Synthesis and Structure−Activity Relationship of α-Sulfonylhydroxamic Acids as Novel, Orally Active Matrix Metalloproteinase Inhibitors for the Treatment of Osteoarthritis

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The matrix metalloproteinases (MMPs) are a family of zinc-containing endopeptidases that play a key role in both physiological and pathological tissue degradation. These enzymes are strictly regulated by endogenous inhibitors such as tissue inhibitors of MMPs and α_2-macroglobulins. Overexpression of these enzymes has been implicated in various pathological disorders such as arthritis, tumor metastasis, cardiovascular diseases, and multiple sclerosis. Developing effective small-molecule inhibitors to modulate MMP activity is one approach to treat these degenerative diseases. The present work focuses on the discovery and SAR of novel *N*-hydroxy-α-phenylsulfonylacetamide derivatives, which are potent, selective, and orally active MMP inhibitors.

Introduction

The matrix metalloproteinases (MMPs) are a large family of calcium-dependent zinc-containing endopeptidases involved in the degradation of extracellular matrix and tissue remodeling. To date, at least 21 mammalian MMPs have been discovered. These include three collagenases (MMP-1, -8, and -13), two gelatinases (MMP-2 and -9), three stromelysins (MMP-3, -10, and -11), five membrane type MMPs (MMP-14 to -17 and MMP-24), and others such as matrilysin (MMP-7) and metalloelastase (MMP-12). These enzymes are strictly controlled by endogenous MMP inhibitors such as α_2-macroglobulins and tissue inhibitors of MMPs (TIMPs). The overexpression of MMPs results in an imbalance between the activity of MMPs and TIMPs and the subsequent degradation of cartilage and loss of joint movement characteristic of pathological conditions such as osteoarthritis and rheumatoid arthritis.[1−4] Presently available drugs in the market alleviate the pain or the inflammation associated with joint synovitis, but they do little to reduce cartilage destruction. In addition to arthritis, tumor metastasis, angiogenesis, pulmonary emphysema, atherosclerosis, and central nervous system (CNS) diseases[5−11] may also be mediataed by the aberrant activity of various MMPs. Therefore, in many of these pathological conditions, selective and orally active small-molecule MMP inhibitors may prove to be clinically efficacious. Another closely related zinc-containing metalloproteinase, tumor necrosis factor-α (TNF-α) converting enzyme[12] (TACE) converts membrane-bound TNF-α to its soluble form, which has been shown to play a major role in the etiology of rheumatoid arthritis. Hence, in the present investigation, compounds synthesized for the MMP inhibitor program were also tested for TACE inhibition. It is the objective of this article to present the synthesis, SAR, and in vivo activity of novel and orally active α-phenylsulfonylacetic acid hydroxamide derivatives **1** (Figure 1) as MMP and TACE inhibitors. In this connection, it should be mentioned that a *β*-sulfonylhydroxamic acid derivative **2** (Figure 1), synthesized by Roche Bio-Science was advanced to phase II clinical trials for osteoarthritis. In addition, several succinic acid and sulfonamide based broad spectrum MMP inhibitors have been investigated in the clinic for cancer (Figure 2).

Chemistry

The compounds of the present investigation, namely, substituted α-phenylsulfonylhydroxamide derivatives, can be conveniently prepared by alkylating the appropriately substituted phenylmercaptan derivatives **3** (Scheme 1) with α-bromoethyl acetate **4** in chloroform and triethylamine at room temperature or in K_2CO_3 in refluxing acetone. The sulfide derivative **5** thus obtained can be oxidized using Oxone in methanol/water or mCPBA in CH_2Cl_2 to give the sulfone derivative **6**, which can be preferentially either monoalkylated using 1 mol of alkyl halide or dialkylated using excess alkyl halide in boiling acetone/K_2CO_3 and 18-crown-6. Next, the bisalkylated compound **8** or the monoalkylated product **7** can be hydrolyzed to the corresponding carboxylic acid **9** using 10 N NaOH in THF/MeOH at room temperature. The saponified product was subsequently converted to the hydroxamic acid derivative **1** using oxalyl chloride/hydroxylamine hydrochloride, and triethylamine. Compounds **56** and **57** were prepared from 4-hydroxythiophenol **10** as shown in Scheme 2.

