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Synthesis and evaluation of nitric oxide-releasing derivatives of farnesylthiosalicylic acid as anti-tumor agents

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ABSTRACT

Novel furoxan-based nitric oxide (NO)-releasing derivatives (**11a–p**) of farnesylthiosalicylic acid (FTA) were synthesized. Compounds **11d**, **11f**, **11k**, and **11m–o** displayed anti-tumor activities superior to FTA and sorafenib in most cancer cells tested. Analysis of six compounds revealed that **11d**, **11f**, **11n**, **11o**, and **11p**, but not **11a** that had low anti-tumor activity, produced high levels of NO, associated with their strong anti-tumor activity. Furthermore, the anti-tumor activity of **11f** was partially mimicked by the furoxan moiety, but reduced by pre-treatment with hemoglobin. Importantly, treatment with **11f** inhibited Ras-related signaling in cancer cells. Apparently, the high anti-tumor activity of **11f** was attributed to the synergic effect of high levels of NO production and inhibition of Ras-related signaling in cancer cells. Our findings suggest that the furoxan/FTA hybrids may hold greater promise as therapeutic agents for the intervention of human cancers.

1. Introduction

Ras proteins are membrane-anchored guanine-nucleotide binding proteins, and function as biological switches that can mediate signal transduction between G-protein coupled receptors and downstream events such as MAPK or Akt.[1,2] The activation of MAPK or Akt signaling regulates cell proliferation, migration, differentiation, and apoptosis.[3–7] Notably, the mutations of the Ras genes usually result in the constitutive activation of Ras-GTP proteins and overstimulation of downstream signaling, promoting the development and progression of tumors in human.[8] Hence, the Ras-related signaling events are the therapeutic targets for intervention of human cancers.

Many efforts to regulate the Ras-related signal pathway have been made to inhibit cancer progression and some new drugs have been developed. Farnesylthiosalicylic acid (FTA) is a novel Ras inhibitor by dislodging all isoforms of Ras from galectin membrane binding sites.[9,10] FTA has been used for the treatment of a wide range of malignancies, including pancreatic, and lung cancers.[11–13] However, its therapeutic efficacy is limited. Therefore, development of new Ras inhibitors with potent anti-tumor activity should be of great significance.

Nitric oxide (NO) is naturally generated from L-arginine by the action of NO synthase (NOS) and a key signaling molecule involved in regulating the numerous physiologic and pathologic processes.[14] High levels of NO and its metabolic derivatives, the reactive nitrogen species (RNS) and reactive oxygen species (ROS), can modify functional proteins by *S*-nitrosylation, nitration, and disulfide formation, leading to bio-regulation, inactivation, and cytotoxicity, particularly in tumor cells.[15] Indeed, previous studies have shown that synthesized NO-releasing compounds have strong cytotoxicity against human carcinoma cells in vitro and inhibit cancer growth and metastasis in vivo.[16–19] Furoxans are thermally stable compounds and represent an important class of NO-donors, which can produce high levels of NO in vitro, and inhibit the growth of tumors in vivo.[18,20,21] Accordingly, we hypothesized that new types of synthesized furoxan/FTA hybrids could have Ras inhibitory activity and produce high levels of NO, leading to potent cytotoxicity against broad types of cancer cells.

Given that amino acid-coupling compounds can help in delivering the compounds to tumor cells,[22] a total of 16 target compounds (**11a–p**) were designed by coupling the carboxyl group of FTA with phenylsulfonyl-substituted furoxan through various amino acids. Their anti-tumor activity, NO-releasing ability, and Ras inhibitory effect were evaluated in vitro. Herein, we report the synthesis and biological evaluation of the target compounds.

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2. Results and discussion

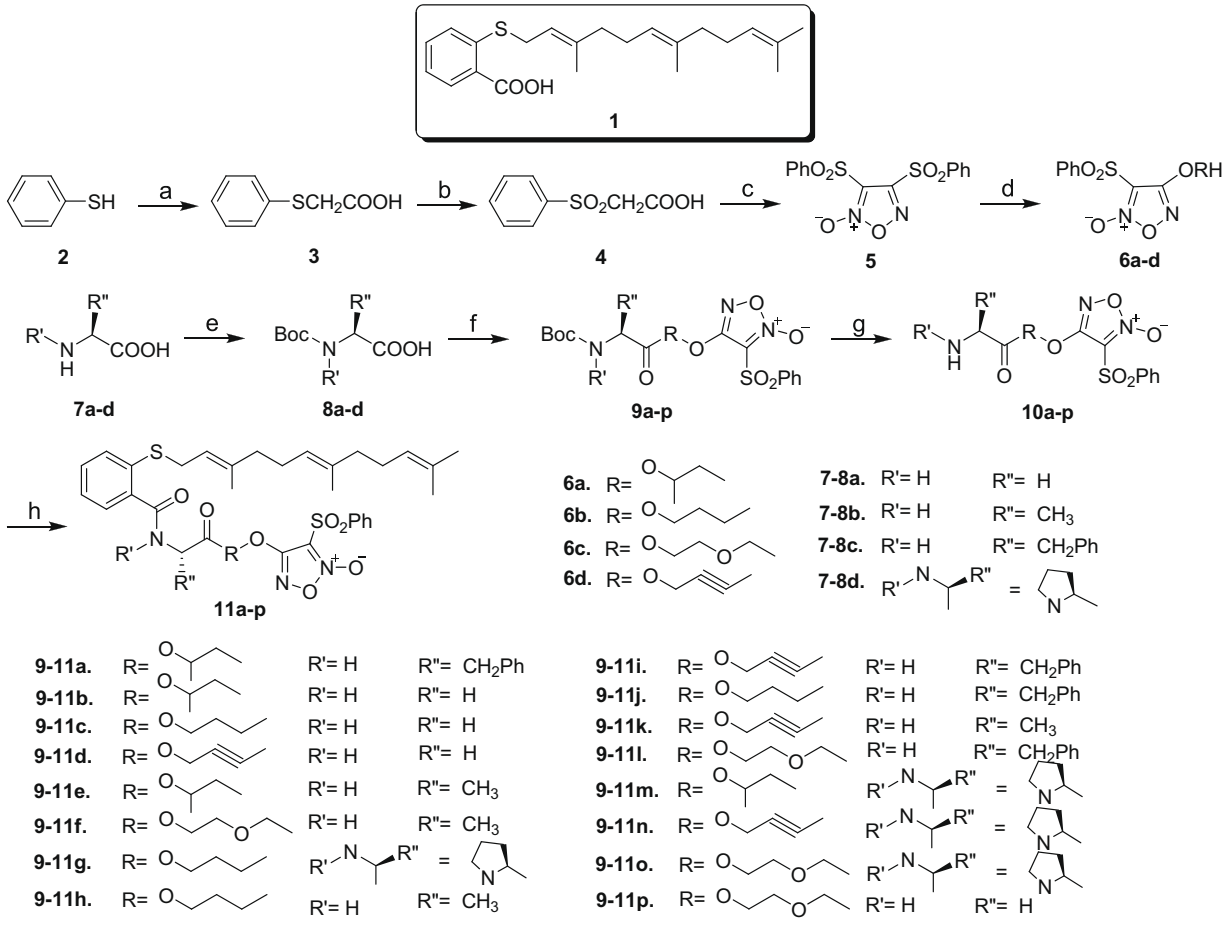
2.1. Chemistry

The synthetic routes of **11a–p** are outlined in Scheme 1. The substituted furoxans were prepared in a four-step sequence. The starting material benzenethiol (**2**) was converted to 2-(phenylthio) acetic acid (**3**) by treatment with chloroacetic acid in 97% yield. Compound **3** was oxidized by 30% H_2O_2 aqueous solution to generate 2-(phenylsulfonyl) acetic acid (**4**), and then treated with fuming HNO_3 to produce diphenylsulfonylfuroxan (**5**). Subsequently, **5** was treated with corresponding diol (butane-1, 3-diol, butane-1, 4-diol, 2-butyne-1, 4-diol or 2,2′-oxydiethanol) to form various monophenylsulfonylfuroxans (**6a–d**) with the yields of 57–73%. Furthermore, glycocine (**7a**), L-phenylalanine (**7b**), L-alanine (**7c**) or L-proline (**7d**) was treated with di-*tert*-butyl dicarbonate in the presence of Et_3N and *t*-BuOH at room temperature to give *N*-Boc amino acids (**8a–d**) in 62–78% yields, respectively. These N-protected amino acids were reacted with each substituted furoxans (**6a–d**) in CH_2Cl_2 in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) afforded esters (**9a–p**) in 57–77% yields. The N-protected groups of **9a–p** were removed by CF_3COOH to provide the intermediates (**10a–p**), which were directly treated with **1** in CH_2Cl_2 in the presence of 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and DMAP to generate the target compounds (**11a–p**) in yields of 46–58%, respectively. The final products were purified by column chromatography and their structures were characterized by IR, ^1H NMR, MS, and elemental analyses.

