.4, 115.0, 114.8, 67.6, 51.2, 32.2, 28.4, 28.3, 25.2, 25.0. HRMS (ESI) calcd for $C_{17}H_{22}NO_5$ $[M-H]^-$ 320.1503, found 320.1500.

4.1.29. (1aR,7aS,8S,10aS,10bS,E)-5-(hydroxymethyl)-1a,8-Dimethyl-2,3,6,7,7a,8,10a,10b-octahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-9(1aH)-one (33)

To a solution of MMB (450 mg, 1.7 mmol) in EtOH was added $NaBH_4$ (71 mg, 1.87 mmol) at 0 °C, the mixture was stirred for 4 h at the room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4 and concentrated to give an oily crude product, which was purified on a silica gel column [PE:EA = 1:1] to yield compound **33** (337 mg, yield: 74%), as a white soild. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (t, J = 7.8 Hz, 1H), 4.08 (q, J = 12.5 Hz, 2H), 3.83 (t, J = 9.5 Hz, 1H), 2.75 (d, J = 9.4 Hz, 1H), 2.50–2.08 (m, 7H), 1.90 (td, *J* = 12.1, 2.5 Hz, 1H), 1.68–1.46 (m, 5H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.07 (t, *J* = 12.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 178.0, 139.9, 127.3, 81.3, 65.9, 63.7, 60.0, 46.6, 41.6, 37.1, 26.8, 24.3, 23.7, 18.0, 13.2. HRMS (ESI) calcd for $C_{15}H_{22}NaO_4$ $[M+Na]^+$ 289.1410, found 289.1413.

4.1.30. *((1aR,7aS,8S,10aS,10bS,E)-1a,8-Dimethyl-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl) methyl (E)-3-(4-hydroxyphenyl)acrylate (**34**)*

To a solution of compound **33** (400 mg, 1.50 mmol), PPh_3 (595.8 mg, 2.27 mmol) and coumalic acid (318 mg, 2.27 mmol) in dry THF (15 mL) were added DIAD (0.45 mL, 2.27 mmol) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 4 h. Then, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:1] to give compound **34** (442 mg, yield: 71%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.65 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 6.86 (d, *J* = 7.9 Hz, 2H), 6.29 (d, *J* = 16.2 Hz, 2H), 5.69 (t, *J* = 8.0 Hz, 1H), 4.78 (d, *J* = 12.6 Hz, 1H), 4.55 (d, *J* = 12.6 Hz, 1H), 3.86 (t, *J* = 9.5 Hz, 1H), 2.80 (d, *J* = 9.3 Hz, 1H), 2.56–2.41 (m, 1H), 2.39–2.11 (m, 6H), 2.10-1.95 (m, 1H), 1.64–1.59 (m, 1H), 1.56 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.10 (t, *J* = 13.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 178.3, 167.3, 158.4, 145.6, 135.4, 130.2, 129.9, 126.9, 116.1, 114.7, 81.4, 66.3, 63.7, 60.2, 46.4, 41.7, 37.0, 26.9, 24.6, 23.9, 18.0, 13.2. HRMS (ESI) calcd for $C_{24}H_{28}NaO_6$ $[M+Na]^+$ 435.1778, found 435.1782.

4.1.31. *((1aR,7aS,8S,10aS,10bS,E)-1a,8-Dimethyl-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl) methyl (E)-3-(4-((7-oxo-7-((trityloxy)amino)heptyl)oxy)phenyl)acrylate (**35**)*