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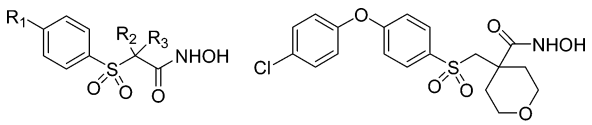


1 **2**

Figure 1.

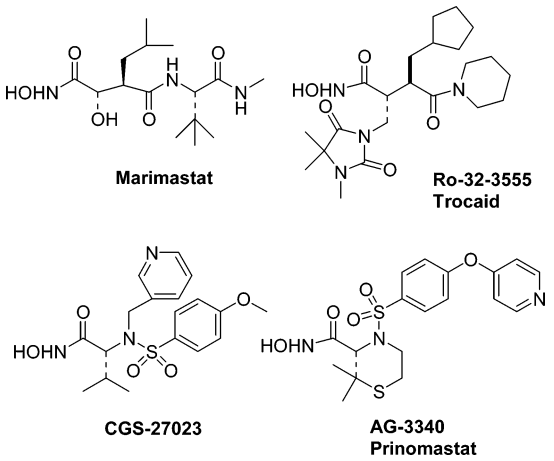


Figure 2.

4-Hydroxythiophenol **10** was reacted with ethyl 2-bromopropionate **11** in chloroform/triethylamine at room temperature to give **12** in almost quantitative yield. This was alkylated on the phenolic oxygen using either bromoethane or 1-bromobutane to yield **13** or **14**, respectively, which were readily converted to sulfone **15** or **16** using Oxone. Reaction of 4-(2-*N*,*N*-diethylaminoethoxy)benzyl chloride **17a** with **15** or 4-(2-piperidin-1-ylethoxy)benzyl chloride **17b** with **16** in boiling acetone/K_2CO_3/18-crown-6 gave **18** and **19**, respectively. The esters **18** and **19** were converted to **56** or **57** via their respective carboxylic acid derivatives as shown in Scheme 2.

Compound **58** was prepared starting from 4-bromothiophenol **22** (Scheme 3). The intermediate **24** on reaction with 2-(tributylstannyl)furan/$(Ph_3P)_4Pd$ yielded **25** in 95% yield. Alkylation of **25** was followed by ester hydrolysis and transformation into the corresponding hydroxamic acid **58** by the sequence depicted in Scheme 3. The other compounds mentioned in this paper (**28**−**65**) were prepared according to Schemes 1−3 starting from the appropriately substituted mercaptan derivatives. The intermediate 4-(2-*N*,*N*-diethylaminoethoxy)benzyl chloride **17a** and other analogues were synthesized by a known literature procedure.[13]