2.2. Biological evaluation

The cytotoxicity of individual compounds against human glioblastoma cells (U87, U251), human breast cancer cells (MCF-7), human breast adenocarcinoma cells (MDA-MB-231), and human gastric cancer cells (SGC-7901) was evaluated by MTT assay using FTA and sorafenib as positive controls. The IC_{50} values of individual compounds against each tumor cell line are presented in Table 1. Twelve out of 16 compounds displayed cytotoxicity superior to FTA, some even stronger than that of sorafenib. For example, the anti-tumor activity of **11n** was 50-fold more potent than FTA (IC_{50}: 1.07 vs 51.22 μM) and fourfold than sorafenib (IC_{50}: 1.07 vs 4.77 μM) against MDA-MB-231 cells. Furthermore, those active hybrids had more potent cytotoxicity against cancer cells than that of their relevant NO-donors. For example, the IC_{50} values of **11f**, **11g**, **11k**, **11m–p** in MDA-MB-231 cells were much smaller than that of **6a** (15.32 μM), **6b** (9.87 μM), **6c** (20.48 μM), and **6d** (6.97 μM), respectively.

Furthermore, we tested whether the levels of NO production by the indicated compounds in each type of human cancer cells were associated with their cytotoxicities. MCF-7, MDA-MB-231, U251, U87, and SGC-7901 cells were exposed to each compound (100 μM) for varying durations (30–300 min). The levels of nitrite/nitrate produced in the cell lysates of different types of cells were characterized using the Griess assay (Fig. 1). As expected, treatment with FTA resulted in little nitrite/nitrate in any of the tested cells. In contrast, treatment with a single furoxan/FTA hybrid promoted comparable levels of nitrite/nitrate production



Scheme 1. General method for the synthesis of **11a–p**. Reagents and conditions: (a) $ClCH_2COOH$, NaOH (aq), 140 °C, 2 h; (b) 30% H_2O_2, AcOH, rt, 3 h; (c) fuming HNO_3, 90 °C, 4 h; (d) diol, THF, 30% NaOH, rt, 4–8 h; (e) $(Boc)_2O$, *t*-BuOH, 2.5% NaOH, rt, 6–12 h; (f) **6a–d**, DCC, DMAP, CH_2Cl_2, rt, 6–12 h; (g) CF_3COOH, rt, 2 h; (h) **1**, EDCI, DMAP, CH_2Cl_2, rt, 24 h.

Table 1
IC_{50} values of **11a–p** against five human cancer cell lines

Compound	In vitro cytotoxicity (IC_{50}, μM)[a]				
	MCF-7	MDA-MB-231	U251	U87	SGC-7901
FTA	46.75	51.22	46.91	53.95	37.74
Sorafenib	8.83	4.77	24.71	21.07	10.37
11a	>50	>50	>50	>50	>50
11b	9.11	7.26	10.78	15.35	11.91
11c	25.06	9.99	28.22	>50	>50
11d	6.91	7.23	11.72	14.82	11.37
11e	11.14	5.05	15.32	20.38	>50
11f	7.68	4.21	8.04	18.08	11.27
11g	7.47	3.14	6.99	9.00	22.53
11h	8.68	>50	7.95	26.36	44.57
11i	>50	>50	>50	>50	>50
11j	>50	>50	>50	>50	>50
11k	5.03	1.01	7.31	5.18	11.37
11l	>50	>50	>50	>50	>50
11m	6.50	1.54	7.93	8.47	13.93
11n	5.49	1.07	3.56	13.49	7.35
11o	8.77	3.16	4.83	12.92	7.86
11p	6.59	2.41	8.58	7.34	19.50

[a] The cytotoxicity of individual compounds against each of the cancer cell lines was determined by the MTT assay and expressed as the IC_{50} (a dose achieved 50% inhibition in the growth of cancer cells cultured.

in different types of cancer cells while treatment with the tested furoxan/FTA hybrids produced significantly variable levels of nitrate/nitrite in any of the cancer cells tested. Treatment with low cytotoxic compound **11a** produced lower levels of nitrate/nitrite in all of the tested cells. However, treatment with any of the compounds (**11d**, **11f**, **11n**, **11o** or **11p**) with a high cytotoxicity produced significantly higher levels of nitrate/nitrite in these cells. Apparently, the levels of nitrate/nitrite produced by individual compounds were associated with their cytotoxicities against these cancer cells in vitro.

To further determine the contribution of NO to the cytotoxicity of furoxan/FTA hybrids, **11f** was selected for testing its cytotoxicity, as compared with its furoxan moiety in the presence or absence of NO scavenger hemoglobin. MDA-MB-231 cells were pre-treated with, or without, different concentrations of hemoglobin for 1 h and then treated with the indicated concentrations of **11f** or furoxan moiety **6a**. The effects of different treatments on the growth of MDA-MB-231 cells and the production of nitrate/nitrite were determined by the MTT and Griess assays, respectively (Fig. 2). Treatment with **11f** alone greatly inhibited the growth of MDA-MB-231 cells and treatment with **6a** alone mimicked the partial inhibition of **11f** on the growth of MDA-MB-231 cells, which were associated with various levels of nitrate/nitrite. Furthermore, the inhibitory effects of **11f** or **6a** on the growth of MDA-MB-231 cells were dramatically reduced by pre-treatment with hemoglobin, which appeared to be dose-dependent. Similar patterns of reduced levels of nitrate/nitrite in the cell lysates were observed. These data clearly demonstrated that high levels of NO production by the compound contributed to its cytotoxicity against human cancer cells in vitro.

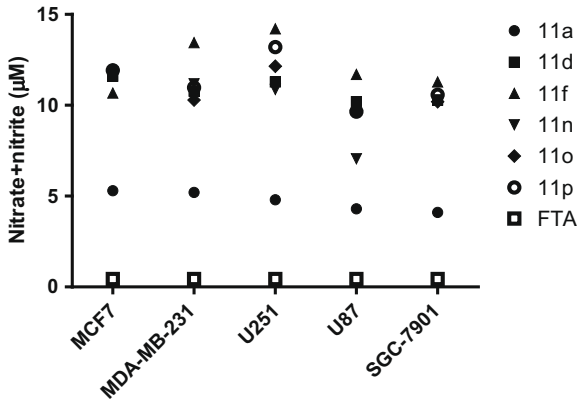


Figure 1. Variable levels of NO were produced by the compounds. Human cancer cells were treated with each compound at 100 μM and the contents of nitrate/nitrite in the cell lysates were determined by Griess assay through the duration of 30–300 min. The individual values were determined by measuring absorbance at 540 nm, and calculated according to the standard curve. Data shown are the mean value of two experiments for each compound at 240 min post-treatment in individual types of cells, and similar patterns of nitrate/nitrite production in these cells were observed at other experimental time points (data not shown).

Finally, we examined whether the furoxan/FTA hybrids could still retain the Ras inhibitor activity. MDA-MB-231 cells were treated with vehicle control or different doses of **11f** and the expression and activation of the Ras-related signal events, Akt, ERK, and Raf were determined by immunoblotting assays (Fig. 3). Obviously, treatment with 5 μM **11f** significantly reduced the expression of Akt, and ERK in our experimental condition. Importantly, treatment with **11f** dramatically inhibited the activation of Akt, ERK, and Raf. Evidentially, the levels of phosphor-Akt, -ERK, and -Raf were almost abolished in the cells treated with 5 μM **11f**. However, treatment with 5 μM of FTA did not effectively inhibit the Ras signaling (data not shown), similar to a previous report.[23] These data suggest that high levels of NO produced by **11f** may contribute to the low concentration of **11f**-mediated inhibition of Ras signaling.[24] Given that the Ras-related MAPK and Akt signal pathways are associated with the growth and anti-apoptosis of many types of cells the significantly reduced activation of these pathways by **11f** should increase the susceptibility of cells to cytotoxic triggers, contributing to the cytotoxicity of the furoxan/FTA hybrids.

Analysis of structure–activity relationships revealed that **11a–p** with different amino acid linkers had tremendous difference in their cytotoxicities. The compounds (**11g**, **11m**, **11n**, and **11o**) linked with praline had better anticancer activities, while the compounds (**11a, 11i, 11j**, and **11l**) containing phenylalanine had little cytotoxicity. The cytotoxicity of different hybrids with varying amino acid linkers was as following sequence: proline>alanine>glycine>phenylalanine. The lack of cytotoxicity against human cancer cells may be due to the low levels of NO production. Evidentially, treatment with **11a** that had little cytotoxicity produced significantly lower levels of NO in MDA-MB-231 cells, as compared with that by high cytotoxic **11f**. Furthermore, the low cytotoxicity may also stem from low efficacy of the compounds in entering to the cells and/or loss of the Ras inhibitor activity. We are interested in further determining the SAR of furoxan/FTA hybrids, which will provide a new insight into design of novel anticancer drugs.