To a solution of compound **10** (393.5 mg, 0.84 mmol) and compound **34** (116 mg, 0.28 mmol) in dry DMF 2.8 mL, K_2CO_3 (155 mg, 1.12 mmol) was added. The mixture was stirred at 40 °C for 4 h. The reaction was quenched with saturated brine and extracted with EA (3 × 15 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified on a silica gel column [PE/EA = 2:1–1:1] to give compound **35** as a yellow solid (163 mg, yield: 73%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.66 (d, *J* = 16.0 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 5H), 7.31 (d, *J* = 18.4 Hz, 16H), 6.88 (d, *J* = 7.7 Hz, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 5.70 (t, *J* = 8.1 Hz, 1H), 4.79 (d, *J* = 12.6 Hz, 1H), 4.54 (d, *J* = 12.6 Hz, 1H), 3.93 (t, *J* = 5.8 Hz, 2H), 3.85 (t, *J* = 9.4 Hz, 1H), 2.79 (d, *J* = 9.2 Hz, 1H), 2.55–2.42 (m, 1H), 2.37–2.11 (m, 6H), 2.01 (d, *J* = 10.8 Hz, 1H), 1.74–1.68 (m, 2H), 1.62 (d, *J* = 11.1 Hz, 4H), 1.56 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 4H), 1.10 (t, *J* = 12.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 177.9, 167.1, 161.3, 145.4, 135.5, 130.0, 129.9, 129.3, 129.2, 128.3, 127.4, 126.8, 115.0, 114.8, 81.2, 68.1, 66.2, 63.6, 59.9, 46.5, 41.6, 37.0, 29.8, 29.0, 28.9, 26.9, 25.8, 24.6, 23.9, 18.0, 13.3. HRMS (ESI) calcd for $C_{50}H_{54}NO_8$ $[M-H]^-$ 796.3855, found 796.3853.

4.1.32. *((1aR,7aS,8S,10aS,10bS,E)-1a,8-Dimethyl-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl)methyl (E)-3-(4-((7-(hydroxyamino)-7-oxoheptyl)oxy)phenyl)acrylate (**36**)*

Compound **35** (120 mg, 0.15 mmol) was dissolved in dichloromethane (2 mL). The reaction mixture was then cooled in an ice bath, TFA and Et_3SiH were added alternately dropwise until the yellow color disappeared. Then the solvent was evaporated to give an oily crude product, which was purified by a silica gel column to yield a colorless oil compound **36** (44 mg, yield: 53%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.80 (s, 1H), 7.64 (d, *J* = 15.9 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 7.9 Hz, 2H), 6.29 (d, *J* = 15.9 Hz, 1H), 5.68 (t, *J* = 7.9 Hz, 1H), 4.77 (d, *J* = 12.6 Hz, 1H), 4.54 (d, *J* = 12.6 Hz, 1H), 3.95 (t, *J* = 5.9 Hz, 2H), 3.84 (t, *J* = 9.4 Hz, 1H), 2.79 (d, *J* = 9.3 Hz, 1H), 2.48 (d, *J* = 5.0 Hz, 1H), 2.38–2.09 (m, 8H), 2.02 (d, *J* = 10.9 Hz, 1H), 1.76 (s, 2H), 1.62 (d, *J* = 26.4 Hz, 3H), 1.55 (s, 3H), 1.45 (s, 2H), 1.37 (d, *J* = 7.1 Hz, 2H), 1.29 (d, *J* = 7.2 Hz, 4H), 1.10 (d, *J* = 12.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 178.1, 171.5, 167.1, 161.2, 145.4, 135.5, 130.0, 129.8, 126.9, 115.0, 114.8, 81.3, 68.1, 66.2, 63.6, 60.0, 46.4, 41.6, 37.0, 29.8, 29.0, 28.9, 26.9, 25.8, 25.3, 24.7, 23.9, 18.0, 13.2. HRMS (ESI) calcd for $C_{31}H_{40}NO_8$ $[M-H]^-$ 554.2759, found 554.2756.

4.1.33. *Procedure for the synthesis of compound **37***

Compound **3** was readily obtained from MMB according to a reported procedure [33].