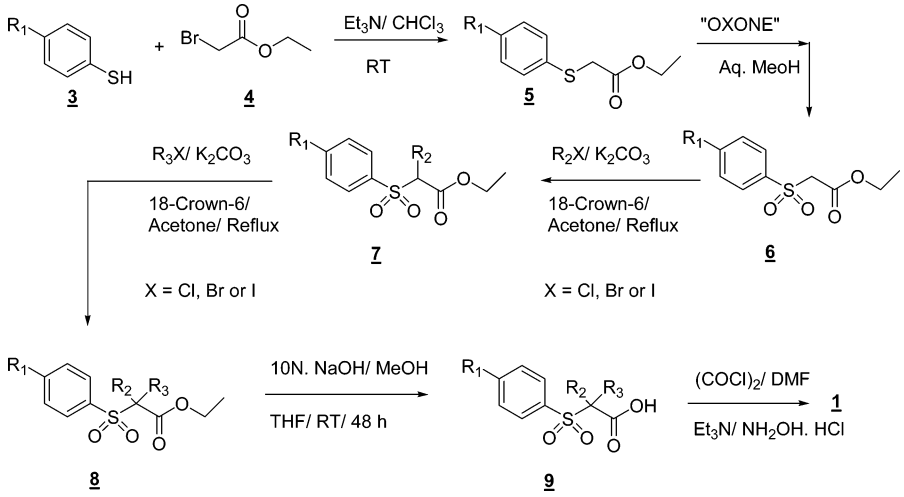
Biology

All final hydroxamic acid derivatives were evaluated in vitro[14] for their ability to inhibit MMP-1, MMP-9, MMP-13, and TACE [15] (Tables 1−3). Inhibitors of MMP-9 are potentially valuable for arresting tumor metastasis,[16] while inhibiting MMP-13 can offer protection from the cartilage degradation associated with osteoarthritis.[17] Inhibitors of TACE are potentially valuable for the treatment of rheumatoid arthritis, Crohn's disease, and other inflammatory diseases.[18] We desired selective compounds that inhibited MMP-9, MMP-13, or TACE and spared MMP-1 in order to examine whether the inhibition of MMP-1 is a possible source of the musculoskeletal side effects that have been seen in clinical trials of broad spectrum MMP inhibitors.[19] In our discovery pathway, the most selective and potent inhibitors of MMP-13 were examined in an in vivo bioactivity model known as the dialysis implant assay.[20] In this model, a solution containing the target enzyme was put inside dialysis tubing, which was implanted subcutaneously in the back of a mouse. Groups of mice were dosed with drug or vehicle, and after 1 h of exposure, the dialysis bag was retrieved from the mouse. The activity of the enzyme inside the dialysis bag was measured by a spectrophotometric assay and compared to the enzyme activity recovered from dialysis bags from vehicle-treated mice. Compounds active in this assay were then put into an in vivo efficacy model known as the rat sponge-wrapped cartilage model.[21] In this model a sponge containing bovine cartilage and mycobacterium is implanted subcutaneously on the back of the animal (in the present case it is rat). This leads to granuloma formation, and cytokines induce MMP production by the chondrocytes in the cartilage. Compounds were given orally for 3 weeks, and at the end, the collagen content of the cartilage was measured.