3. Conclusion

In summary, we have synthesized 16 novel furoxan-based NO-releasing derivatives of FTA using various amino acids as chemical linkers and evaluated their cytotoxicities against human breast, glioblastoma, and gastric cancer cells in vitro. We found that most compounds displayed strong cytotoxicity against these cancer cells, particularly for compounds **11f, 11n**, and **11o**, which had a great potency superior to FTA and sorafenib. Furthermore, the compounds with strong cytotoxicity against human cancer cells produced high levels of NO in these cancer cells. In addition, the cytotoxicity of **11f** was partially mimicked by furoxan moiety **6a**, but reduced by NO scavenger hemoglobin in a dose-dependent manner. Moreover, compound **11f** had strong Ras inhibitory activity and inhibited the expression and activation of the Ras-related Akt and Erk signaling in human breast carcinoma cells. Apparently, the synergic effect of both high levels of NO production and strong

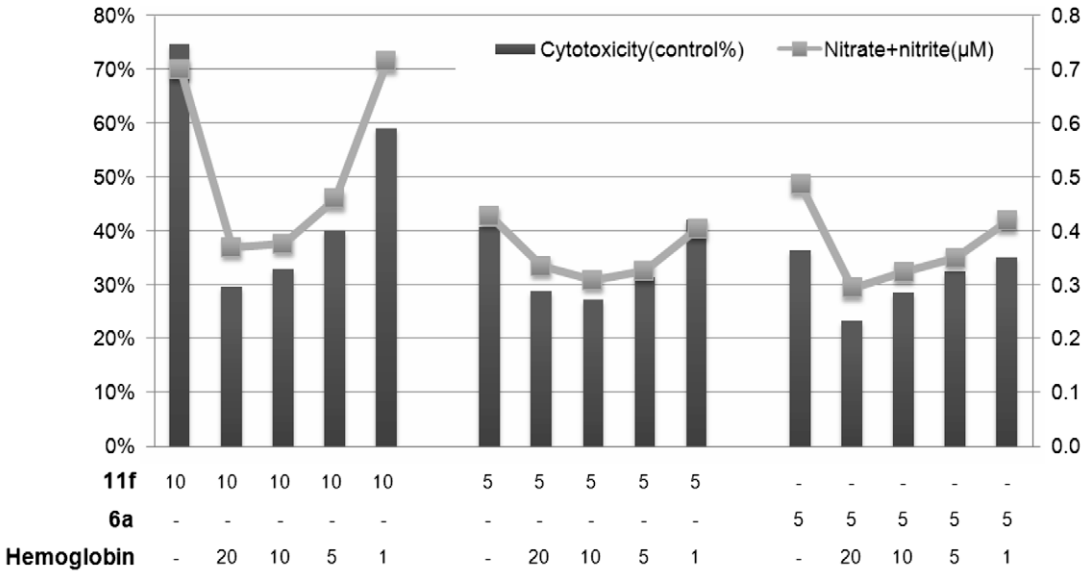


Figure 2. NO produced by the compound **11f** contributed to its cytotoxicity. MDA-MB-231 cells were pretreated with, or without, the indicated concentrations of hemoglobin for 1 h and treated with 5 or 10 μM of **11f** or furoxan moiety **6a** for 24 h. The cell growth and nitrate/nitrite production were determined by the MTT and Griess assays, respectively. Data are expressed as mean% of inhibition on the growth of MDA-MB-231 cells and mean values of the levels of nitrate/nitrite from three independent experiments. The intra-group and inter-experimental variations were less than 10% and the cells treated with 1% Triton x-100 were used as positive controls and considered as 100%. The cells treated with different concentrations of hemoglobin alone did not affect their growth (data not shown).

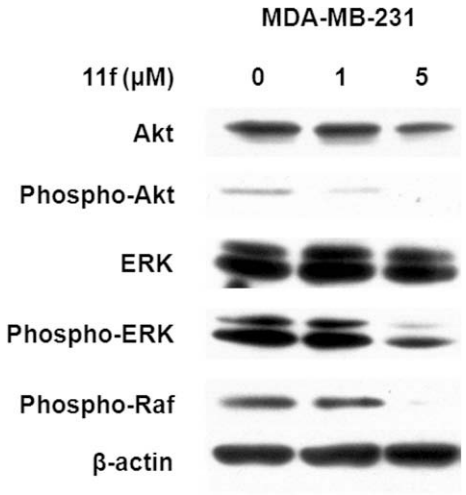


Figure 3. Effect of **11f** on the Ras-related signaling. MDA-MB-231 cells at 1.5×10^5/mL were treated with 1 or 5 μM **11f** or vehicle control for 8 h. After harvested and lyzed, the cell lysates were separated by SDS–PAGE and probed with anti-Akt, anti-phospho-Akt (Ser473), anti-ERK, anti-phospho-ERK (Thr202/Tyr204), anti-Phospho-Raf (Ser259) and anti-β-actin antibodies (Cell Signaling, Boston), respectively. The immunoblotting was visualized by HRP-conjugated second antibodies and enhanced chemiluminescent. Data shown are a representative of two separated experiments.

Ras inhibitor activity contributed to the potent cytotoxicity of these furoxan/FTA hybrids. Therefore, our novel findings provide a proof of principle in design of new NO-releasing furoxan/FTA hybrids for the intervention of human cancers. We are interested in further investigating the effect of these hybrids on the growth of human cancer cells in vivo and the mechanisms underlying the action of these hybrids in inhibition of human tumorigenesis.

4. Experiment

Melting points were determined on a Mel-TEMP II melting point apparatus and uncorrected. Optical rotations were measured with a JASCO P-1020 polarimeter (cell length: 100 mm). Infrared (IR) spectra (KBr) were recorded on a Nicolet Impact 410 instrument (KBr pellet). ^{1}H NMR spectra were recorded with a Bruker Avance 300 MHz spectrometer at 300 K, using TMS as an internal standard. MS spectra were recorded on a Shimadzu GC–MS 2010 (EI) or a Mariner Mass Spectrum (ESI). Element analysis was performed on an Eager 300 instrument. All compounds were routinely checked by TLC and ^{1}H NMR. TLCs and preparative thin-layer chromatography were performed on silica gel GF/UV 254, and the chromatograms were conducted on silica gel (200–300 mesh) and visualized under UV light at 254 and 365 nm. All solvents were reagent grade and, when necessary, were purified and dried by standards methods. Solutions after reactions and extractions were concentrated using a rotary evaporator operating at a reduced pressure of ca. 20 Torr. Organic solutions were dried over anhydrous sodium sulfate. Compounds **1**, **2**, and **7** were commercially available. Compounds **3–6** were synthesized according to the reported procedure.[26]

4.1. Synthesis

4.1.1. Synthesis of *N*-Boc amino acids (8)

4.1.1.1. 2-(*tert*-Butoxycarbonylamino) acetic acid (8a). To a solution of **7a** (496 mg, 6.62 mmol) and 2.5% NaOH (12 mL) in *t*-BuOH (12 mL) at 0 °C was added Boc_2O (2.2 mL, 7.98 mmol) by slow dropwise. The solution was allowed to warm to room temperature and stirred for 12 h. The solvent was removed under reduced pressure. The crude residue was dissolved in water and washed with ether (3×10 mL). The water layer was acidified with 1 M HCl to pH 2, and then extracted with AcOEt (3×12 mL). The organic extracts were combined, dried with $MgSO_4$, filtered, and concentrated to afford **8a** as white solid (904 mg, 78%), mp 88–90 °C [lit.[25] 88 °C].

4.1.1.2. (*S*)-2-(*tert*-Butoxycarbonylamino) propanoic acid (8b). Compound **8b** was synthesized from **7b** (491 mg, 5.52 mmol), 2.5% NaOH (12 mL), and Boc_2O (2 mL, 7.25 mmol), according to the synthetic procedure of **8a** in a yield of 74%, white solid 770 mg, mp 80–83 °C [lit.[25] 82 °C].

4.1.1.3. (*S*)-2-(*tert*-Butoxycarbonylamino)-3-phenyl propanoic acid (8c). Compound **8c** was synthesized from **7c** (956 mg, 5.80 mmol), 2.5% NaOH (12 mL), and Boc_2O (2 mL, 7.25 mmol), according to the synthetic procedure of **8a** in a yield of 63%, white solid 968 mg, mp 87–89 °C [lit.[25] 87 °C].

4.1.1.4. (*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxylic acid (8d). Compound **8d** was synthesized from **7d** (634 mg, 5.52 mmol), 2.5% NaOH (12 mL), and Boc_2O (2 mL, 7.25 mmol), according to the synthetic procedure of **8a** in a yield of 62%, white solid 735 mg, mp 135–137 °C [lit.[25] 136 °C].