4.1.33.1. *((1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2′,3′:9,10]cyclodeca[1,2-b]furan-5-yl) methyl cinnamate (**37**).*

White amorphous solid (yield: 86%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.68 (d, *J* = 16.0 Hz, 1H), 7.54–7.46 (m, 2H), 7.45–7.34 (m, 3H), 6.41 (d, *J* = 16.0 Hz, 1H), 6.22 (d, *J* = 3.5 Hz, 1H), 5.72 (t, *J* = 8.2 Hz, 1H), 5.55 (d, *J* = 3.1 Hz, 1H), 4.77 (d, *J* = 12.5 Hz, 1H), 4.59 (d, *J* = 12.5 Hz, 1H), 3.85 (t, *J* = 9.3 Hz, 1H), 3.01–2.91 (m, 1H), 2.87 (d, *J* = 9.4 Hz, 1H), 2.49–2.11 (m, 6H), 1.72–1.64 (m, 1H), 1.54 (s, 3H), 1.10 (t, *J* = 12.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.3, 166.5, 145.4, 138.6, 134.8, 133.9, 130.6, 130.5, 128.8, 128.0, 120.2, 117.2, 80.9, 66.8, 63.2, 59.9, 42.5, 36.5, 25.7, 24.4, 23.7, 17.9. HRMS (ESI) calcd for $C_{24}H_{30}NO_5$ $[M+NH_4]^+$ 412.2118, found 412.2122.

4.2. *Cell culture and MTT assay*

HL-60 cells were purchased from American Type Culture Collection (ATCC, USA); HL-60/ADR cells were purchased from Chinese Academy of Medical Sciences. And both cells were cultured in 1640 medium supplement with 10% FBS at 37 °C in 5% CO_2. As to MTT assay, HL-60 cells and HL-60/ADR cells were seeded respectively into 96 well plate with 5000 cells each well. Then the compounds were added with a series of concentrations. After the compounds incubated with cells for 72 h, MTT solution (5 mg/mL) was added. After incubation for 4 h, the supernatant was discovered and the precipitate was dissolved with DMSO. After that the absorbance of OD 570 nm was detected using a micro-plate reader. The IC_{50} values were calculated by GraphPad Prism 5.

4.3. *Cell apoptosis assay*

HL-60/ADR cells were seeded into 6 well plate with a concentration of 1 × 10^5/mL. Then the compound **26** was added with the concentration of 0.2 μM, 0.5 μM, 1 μM and 2 μM. After incubated with cells for 48 h, the cells were collected and washed with phosphate-buffered saline (PBS). Subsequently, the cells were resuspended with 1 × binding buffer and incubated with Annexin-V-APC and PI for 15 mins at room temperature. Then the samples were analyzed with flow cytometry.

4.4. *Western blot assay*

HL-60/ADR cells were incubated with 0, 0.05 μM, 0.1 μM, 0.2 μM or 0.5 μM compound **26** for 24 h. Then the cells were washed with phosphate-buffered saline (PBS) and suspended with lysate for 30mins on ice. The cell lysates with equal amounts were separated by gel electrophoresis and then transferred onto PVDF membranes. After being blocked with 5% nonfat milk, the membranes were incubated with anti-HDAC1, anti-HDAC6, anti-ABCC1, anti-Bax, anti-Bcl-2, anti-Cytochrome *C*, anti-caspase 9, anti-caspase 3, anti-PARP and anti-β-actin respectively at 4 °C overnight. Subsequently, the membranes were washed with PBST buffer for 5 times and incubated with the appropriate anti-HRP secondary antibody for 2 h at room temperature. Then the membranes were washed with PBST buffer for 5 times and visualized by Tanon Chemiluminescent Imaging System.

Acknowledgments

This work was supported by the Natural Science Foundation of Tianjin (NO. 17JCQNJC13400), National Natural Science Foundation of China (NO. 81573308 to Q.Z.; NO. 81573282 to Y.C.), The National Science Fund for Distinguished Young Scholars (NO. 81625021) to Y.C., and the Fundamental Research Funds for the Central Universities to Y.D.

Appendix A. Supplementary material

Copies of $^{1}H/^{13}C$ NMR spectra of compounds **3–37**. Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.03.056.

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