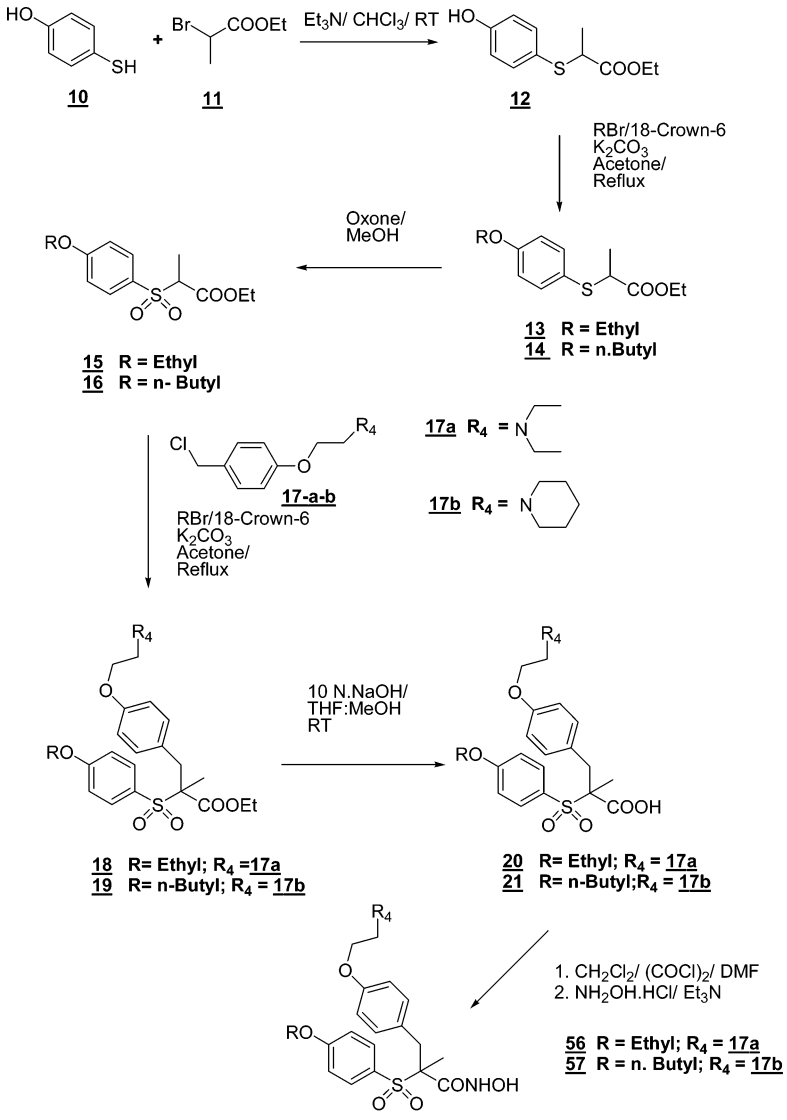
SAR

The IC_{50} values of the compounds synthesized are tabulated in Tables 1−3. An examination of these tables reveals that monosubstitution α to the hydroxamic acid functionality decreases MMP inhibitor activity when compared to the disubstituted compounds. For example, compound **29** (R_3 = benzyl, R_2 = methyl) is almost 10 times more potent against MMP-9 and MMP-13 than compound **28** (R_3 = benzyl, R_2 = H). A similar activity profile is observed with examples **30** and **31**. When both R_2 and R_3 are substituted with isoprenyl **34**, potency against MMP-9 and MMP-13 and selectivity over MMP-1 increase. This compound also exhibits weak TACE activity. However, when the isoprenyl moiety is replaced with an allyl group, as in example **35**, the MMP and TACE potencies decrease. Further deterioration in activity takes place when the double bond in the allyl moiety is changed to the *n*-propyl derivative **37**. Comparison of examples **38** and **39** reveals that among the monosubstituted compounds, a branched substituent such as an isopropyl group α to the hydroxamic acid moiety decreases MMP-9 and MMP-13 potency. Lengthening the α-substituent to 12 carbon atoms further decreases potency (example **41**). A bispropargyl group α to the hydroxamic acid **42** slightly increases the potency of MMP-13 inhibition relative to allyl analogue **35**. Even though many of these analogues were very potent against MMPs, these compounds were inactive in the dialysis implant assay. It has been shown by different workers[17] that introduction of basic water solubilizing groups in the molecule increases the in vivo activity. Hence, we decided to introduce a water solubilizing basic group such as a 3-picolyl group. The in vivo aspects of these molecules will be discussed at the latter portion of this article. Example **43**, where R_2 =

Scheme 1. General Method To Synthesize α-Phenylsulfonylacetic Acid Hydroxamides **1**



Scheme 2. Synthesis of Compounds **56** and **57**



methyl and R_3 = 3-picolyl, showed good in vitro activity and moderate selectivity for MMP-13 over MMP-1 (~10-fold). Replacement of the methyl group in compound **43** with an isoprenyl group (example **44**) increased the potency of MMP-13 inhibition and also increased selectivity over MMP-1. When the methyl group (R_2 = methyl) in example **43** is replaced with other long-chain alkyl substituents (examples **45**−**48**), both the potency

Scheme 3. Synthesis of Compounds **58**

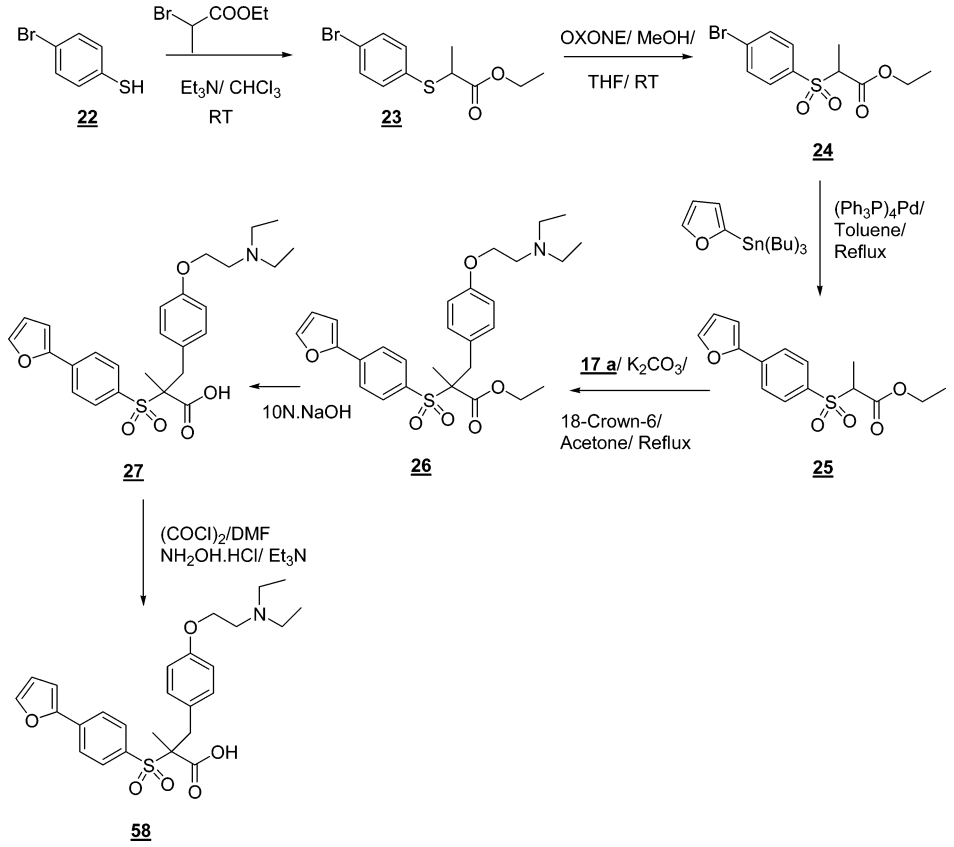
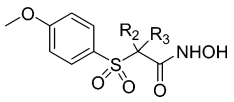