4.1.2. Synthesis of mono-phenylsulfonylfuroxans *N*-Boc amino ester (9)

4.1.2.1. 4-(3-((*S*)-2-(*tert*-Butoxycarbonylamino)-3-phenylpropanoyloxy) butoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9a). To a solution of **8c** (530 mg, 2.00 mmol) in dry CH_2Cl_2 (40 mL), **6a** (628 mg, 2.00 mmol), DCC (415 mg, 2.00 mmol), and DMAP (317 mg, 2.60 mmol) was added and the mixture was stirred at room temperature for 12 h. After filtration, the filtrate was evaporated to dryness in vacuo, and the crude product was purified by column chromatography (PE/EtOAc = 10:1–5:1) to yield **9a** as a white solid (864 mg, 77%), mp 120–122 °C. Analytical data for **9a**: $[\alpha]_D^{26}$ −3.7; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, 2H, J = 7.8 Hz, Ar-H), 7.74 (m, 1H, Ar-H), 7.62 (m, 2H, Ar-H), 7.28 (m, 1H, Ar-H), 7.22 (m, 2H, Ar-H), 7.15 (m, 2H, Ar-H), 5.12 (m, 1H, NC*H*), 4.51 (m, 1H, COOC*H*), 4.32 (m, 2H, OCH_2CH_2) 3.05 (d, 2H, J = 6.0 Hz, NHCHCH_2), 2.07 (m, 2H, COOCHCH_2), 1.30–1.41 (m, 12H, 4 × CH_3); MS (ESI) m/z = 562 $[M+1]^+$; Anal. Calcd for $C_{26}H_{31}N_3O_9S$: C, 55.60; H, 5.56; N, 7.48. Found: C, 55.87; H, 5.70; N, 7.23.

4.1.2.2. 4-(3-(2-(*tert*-Butoxycarbonylamino) acetoxy) butoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9b). Compound **9b** was synthesized from **8a** (350 mg, 2.00 mmol) and **6a** (628 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 72%, white solid 678 mg, mp 195–197 °C [lit.[26] 196 °C]. MS (ESI) m/z = 472 $[M+1]^+$.

4.1.2.3. 4-(4-(2-(*tert*-Butoxycarbonylamino) acetoxy) butoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9c). Compound **9c** was synthesized from **8a** (350 mg, 2.00 mmol) and **6b** (628 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 74%, white solid 697 mg, mp 60–62 °C. Analytical data for **9c**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, 2H, J = 7.5 Hz, Ar-H), 7.77 (m, 1H, Ar-H), 7.61 (m, 2H, Ar-H), 5.06 (br s, 1H, –NH–), 4.44 (t, 2H, J = 6.0 Hz, COOCH_2), 4.23 (t, 2H, J = 6.0 Hz, CH_2OC═N), 3.92–3.94 (s, 2H, NCH_2), 1.95–1.99 (m, 2H, $COOCH_2CH_2CH_2$), 1.85–1.87 (m, 2H, $COOCH_2CH_2$), 1.45 (s, 9H, 3 × CH_3); MS (ESI) m/z = 472 $[M+1]^+$; Anal. Calcd for $C_{19}H_{25}N_3O_9S$: C, 48.40; H, 5.34; N, 8.91. Found: C, 48.22; H, 5.39; N, 8.78.

4.1.2.4. 4-(4-(2-(*tert*-Butoxycarbonylamino) acetoxy) but-2-ynyloxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9d). Compound **9d** was synthesized from **8a** (350 mg, 2.00 mmol) and **6d** (620 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 66%, white solid 812 mg, mp 88–90 °C. Analytical data for **9d**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.03 (d, 2H, J = 7.5 Hz, Ar-H), 7.88 (m, 1H, Ar-H), 7.73 (m, 2H, Ar-H), 7.28 (br s, 1H, –NH–), 5.22 (s, 2H, $COOCH_2$), 4.88 (s, 2H, OCH_2), 3.70–3.75 (m, 2H, NCH_2), 1.38 (m, 9H, 3 × CH_3); MS (ESI) m/z = 468 $[M+1]^+$; Anal. Calcd for $C_{19}H_{21}N_3O_9S$: C, 48.82; H, 4.53; N, 8.99. Found: C, 48.58; H, 4.64; N, 8.81.

4.1.2.5. 4-(3-((*S*)-2-(*tert*-Butoxycarbonylamino) propanoyloxy) butoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9e). Compound **9e** was synthesized from **8b** (378 mg, 2.00 mmol) and **6a** (628 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 71%, white solid 689 mg, mp 110–112 °C [lit.[25] 110 °C]. MS (ESI) m/z = 486 $[M+1]^+$.

4.1.2.6. (*S*)-3-(Phenylsulfonyl)-4-(2,2,6-trimethyl-4,7-dioxo-3,8,11-trioxa-5-azatridecan-13-yloxy)-1,2,5-oxadiazole-2-oxide (9f). Compound **9f** was synthesized from **8b** (378 mg, 2.00 mmol) and **6c** (660 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 74%, white solid 741 mg, mp 127–129 °C [lit.[26] 128 °C]. MS (ESI) m/z = 502 $[M+1]^+$.

4.1.2.7. (*S*)-4-(4-(1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carbonyloxy)butoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9g). Compound **9g** was synthesized from **8d** (430 mg, 2.00 mmol) and **6b** (628 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 67%, colorless viscous liquid 685 mg, Analytical data for **9g**: $[\alpha]_D^{26}$ −12.7; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, 2H, J = 7.5 Hz, Ar-H), 7.74 (m, 1H, Ar-H), 7.61 (m, 2H, Ar-H), 4.45 (m, 1H, NC*H*), 4.22 (m, 4H, 2 × OCH_2), 3.48 (m, 2H, NCH_2), 1.94–1.99 (m, 6H, $NCHCH_2$, $OCH_2CH_2CH_2CH_2OOC$), 1.68 (m, 2H, NCH_2CH_2), 1.45–1.51 (m, 9H, 3 × CH_3); MS (ESI) m/z = 512 $[M+1]^+$; Anal. Calcd for $C_{22}H_{29}N_3O_9S$: C, 51.65; H, 5.71; N, 8.21. Found: C, 51.26; H, 5.68; N, 7.86.

4.1.2.8. (*S*)-4-(4-(2-(*tert*-Butoxycarbonylamino) propanoyloxy) butoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9h). Compound **9h** was synthesized from **8b** (378 mg, 2.00 mmol) and **6b** (628 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 72%, white solid 698 mg, mp 124–126 °C [lit.[26] 124 °C]. MS (ESI) m/z = 486 $[M+1]^+$.

4.1.2.9. (*S*)-4-(4-(2-(*tert*-Butoxycarbonylamino)-3-phenylpropanoyloxy)but-2-ynyloxy)-3-(phenyl sulfonyl)-1,2,5-oxadiazole-2-oxide (9i). Compound **9i** was synthesized from **8c** (530 mg, 2.00 mmol) and **6d** (620 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 68%, colorless viscous liquid 758 mg. Analytical data for **9i**: $[\alpha]_D^{25}$ −6.6; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, 2H, J = 8.4 Hz, Ar-H), 7.76 (m, 1H, Ar-H), 7.62 (m, 2H, Ar-H), 7.31 (m, 3H, Ar-H), 7.14 (d, 2H, J = 7.2 Hz, Ar-H), 5.11 (s, 2H, $COOCH_2$), 4.61–4.95 (m, 3H, CH_2OC═N, NC*H*), 3.11 (m, 2H, $NHCH_2$), 2.07 (m, 2H, $COOCHCH_2$), 1.41 (m, 9H, 3 × CH_3); MS (ESI) m/z = 558 $[M+1]^+$; Anal. Calcd for $C_{26}H_{27}N_3O_9S$: C, 56.01; H, 4.88; N, 7.54. Found: C, 56.22; H, 5.02; N, 7.31.

4.1.2.10. (*S*)-4-(4-(2-(*tert*-Butoxycarbonylamino)-3-phenylpropanoyloxy)butoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9j). Compound **9j** was synthesized from **8c** (530 mg, 2.00 mmol) and **6b** (628 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 65%, white solid 729 mg, mp 130–132 °C [lit.[26] 130 °C]. MS (ESI) m/z = 562 $[M+1]^+$.

4.1.2.11. (*S*)-4-(4-(2-(*tert*-Butoxycarbonylamino) propanoyloxy) but-2-ynyloxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9k). Compound **9k** was synthesized from **8b** (378 mg, 2.00 mmol) and **6d** (620 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 61%, white solid 587 mg, mp 135–137 °C [lit.[26] 135 °C]. MS (ESI) m/z = 482 $[M+1]^+$.