Table 1. In Vitro Data (IC_{50} Values[a] (nM) and % Inhibition)



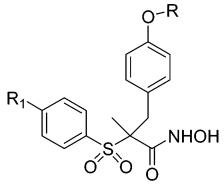
compd	R_2	R_3	MMP-1	MMP-9	MMP-13	TACE
28	benzyl	H	313 ± 4	107 ± 2	100 ± 2	NT
29	benzyl	Me	100 ± 2	11 ± 1	11 ± 1	15%[b]
30	2-CH_2-naphthyl	H	583 ± 14	197 ± 6	14 ± 2	160 ± 5
31	2-CH_2-naphthyl	Me	139 ± 8	8 ± 2	9 ± 2	NT
32	4-CH_2-biphenyl	Me	158 ± 6	23 ± 3	8 ± 2	17%[b]
33	isoprenyl	Me	239 ± 9	11 ± 2	14 ± 2	626 ± 21
34	isoprenyl	isoprenyl	25 ± 2	0.5 ± 0.2	0.4 ± 0.1	805 ± 18
35	allyl	allyl	211 ± 11	35 ± 2	39 ± 3	7%[b]
36	$-CH_2-CH=CH-Ph$	Me	299 ± 13	16 ± 2	12 ± 2	65%[b]
37	*n*-propyl	*n*-propyl	30%[b]	447 ± 16	141 ± 9	24%[b]
38	isopropyl	H	647 ± 21	27%[b]	188 ± 16	52%[b]
39	*n*-butyl	H	8%[b]	128 ± 6	64 ± 4	54%[b]
40	$-CH_2$-cyclohexyl	Me	325 ± 26	9 ± 2	24 ± 3	180 ± 8
41	*n*-$C_{12}H_{25}$	H	18%[b]	2930 ± 22	319 ± 6	942 ± 9
42	propargyl	propargyl	300 ± 10	141 ± 10	12 ± 2	20%[b]
43	3-picolyl	Me	258 ± 9	38 ± 4	22 ± 3	17%[b]
44	3-picolyl	isoprenyl	156 ± 6	9 ± 1	3 ± 1	203 ± 7
45	3-picolyl	$-CH_2-CH(CH_3)$	1000 ± 15	63 ± 4	13 ± 1	42%[b]
46	3-picolyl	$-(CH_2)_2-CH(CH_3)_2$	574 ± 12	120 ± 6	90 ± 4	41%[b]
47	3-picolyl	$-(CH_2)_3-CH_3$	1140 ± 15	88%[b]	127 ± 7	764 ± 8
48	3-picolyl	$-(CH_2)_7-CH_3$	522 ± 8	174 ± 3	43 ± 2	669 ± 18
49	3-picolyl	propargyl	672 ± 15	83 ± 4	32 ± 2	23%[b]
	CGS-27023A		15 ± 2	9 ± 1	8 ± 1	231 ± 6

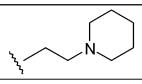
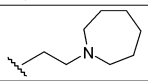
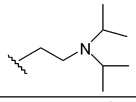
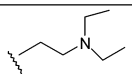
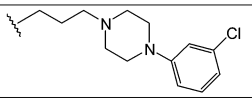
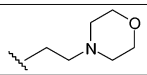
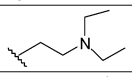
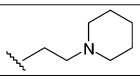
[a] Inhibitor concentrations were run in triplicate. MMP IC_{50} values determinations were calculated from a four-parameter logistic fit of the data within a single experiment. The final values given here are the mean of the triplicate values of the sample. NT = not tested.[b] % inhibition at 10 μM concentration. Dose−response curves were not generated for compounds at <60% incubation at 10 μM concentration. All the compounds listed here are racemic.

against MMP-13 and the selectivity versus MMP-1 decrease. It is therefore clear that the presence of smaller substituents, such as a methyl group in the R_2 position, favor MMP inhibition.