4.1.2.12. (*S*)-4-(6-Benzyl-2,2-dimethyl-4,7-dioxo-3,8,11-trioxa-5-azatridecan-13-yloxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9l). Compound **9l** was synthesized from **8c** (530 mg, 2.00 mmol) and **6c** (660 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 67%, white solid 773 mg, mp 107–109 °C [lit.[26] 108 °C]. MS (ESI) m/z = 578 $[M+1]^+$.

4.1.2.13. 4-(3-((*S*)-1-(*tert*-Butoxycarbonyl) pyrrolidine-2-carbonyloxy)butoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9m). Compound **9m** was synthesized from **8d** (430 mg, 2.00 mmol) and **6a** (628 mg, 2.00 mmol) according to the synthetic procedure of **9a** in

yield 65%, colorless viscous liquid 664 mg. Analytical data for **9m**: $[\alpha]_D^{25}$ −20.4; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, 2H, J = 7.5 Hz, Ar-H), 7.75 (m, 1H, Ar-H), 7.62 (m, 2H, Ar-H), 4.46 (m, 2H, OC*H*, NC*H*), 4.23 (m, 2H, OCH_2), 3.46 (m, 2H, NCH_2), 1.86–1.91 (m, 4H, OCH_2CH_2, $NCHCH_2$), 1.50 (m, 2H, NCH_2CH_2), 1.25–1.45 (m, 12H, 4 × CH_3); MS (ESI) m/z = 512 $[M+1]^+$; Anal. Calcd for $C_{22}H_{29}N_3O_9S$: C, 51.65; H, 5.71; N, 8.21. Found: C, 51.26; H, 6.18; N, 8.03.

4.1.2.14. (*S*)-4-(4-(1-(*tert*-Butoxycarbonyl) pyrrolidine-2-carbonyloxy)but-2-ynyloxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9n). Compound **9n** was synthesized from **8d** (430 mg, 2.00 mmol) and **6d** (620 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 57%, colorless viscous liquid 578 mg. Analytical data for **9n**: $[\alpha]_D^{24}$ −18.9; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, 2H, J = 7.5 Hz, Ar-H), 7.75 (m, 1H, Ar-H), 7.62 (m, 2H, Ar-H), 5.09 (s, 2H, $COOCH_2$), 4.78 (s, 2H, OCH_2), 4.46 (m, 1H, NC*H*), 3.49 (m, 2H, NCH_2), 1.98–2.00 (m, 2H, $NCHCH_2$), 1.46 (m, 2H, NCH_2CH_2), 1.25–1.30 (m, 9H, 3 × CH_3); MS (ESI) m/z = 508 $[M+1]^+$; Anal. Calcd for $C_{22}H_{25}N_3O_9S$: C, 52.06; H, 4.97; N, 8.28. Found: C, 51.83; H, 5.10; N, 8.12.

4.1.2.15. (*S*)-4-(2-(2-(1-(*tert*-Butoxycarbonyl) pyrrolidine-2-carbonyloxy)ethoxy)ethoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9o). Compound **9o** was synthesized from **8d** (430 mg, 2.00 mmol) and **6c** (660 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 61%, colorless viscous liquid 643 mg. Analytical data for **9i**: $[\alpha]_D^{25}$ −15.0; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, 2H, J = 8.1 Hz, Ar-H), 7.66 (m, 2H, Ar-H), 7.56 (m, 1H, Ar-H), 4.56 (t, 2H, J = 4.5 Hz, $COOCH_2$), 4.25 (m, 1H, NCH), 4.19 (t, 2H, J = 4.5 Hz, CH_2OC=N), 3.91 (t, 2H, J = 4.5 Hz, $COOCH_2CH_2O$), 3.79 (t, 2H, J = 4.5 Hz, OCH_2CH_2OC=N), 3.50 (m, 2H, NCH_2), 1.96 (m, 2H, $NCHCH_2$), 1.71 (m, 2H, NCH_2CH_2), 139–1.45 (m, 9H, 3 × CH_3); MS (ESI) m/z = 528 $[M+1]^+$; Anal. Calcd for $C_{22}H_{29}N_3O_{10}S{\cdot}CH_3COCH_3$: C, 51.27; H, 6.02; N, 7.18. Found: C, 51.34; H, 5.98; N, 6.61.

4.1.2.16. 4-(2,2-Dimethyl-4,7-dioxo-3,8,11-trioxa-5-azatridecan-13-yloxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (9p). Compound **9p** was synthesized from **8a** (350 mg, 2.00 mmol) and **6c** (660 mg, 2.00 mmol) according to the synthetic procedure of **9a** in yield 72%, white solid 701 mg, mp 89–91 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.03 (d, 2H, J = 7.5 Hz, Ar-H), 7.88 (m, 1H, Ar-H), 7.72 (m, 2H, Ar-H), 7.19 (br s, 1H, –NH–), 4.50 (t, 2H, J = 6.0 Hz, CH_2OC=N), 4.18–4.21 (t, 2H, J = 6.0 Hz, $COOCH_2$), 3.79 (m, 2H, OCH_2CH_2OC=N), 3.63–3.71 (m, 4H, $COOCH_2CH_2$, NCH_2), 1.37 (m, 9H, 3 × CH_3); MS (ESI) m/z = 488 $[M+1]^+$; Anal. Calcd for $C_{19}H_{25}N_3O_{10}S$: C, 46.81; H, 5.17; N, 8.62. Found: C, 46.55; H, 5.24; N, 8.76.

4.1.3. Synthesis of furoxan/FTA hybrids (11)

4.1.3.1. 4-(3-((*S*)-3-Phenyl-2-(2-((2*E*,6*E*)-3,7,11-trimethyldod eca-2,6,10-trienylthio)benzamido) propanoyloxy)butoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (11a). A solution of **9a** (449 mg, 0.80 mmol) and CF_3COOH (1 mL) in dry CH_2Cl_2 (4 mL) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The crude residue was dissolved in 15 mL dichloromethane and 2 mL Et_3N was slowly added to the solvent, and stirred at room temperature for 30 min. The salts were removed by filtration over a pad of Celite. The filtrate was mixed with **1** (286 mg, 0.80 mmol), EDCI (153 mg, 0.8 mmol), DMAP (97 mg, 0.80 mmol). The mixture was stirred at room temperature for 24 h. After filtration, the filtrate was evaporated to dryness in vacuo, and the crude product was purified by column chromatography (PE/EtOAc = 6:1–3:1) to yield **11a** as a white waxy solid (333 mg, 52%). Analytical data for **11a**: $[\alpha]_D^{26}$ −8.6; IR (KBr, cm^{-1}): 3397, 2928, 1736, 1641, 1614, 1553, 1450, 1361, 1169; ^{1}H NMR ($CDCl_3$-d_6): δ 8.04 (d, 2H, J = 7.5 Hz, Ar-H), 7.86 (m, 1H, Ar-H), 7.52–7.67 (m, 5H, Ar-H), 7.20–7.37 (m, 6H, Ar-H), 5.18 (t, 1H, J = 8.1 Hz, SCH_2CH), 5.08 (m, 3H, 2 × CH_2CH=CCH_3, NC*H*), 4.00 (m, 1H, OC*H*), 3.42 (t, 2H, J = 9.0 Hz, $COOCH_2CH_2$), 3.24 (m, 4H, SCH_2, CH_2Ph), 1.97–2.07 (m, 10H, 2 × $CHCH_2CH_2CH$, $OCHCH_2$), 1.47–1.67 (m, 15H, 4 × CH=CCH_3, $CHCH_3$); MS (ESI) m/z = 802 $[M+1]^+$; Anal. Calcd for $C_{43}H_{51}N_3O_8S_2$: C, 64.40; H, 6.41; N, 5.24. Found: C, 63.90; H, 6.36; N, 5.07.

4.1.3.2. 3-(Phenylsulfonyl)-4-(3-(2-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzamido) acetoxy) butoxy)-1,2,5-oxadiazole-2-oxide (11b). Compound **11b** was synthesized from **9b** (377 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 51%, a white foam 290 mg. Analytical data for **11b**: IR (KBr, cm^{-1}): 3424, 2927, 1753, 1629, 1552, 1450, 1371, 1168; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, 2H, J = 8.1 Hz, Ar-H), 7.70 (m, 1H, Ar-H), 7.58 (m, 2H, Ar-H), 7.40 (m, 2H, Ar-H), 7.29 (m, 2H, Ar-H), 5.25 (t, 1H, J = 6.6 Hz, SCH_2CH), 5.06 (t, 2H, J = 6.6 Hz, 2 × CH_2CH=CCH_3), 4.30 (m, 2H, NCH_2), 4.48 (t, 2H, J = 6.0 Hz, CH_2O), 4.25 (m, 1H, OC*H*), 3.54 (d, 2H, J = 7.5 Hz, SCH_2), 2.20 (m, 2H, $OCHCH_2$), 1.98–2.05 (m, 8H, 2 × $CHCH_2CH_2CH$), 1.51–1.68 (m, 12H, 4 × CH=CCH_3), 1.39 (d, 3H, J = 6.3 Hz, $CHCH_3$); MS (ESI) m/z = 712 $[M+1]^+$; Anal. Calcd for $C_{36}H_{45}N_3O_8S_2$: C, 60.74; H, 6.37; N, 5.90. Found: C, 60.41; H, 6.34; N, 5.76.

4.1.3.3. 4-(Phenylsulfonyl)-3-(4-(2-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzamido) acetoxy)butoxy)-1,2,5-oxadiazole-2-oxide (11c). Compound **11c** was synthesized from **9c** (377 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 55%, a white waxy solid 313 mg. Analytical data for **11c**: IR (KBr, cm^{-1}): 3259, 2928, 1727, 1621, 1559, 1450, 1163; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, 2H, J = 7.2 Hz, Ar-H), 7.73 (m, 2H, Ar-H), 7.58 (m, 2H, Ar-H), 7.36 (m, 2H, Ar-H), 7.27 (m, 1H, Ar-H), 5.24 (t, 1H, J = 7.5 Hz, SCH_2CH), 5.06 (t, 2H, J = 6.9 Hz, 2 × CH_2CH=CCH_3), 4.45 (t, 2H, J = 6.0 Hz, $COOCH_2CH_2CH_2CH_2O$), 4.28 (m, 4H, NCH_2, $COOCH_2CH_2$), 3.55 (d, 2H, J = 7.5 Hz, SCH_2), 1.99 (m, 10H, 2 × $CHCH_2CH_2CH$, $COOCH_2CH_2CH_2$), 1.51–1.69 (m, 14H, 4 × CH=CCH_3, $COOCH_2CH_2$); MS (ESI) m/z = 712 $[M+1]^+$; Anal. Calcd for $C_{36}H_{45}N_3O_8S_2$: C, 60.74; H, 6.37; N, 5.90. Found: C, 60.50; H, 6.52; N, 5.92.

4.1.3.4. 3-(Phenylsulfonyl)-4-(4-(2-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzamido) acetoxy) but-2-ynyloxy)-1,2,5-oxadiazole-2-oxide (11d). Compound **11d** was synthesized from **9d** (374 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 47%, colorless viscous liquid 266 mg. Analytical data for **11d**: IR (KBr, cm^{-1}): 3418, 2928, 1758, 1617, 1548, 1451, 1361, 1169; ^{1}H NMR ($CDCl_3$-d_6): δ 8.06 (d, 2H, J = 7.5 Hz, Ar-H), 7.74 (m, 2H, Ar-H), 7.61 (t, 2H, J = 7.5 Hz, Ar-H), 7.30 (m, 3H, Ar-H), 5.24 (m, H, SCH_2CH), 5.06 (m, 4H, 2 × CH_2CH_2CH=CCH_3, CH_2O), 4.86 (s, 2H, $COOCH_2$), 4.31 (d, 2H, J = 5.4 Hz, NCH_2), 3.55 (d, H, J = 7.8 Hz, SCH_2), 1.98–2.12 (m, 8H, 2 × $CHCH_2CH_2CH$), 1.42–1.67 (m, 12H, 4 × CH_3); MS (ESI) m/z = 708 $[M+1]^+$; Anal. Calcd for $C_{36}H_{41}N_3O_8S_2$: C, 61.08; H, 5.84; N, 5.94. Found: C, 60.76; H, 5.81; N, 5.87.

4.1.3.5. 3-(Phenylsulfonyl)-4-(3-((*S*)-2-(2-((2*E*,6*E*)-3,7,11-trimeth yldodeca-2,6,10-trienylthio)benzamido) propanoyloxy)butoxy)-1,2,5-oxadiazole-2-oxide (11e). Compound **11e** was synthesized from **9e** (388 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 58%, a white foam 336 mg. Analytical data for **11e**: $[\alpha]_D^{25}$ −8.1; IR (KBr, cm^{-1}): 3297, 2924, 1737, 1633, 1555, 1450, 1356, 1168; ^{1}H NMR ($CDCl_3$-d_6): δ 8.06 (d, 2H, J = 7.8 Hz, Ar-H), 7.71 (m, 2H, Ar-H), 7.59 (m, 2H, Ar-H), 7.51 (m, 1H, Ar-H), 7.38 (m, 2H, Ar-H), 5.18 (m, 2H, SCH_2CH, NC*H*), 5.08 (m, 2H, 2 × CH_2CH=CCH_3), 4.74

(m, 1H, OC*H*), 4.46 (t, 2H, *J* = 6.0 Hz, OCH_2CH$_2$), 3.54 (d, 2H, *J* = 7.5 Hz, SCH_2), 2.17 (m, 2H, OCH$_2$CH_2), 1.98 (m, 8H, 2 × CHCH_2CH_2CH), 1.59–1.67 (m, 12H, 4 × CH=CCH_3), 1.51 (d, 2H, *J* = 7.2 Hz, NCHCH_3), 1.38 (d, 2H, *J* = 6.0 Hz, OCHCH_3); MS (ESI) *m/z* = 726 [M+1]$^+$; Anal. Calcd for $C_{37}H_{47}N_3O_8S_2{\cdot}H_2O$: C, 59.74; H, 6.64; N, 5.65. Found: C, 59.65; H, 6.68; N, 5.23.

4.1.3.6. 3-(Phenylsulfonyl)-4-(2-(2-((*S*)-2-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzamido) propanoyloxy)ethoxy)ethoxy)-1,2,5-oxadiazole-2-oxide (11f). Compound **11f** was synthesized from **9f** (401 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 51%, a white foam 302 mg. Analytical data for **11f**: $[\alpha]_D^{15}$ −19.2; IR (KBr, cm^{-1}): 3421, 2928, 1739, 1640, 1614, 1554, 1452, 1356, 1168; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.04 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.70 (m, 2H, Ar-H), 7.59 (m, 3H, Ar-H), 7.34 (m, 2H, Ar-H), 5.27 (t, 1H, *J* = 7.2 Hz, SCH$_2$C*H*), 5.05 (m, 2H, 2 × CH$_2$C*H*=CCH$_3$), 4.84 (m, 1H, NC*H*), 4.54 (m, 2H, COOCH$_2$CH$_2$OCH$_2$CH_2O), 4.38 (m, 2H, COOCH_2CH$_2$), 3.93 (m, 2H, COOCH$_2$CH$_2$OCH_2), 3.83 (t, 2H, *J* = 4.2 Hz, COOCH$_2$CH_2), 3.54 (d, 2H, *J* = 7.8 Hz, SCH_2), 2.01 (m, 8H, 2 × CHCH_2CH_2CH), 1.52–1.67 (m, 12H, 4 × CH=CCH$_3$), 1.38 (d, 3H, *J* = 7.5 Hz, NCHCH_3); MS (ESI) *m/z* = 742 [M+1]$^+$; Anal. Calcd for $C_{37}H_{47}N_3O_9S_2$: C, 59.90; H, 6.39; N, 5.66. Found: C, 59.90; H, 6.52; N, 5.32.

4.1.3.7. 3-(Phenylsulfonyl)-4-(4-((*S*)-1-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzoyl) pyrrolidine-2-carbonyloxy)butoxy)-1,2,5-oxadiazole-2-oxide (11g). Compound **11g** was synthesized from **9g** (409 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 49%, colorless viscous liquid 294 mg. Analytical data for **11g**: $[\alpha]_D^{24}$ −14.5; IR (KBr, cm^{-1}): 3437, 2926, 1743, 1619, 1552, 1449, 1365, 1169; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.04 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.75 (m, 1H, Ar-H), 7.60 (m, 2H, Ar-H), 7.34 (m, 1H, Ar-H), 7.32 (m, 2H, Ar-H), 7.20 (m, 1H, Ar-H), 5.27 (t, 1H, *J* = 7.5 Hz, SCH$_2$C*H*), 5.05 (t, 2H, *J* = 5.1 Hz, 2 × CH2C*H*=CCH$_3$), 4.67 (m, 1H, NC*H*), 4.47 (t, 2H, *J* = 6.0 Hz, COOCH$_2$CH$_2$CH$_2$CH_2O), 4.29 (m, 2H, COOCH_2CH$_2$), 3.57 (d, 2H, *J* = 7.8 Hz, SCH_2), 3.35 (m, 1H, NCH_2), 2.02 (m, 10H, CH_2CHCOO, 2 × CHCH_2CH_2CH), 1.90 (m, 2H, COOCH$_2$CH$_2$CH_2), 1.53–1.67 (m, 16H, 4 × CH=CCH_3, COOCH$_2$CH_2, NCH$_2$CH_2); MS (ESI) *m/z* = 752 [M+1]$^+$; Anal. Calcd for $C_{39}H_{49}N_3O_8S_2$: C, 62.29; H, 6.57; N, 5.59. Found: C, 62.04; H, 6.61; N, 5.44.