Next we investigated the effect of different R_1 substituents on these molecules because they presumably occupy the S_1' pocket of these enzymes. Selectivity for MMP-13 vs MMP-1 can be tuned by varying the R_1

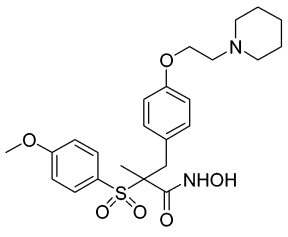
Table 2. In Vitro IC_{50} Values[d] and Dialysis Implant Model Data



Cpd #	R_1	R	MMP-1 (nM)	MMP-9 (nM)	MMP-13 (nM)	TACE % Inhibition[b]	Dialysis Implant Data % Inhibition
50	-OMe		238(+/-)8	9(+/-)1	1(+/-)1	41	78(+/-)2 vs 77[a] (+/-)3 (1)[c]
51	-OMe		540(+/-)14	19(+/-)4	12(+/-)3	29	65(+/-)3 vs 66[a] (+/-)4, (1)[c]
52	-OMe		423(+/-)18	15(+/-)3	19(+/-)4	31	83(+/-)4 vs 85[a] (+/-)3, (1)[c]
53	-OMe		318(+/-)12	13(+/-)3	15(+/-)4	39	68(+/-)2 vs 66[a] (+/-)4, (1)[c]
54	-OMe		593(+/-)23	7(+/-)2	4(+/-)1	40	72(+/-)3 vs 73[a] (+/-)4, (1)[c]
55	-OMe		413(+/-)14	21(+/-)4	31(+/-)4	47	48(+/-)4 vs 67[a] (+/-)3, (0.7)[c]
56	-OEt		627(+/-)23	11(+/-)2	16(+/-)3	NT	74(+/-)3 vs 76[a] (+/-)4, (1)[c]
57	-O-n-Bu		761(+/-)14	3(+/-)1	2(+/-)1	30	64(+/-)3 vs 53[a] (+/-)4, (1.2)[c]

[a] % inhibition for CGS-27023 at 25 mg/kg, po. [b] % inhibition at 10 μM concentration. Dose−response curves were not generated for compounds at <60% incubation at 10 μM concentration. [c] Compounds were dosed at 25 mg/kg, po, and the data were expressed relative to the activity of CGS-27023 (such that CGS-27023 = 1). [d] Inhibitor concentrations were run in triplicate. MMP IC_{50} values determinations were calculated from a four-parameter logistic fit of the data within a single experiment. The final values given here are the mean of the triplicate values of the sample.

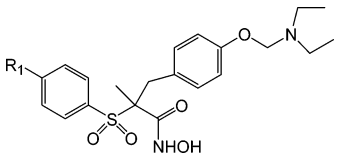
substituent. Examples **50** and **57** (Table 2) reveal that



50

when the R_1 substituent is changed from methoxy to *n*-butoxy, MMP-13 potency is retained while MMP-1 activity is significantly lowered (238 vs 760 nM, respectively). This can be attributed to the fact that in MMP-1 the depth of the S_1' pocket is shallow while MMP-13 is a deep pocket enzyme that can accommodate the longer butoxy substituent.[22] A similar trend is observed for compounds **53** and **56**. However, replacing the ether functionality with an aryl moiety, such as in the 2-furyl analogue **58** (Table 3), leads to an increase in potency but a decrease in selectivity of MMP-13 vs MMP-1. Comparison of **34** vs **60** (Figure 3 and Table 4) reveals that the replacement of a methoxy substituent with methyl decreases inhibitory potency against MMPs and TACE. Replacement of the aromatic sulfonyl moiety with aliphatic sulfonyl (**61**−**63**) or a heteroaromatic