4.1.3.8. 4-(Phenylsulfonyl)-3-(4-((*S*)-2-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzamido) propanoyloxy)butoxy)-1,2,5-oxadiazole-2-oxide (11h). Compound **11h** was synthesized from **9h** (388 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 53%, a white foam 307 mg. Analytical data for **11h**: $[\alpha]_D^{24}$ −3.9; IR (KBr, cm^{-1}): 3262, 2927, 1730, 1625, 1555, 1450, 1372, 1167; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.04 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.69 (m, 2H, Ar-H), 7.60 (m, 2H, Ar-H), 7.54 (d, 1H, *J* = 6.6 Hz, Ar-H), 7.41 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.29 (m, 1H, Ar-H), 5.24 (t, 1H, *J* = 7.5 Hz, SCH$_2$C*H*), 5.05 (t, 2H, *J* = 6.9 Hz, 2 × CH$_2$C*H*=CCH$_3$), 4.79 (m, 1H, NC*H*), 4.44 (t, 2H, *J* = 6.0 Hz, COOCH$_2$CH$_2$CH$_2$CH_2O), 4.26 (t, 2H, *J* = 6.0 Hz, COOCH_2CH$_2$), 3.54 (d, 2H, *J* = 7.8 Hz, SCH_2), 1.99 (m, 8H, 2 × CHCH_2CH_2CH), 1.88 (m, 2H, COOCH$_2$CH$_2$CH_2), 1.51–1.69 (m, 17H, 4 × CH=CCH_3, COOCH$_2$CH_2, NCHCH_3); MS (ESI) *m/z* = 726 [M+1]$^+$; Anal. Calcd for $C_{37}H_{47}N_3O_8S_2$: C, 61.22; H, 6.53; N, 5.79. Found: C, 61.02; H, 6.80; N, 5.50.

4.1.3.9. 4-(4-((*S*)-3-Phenyl-2-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzamido) propanoyloxy)but-2-ynyloxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (11i). Compound **11i** was synthesized from **9i** (446 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 50%, a white foam 319 mg. Analytical data for **11i**: $[\alpha]_D^{25}$ −7.6; IR (KBr, cm^{-1}): 3267, 1744, 1649, 1617, 1545, 1450, 1360, 1168; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.06 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.77 (m, 2H, Ar-H), 7.64 (m, 1H, Ar-H), 7.59 (m, 2H, Ar-H), 7.38 (m, 2H, Ar-H), 7.26 (m, 5H, Ar-H), 5.17 (t, 1H, *J* = 6.9 Hz, SCH$_2$C*H*), 5.05 (m, 5H, 2 × CH$_2$C*H*=CCH$_3$, COOCH_2, NC*H*), 4.82 (m, 2H, OCH_2), 3.45 (m, 2H, SCH_2), 3.20–3.37 (m, 2H, CHCH_2), 1.96 (m, 8H, 2 × CHCH_2CH_2CH), 1.47–1.57 (m, 12H, 4 × CH=CCH_3); MS (ESI) *m/z* = 798 [M+1]$^+$; Anal. Calcd for $C_{43}H_{47}N_3O_8S_2$: C, 64.72; H, 5.94; N, 5.27. Found: C, 64.55; H, 5.89; N, 5.20.

4.1.3.10. 3-(4-((*S*)-3-Phenyl-2-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzamido) propanoyloxy)butoxy)-4-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (11j). Compound **11j** was synthesized from **9j** (449 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 55%, a white waxy solid 352 mg. Analytical data for **11j**: $[\alpha]_D^{24}$ −3.8; IR (KBr, cm^{-1}): 3301, 2926, 1731, 1644, 1555, 1448, 1373, 1166; ^{1}H NMR (CDCl$_3$-d_6): δ 8.03 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.74 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.61 (m, 3H, Ar-H), 7.51 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.37 (m, 2H, Ar-H), 7.22–7.33 (m, 5H, Ar-H), 5.19 (t, 1H, *J* = 7.8 Hz, SCH$_2$C*H*), 5.06 (m, 3H, 2 × CH$_2$C*H*=CCH$_3$, NC*H*), 4.39 (t, 2H, *J* = 6.0 Hz, COOCH_2CH$_2$), 4.23 (m, 2H, CH$_2$CH_2O), 3.25 (d, 2H, *J* = 6.0 Hz, SCH$_2$), 1.97–2.01 (m, 8H, 2 × CHCH_2CH_2CH), 1.81 (m, 4H, OCH$_2$CH_2CH$_2$CH_2CH$_2$O), 1.57–1.59 (m, 12H, 4 × CH$_3$); MS (ESI) *m/z* = 802 [M+1]$^+$; Anal. Calcd for $C_{43}H_{51}N_3O_8S_2$: C, 64.40; H, 6.41; N, 5.24. Found: C, 64.30; H, 6.39; N, 5.16.

4.1.3.11. 3-(Phenylsulfonyl)-4-(4-((*S*)-2-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzamido) propanoyloxy)but-2-ynyloxy)-1,2,5-oxadiazole-2-oxide (11k). Compound **11k** was synthesized from **9k** (385 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 49%, colorless viscous liquid 283 mg. Analytical data for **11k**: $[\alpha]_D^{15}$ −15.8; IR (KBr, cm^{-1}): 3421, 2926, 1749, 1622, 1548, 1451, 1362, 1169; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.06 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.72 (m, 2H, Ar-H), 7.61 (m, 3H, Ar-H, N*H*), 7.44 (m, 1H, Ar-H), 7.33 (m, 1H, Ar-H), 7.29 (m, 1H, Ar-H), 5.24 (t, 1H, *J* = 7.5 Hz, SCH$_2$C*H*), 5.05–5.13 (m, 4H, 2 × CH$_2$C*H*=CCH$_3$, COOCH_2), 4.90 (m, 3H, NC*H*, CH_2O), 3.54 (d, 2H, *J* = 7.8 Hz, SCH_2), 1.98 (m, 8H, 2 × CHCH_2CH_2CH), 1.50–1.69 (m, 15H, 4 × CH=CCH_3, NCHCH_3); MS (ESI) *m/z* = 722 [M+1]$^+$; Anal. Calcd for $C_{37}H_{43}N_3O_8S_2$: C, 61.56; H, 6.00; N, 5.82. Found: C, 61.42; H, 6.19; N, 5.73.

4.1.3.12. 4-(2-(2-((*S*)-3-Phenyl-2-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzamido) propanoyloxy)ethoxy)ethoxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide (11l). Compound **11l** was synthesized from **9l** (462 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 52%, a white waxy solid 340 mg. Analytical data for **11l**: $[\alpha]_D^{26}$ −2.5; IR (KBr, cm^{-1}): 3286, 2923, 1737, 1642, 1612, 1552, 1453, 1355, 1157; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.03 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.71 (m, 2H, Ar-H), 7.57 (m, 3H, Ar-H), 7.48 (m, 1H, Ar-H), 7.26–7.41 (m, 6H, Ar-H), 5.16–5.22 (m, 3H, 3 × CH$_2$C*H*=CCH$_3$), 4.52 (t, 2H, *J* = 4.5 Hz, COOCH_2), 4.27 (m, 3H, NC*H*, OCH_2), 3.89–3.96 (m, 4H, OCH$_2$CH_2OCH_2), 3.21–3.36 (m, 4H, SCH_2, CHCH_2), 2.01 (m, 8H, 2 × CHCH_2CH_2CH), 1.47–1.67 (m, 12H, 4 × CH=CCH$_3$); MS (ESI) *m/z* = 818 [M+1]$^+$; Anal. Calcd for $C_{43}H_{51}N_3O_9S_2$: C, 63.14; H, 6.28; N, 5.14. Found: C, 62.88; H, 6.35; N, 5.18.