Table 3. In Vitro Activity for Different R_1 Substituents (IC_{50} Values[a])



compd	R_1	MMP-1 (nM)	MMP-9 (nM)	MMP-13 (nM)	TACE % inhibition[b]
53	$-OCH_3$	318 ± 12	13 ± 3	15 ± 4	39
56	−OEt	627 ± 23	11 ± 2	16 ± 3	NT
58	2-furyl	14 ± 2	4 ± 1	2 ± 1	45
59	Br	51 ± 4	58 ± 2	11 ± 2	NT

[a] Inhibitor concentrations were run in triplicate. MMP IC_{50} values determinations were calculated from a four-parameter logistic fit of the data within a single experiment. The final values given here are the mean of the triplicate values of the sample. NT = not tested. [b] 10 μM concentration. Dose−response curves were not generated for compounds at <60% incubation at 10 μM concentration;

group (**64** and **65**) decreases the potency of both MMP inhibition and TACE inhibition activity (Figure 3 and Table 4).

Unfortunately, even though in vitro potency could be increased by changing the R_2 and R_3 substituents, achieving in vivo activity in the dialysis implant model and the sponge-wrapped cartilage model remained

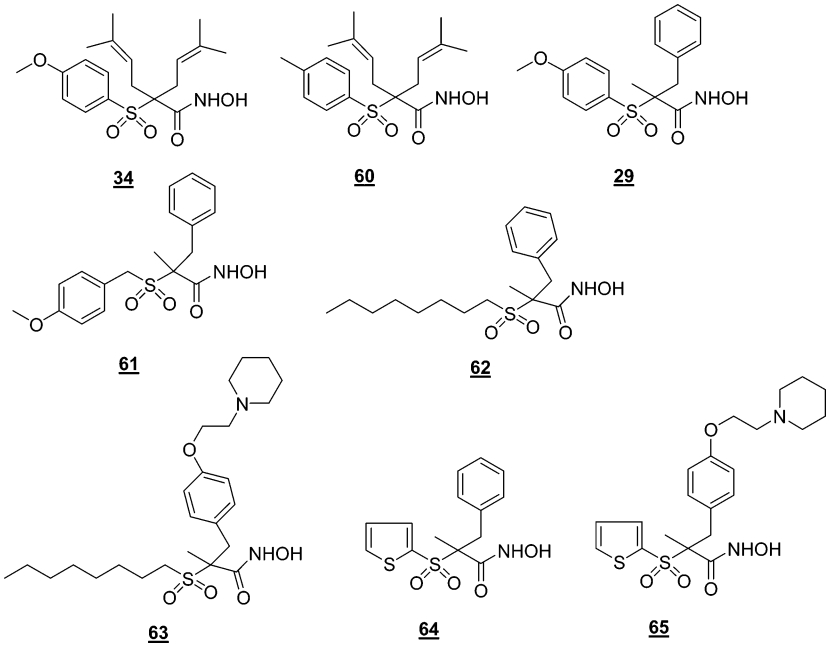


Figure 3.

Table 4. In Vitro Activity IC_{50} Values[a] for Compounds in Figure 3

compd	MMP-1 (nM)	MMP-9 (nM)	MMP-13 (nM)	TACE (nM)
34	25 ± 2	0.5 ± 1	0.4 ± 1	805 ± 18
60	262 ± 6	51 ± 3	6 ± 2	36%[a]
29	100 ± 2	11 ± 1	11 ± 1	15%[a]
61	10%[b]	0%[b]	6%[b]	3%
62	78%[b]	71%[b]	85%[b]	1%[b]
63	10%[b]	23%[b]	55%[b]	NT
64	49%[b]	49%[b]	37%[b]	20%[b]
65	99%[b]	79%[b]	85%[b]	51%[b]

[a] Inhibitor concentrations were run in triplicate. MMP IC_{50} values determinations were calculated from a four-parameter logistic fit of the data within a single experiment. The final values given here are the mean of the triplicate values of the sample. NT = not tested. [b] % inhibition at 10 μM concentration.