4.1.3.13. 3-(Phenylsulfonyl)-4-(3-((*S*)-1-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzoyl) pyrrolidine-2-carbonyloxy)butoxy)-1,2,5-oxadiazole-2-oxide (11m). Compound **11m** was synthesized from **9m** (409 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield

51%, colorless viscous liquid 306 mg. Analytical data for **11m**: $[\alpha]_D^{25}$ −18.6; IR (KBr, cm^{-1}): 3326, 2927, 1743, 1626, 1552, 1449, 1368, 1169; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.07 (d, 2H, J = 7.5 Hz, Ar-H), 7.71 (m, 1H, Ar-H), 7.61 (m, 2H, Ar-H), 7.34 (m, 2H, Ar-H), 7.22 (m, 2H, Ar-H), 5.22 (t, 1H, J = 6.3 Hz, SCH_2CH), 5.08 (t, 2H, J = 5.1 Hz, 2 × CH_2CH=CCH_3), 4.67 (m, 1H, NC*H*), 4.65–4.50 (m, 2H, NC*H*, OC*H*), 3.80 (m, 2H, OCH_2), 3.52 (d, 2H, J = 7.2 Hz, SCH_2), 3.30 (m, 2H, NCH_2), 2.29 (m, 2H, $OCHCH_2$), 1.98 (m, 8H, 2 × $CHCH_2CH_2CH$), 1.52–1.67 (m, 16H, $NCHCH_2$, 4 × CH=CCH_3, NCH_2CH_2), 1.24 (d, 3H, J = 6.3 Hz, $CHCH_3$); MS (ESI) m/z = 752 $[M+1]^+$; Anal. Calcd for $C_{39}H_{49}N_3O_8S_2{\cdot}H_2O$: C, 60.84; H, 6.68; N, 5.46. Found: C, 60.67; H, 6.50; N, 5.68.

4.1.3.14. 3-(Phenylsulfonyl)-4-(4-((*S*)-1-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzoyl) pyrrolidine-2-carbonyloxy)but-2-ynyloxy)-1,2,5-oxadiazole-2-oxide (11n). Compound **11n** was synthesized from **9n** (406 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 46%, colorless viscous liquid 275 mg. Analytical data for **11n**: $[\alpha]_D^{25}$ −30.3; IR (KBr, cm^{-1}): 3439, 2926, 1752, 1618, 1548, 1450, 1362, 1169; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.07 (d, 2H, J = 7.2 Hz, Ar-H), 7.74 (m, 1H, Ar-H), 7.61 (m, 2H, Ar-H), 7.37 (m, 2H, Ar-H), 7.28 (m, 2H, Ar-H), 5.24 (t, 1H, J = 7.5 Hz, SCH_2CH), 5.08 (m, 4H, 2 × CH_2CH=CCH_3, $COOCH_2$), 4.82 (m, 2H, CH_2O), 4.71 (t, 1H, J = 3.9 Hz, NC*H*), 3.57 (d, 2H, J = 7.5 Hz, SCH_2), 3.30 (m, 2H, NCH_2), 2.29 (m, 2H, $OCHCH_2$), 1.98 (m, 10H, 2 × $CHCH_2CH_2CH$, $NCHCH_2$), 1.58–1.75 (m, 14H, 4 × CH=CCH_3, NCH_2CH_2); MS (ESI) m/z = 748 $[M+1]^+$; Anal. Calcd for $C_{39}H_{45}N_3O_8S_2$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.45; H, 6.15; N, 5.57.

4.1.3.15. 3-(Phenylsulfonyl)-4-(2-(2-((*S*)-1-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzoyl) pyrrolidine-2-carbonyloxy)ethoxy)ethoxy)-1,2,5-oxadiazole-2-oxide (11o). Compound **11o** was synthesized from **9o** (422 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 48%, colorless viscous liquid 295 mg. Analytical data for **11o**: $[\alpha]_D^{25}$ −19.1; IR (KBr, cm^{-1}): 3434, 2917, 1744, 1628, 1552, 1448, 1360, 1170; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, 2H, J = 8.1 Hz, Ar-H), 7.73 (m, 2H, Ar-H), 7.61 (m, 2H, Ar-H), 7.23–7.39 (m, 3H, Ar-H), 5.27 (t, 1H, J = 6.3 Hz, SCH_2CH), 5.08 (t, 2H, J = 5.1 Hz, 2 × CH_2CH=CCH_3), 4.57 (t, 2H, J = 4.5 Hz, $COOCH_2$), 4.39 (t, 3H, J = 4.5 Hz, CH_2OCN), 4.11 (m, 1H, NC*H*), 3.93 (t, 2H, J = 4.5 Hz, $COOCH_2CH_2O$), 3.83 (t, 2H, J = 4.5 Hz, $COOCH_2OCH_2$), 3.55 (d, 2H, J = 7.5 Hz, SCH_2), 3.33 (m, 2H, NCH_2), 1.96–2.04 (m, 10H, $NCHCH_2$, 2 × $CHCH_2CH_2CH$), 1.52–1.67 (m, 14H, 4 × CH_3, NCH_2CH_2); MS (ESI) m/z = 768 $[M+1]^+$; Anal. Calcd for $C_{39}H_{49}N_3O_9S_2$: C, 61.00; H, 6.43; N, 5.47. Found: C, 60.63; H, 6.47; N, 5.42.

4.1.3.16. 3-(Phenylsulfonyl)-4-(2-(2-(2-(2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienylthio)benzamido) acetoxy)ethoxy)ethoxy)-1,2,5-oxadiazole-2-oxide (11p). Compound **11p** was synthesized from **9p** (390 mg, 0.80 mmol) and **1** (286 mg, 0.80 mmol) according to the synthetic procedure of **11a** in yield 53%, a white waxy solid 308 mg. Analytical data for **11p**: IR (KBr, cm^{-1}): 3422, 2927, 1749, 1628, 1553, 1449, 1362, 1168; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, 2H, J = 8.1 Hz, Ar-H), 7.73 (m, 2H, Ar-H), 7.62 (m, 2H, Ar-H), 7.39–7.42 (m, 4H, Ar-H), 5.27 (t, 1H, J = 6.3 Hz, SCH_2CH), 5.08 (t, 2H, J = 5.4 Hz, 2 × CH_2CH=CCH_3), 4.56 (t, 2H, J = 4.5 Hz, $COOCH_2$), 4.40 (t, 3H, J = 4.5 Hz, CH_2OCN), 4.31 (m, 2H, NCH_2), 3.93 (t, 2H, J = 4.5 Hz, $COOCH_2CH_2O$), 3.84 (t, 2H, J = 4.5 Hz, $COOCH_2OCH_2$), 3.54 (d, 2H, J = 7.5 Hz, SCH_2), 2.01 (m, 8H, 2 × $CHCH_2CH_2CH$), 1.47–1.67 (m, 12H, 4 × CH_3); MS (ESI) m/z = 728 $[M+1]^+$; Anal. Calcd for $C_{37}H_{47}N_3O_9S_2$: C, 59.40; H, 6.23; N, 5.77. Found: C, 59.22; H, 6.32; N, 5.59.

4.2. Biology

4.2.1. Cytotoxicity assay

The cytotoxic activity of individual compounds in vitro against several cancer cell lines was measured by MTT assay. Human breast carcinoma (MDA-MB-231, MCF-7), gastric carcinoma (SGC-7901), lung carcinoma (A-549) cells at 5–10 × 10^3 cells/well were cultured in RPMI-1640 medium (Hyclone, USA) overnight and treated in triplicate with different concentrations of individual compounds for 48 h. During the last 4 h culture, the cells were exposed to MTT (1 mg/mL) and the resulting formazan crystals were dissolved in 200 μL DMSO and measured at 570 nm with reference wavelength at 595 nm on a microplate reader (Thermo, USA). The unmanipulated cells were used as negative controls while the cells treated with 1% Triton were used as positive controls. The inhibition rate of individual compounds was calculated by (the OD value of negative-experiments/the OD values of negative controls) × 100%. The concentration required for 50% inhibition (IC_{50}) was calculated using the software of cell viability.

4.2.2. Nitrate/nitrite measurement in vitro

The levels of nitrate/nitrite formed from individual compounds in the cells were determined by the colorimetric assay using the nitrate/nitrite colorimetric assay kit (Beyotime, China), according to the manufacturer's instructions. Briefly, MDA-MB-231 cells (5 × 10^6/well) were treated in triplicate with 100 μM of one of the compounds (**11a**, **11d**, **11f**, **11n–p**, FTA) for 24 h. The cells were harvested lyzed. The cell lysates were mixed with Griess for 30–300 min, followed by measuring at 540 nm. The cells treated with diluent were used as negative controls for the background levels of nitrate/nitrite production, while with sodium nitrate at different concentrations was used as positive controls for the standard curve.

4.2.3. Western blot

The Ras inhibitor activity of **11f** was determined by Western blot assay. MDA-MB-231 cells at 1.5 × 10^5/mL were treated with 1 or 5 μM **11f** or vehicle control for 8 h. After harvested and lyzed, the cell lysates (50 μg/lane) were separated by SDS–PAGE (12% gel) and transferred onto nitrocellulose membranes. After blocked with 5% fat-free milk, the target proteins were probed with anti-Akt, anti-phospho-Akt (Ser473), anti-ERK, anti-phospho-ERK (Thr202/Tyr204), anti-Phospho-Raf (Ser259), and anti-β-actin antibodies (Cell Signaling, Boston), respectively. The bound antibodies were detected by HRP-conjugated second antibodies and visualized using the enhanced chemiluminescent reagent.

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