challenging. The picolyl compounds (examples **43**−**49**) (Table 1) did not show any significant activity in the dialysis implant model. To increase the basic nature of the nitrogen, examples **50**−**57** were prepared. Their in vitro and in vivo data are tabulated in Table 2. All these compounds (examples **50**−**57**) showed weak activity against TACE and good potency against MMP-13 and MMP-9. In addition, all of the compounds, listed in Table 2, were active in the dilaysis implant model. The in vivo bioactivity of these compounds were measured relative to CGS 27023 (Figure 2). Thus, compound **50** showed 78% enzyme inhibition in the dialysis implant model, given orally at a dose of 25 mg/kg. In the same experiment, CGS 27023 was used as a standard and showed an enzyme inhibition of 77% at 25 mg/kg, po. On the basis of the selectivity and potency, three compounds, examples **50, 51**, and **57** (Table 2), were chosen for the sponge-wrapped cartilage model. In the same experiments, CGS 27023 was used as a comparator. Compounds were dosed orally at 25 mg/kg, qd, for 3 weeks, and the percentage inhibition of bovine cartilage degradation was measured. The results are shown in Table 5, and all three compounds exhibited slightly better activity than CGS 27023.

Table 5. In Vivo Activity[a] of Selected Compounds in the Sponge-Wrapped Cartilage Model

compd	% inhibition @ 25 mg/kg, po
50	69 ± 5 vs 52 ± 4%[b] (1.3)[c]
51	67 ± 4 vs 58 ± 5%[b] (1.2)[c]
57	44 ± 3 vs 58 ± 5%[b] (0.8)[c]

[a] Mean % inhibition values of three experiments. [b] CGS-27023. [c] Compounds were dosed at 25 mg/kg, po, and the data were expressed relative to the activity of CGS-27023 (such that CGS-27023 = 1).

Table 6. In Vitro Activity IC_{50} Values[a] (nM) and Dialysis Implant Data for the Dextro and Levo Isomers of Compound **50**

compd **50** isomer	MMP-1	MMP-9	MMP-13	% inhibition[c]
dextro	154 ± 3	5 ± 1	4 ± 1	69 ± 4 vs 68[b] ± 3 (1)[d]
levo	2530 ± 18	112 ± 6	86 ± 5	15 ± 3 vs 60[b] ± 4 (0.25)[d]

[a] Inhibitor concentrations were run in triplicate. MMP IC_{50} values determinations were calculated from a four-parameter logistic fit of the data within a single experiment. The final values given here are the mean of the triplicate values of the sample. [b] % inhibition of CGIS-27023 [c] Dialysis implant data. [d] Compounds were dosed at 25 mg/kg, po, and the data were expressed relative to the activity of CGS-27023 (such that CGS-27023 = 1).

On the basis of the above-mentioned facts, examples **50** and **57** turned out to be the best candidates. However, compound **57** in the sponge-wrapped cartilage assay proved to be less active than **50**. Compound **50** protected bovine cartilage by 68.8% (25 mg/kg, po, qd). Its oral bioavailability in rats was found to be 81% with a $t_{1/2}$ of 1.5 h. This compound was always tested as a racemic mixture, and attempts to prepare it in chiral form turned out to be unsuccessful. However, the two enantiomers were separated on a small scale by preparative chiral HPLC. The dextro isomer (stereochemistry not determined) was found to be 20-fold more potent against MMP-13 (Table 6) than the levo isomer. This potency also translated into increased in vivo activity, when tested in the dialysis implant model, in which the levo isomer was found to be 4.6-fold less active than its corresponding dextro isomer.

Conclusion

To summarize the SAR of molecules of general structure **1**, selectivity for MMP-13 vs MMP-1 can be achieved by varying the R_1 substituent. When R_1 is equal to long-chain alkoxy groups, the selectivity for MMP-13 over MMP-1 improves. Aromatic sulfonyl compounds are more potent than aliphatic or heteroaromatic sulfonyl derivatives. Compounds disubstituted at R_2 and R_3 are more potent MMP inhibitors than simple monosubstituted compounds (R_3 = H). To achieve in vivo activity, an aliphatic basic amine is essential. On the basis of the in vivo efficacy, compound **50** turned out to be the candidate of choice for further development even though it has moderate selectivity of MMP-13 over MMP-1.

Experimental Section

General Methods. Melting points were determined in open capillary tubes on a Meltemp melting point apparatus and are uncorrected. ^{1}H NMR spectra were determined with a Bruker DPX-300 spectrometer at 300 MHz. Chemical shifts δ are reported in parts per million relative to residual chloroform (7.26 ppm), TMS (0 ppm), or dimethyl sulfoxide (2.49 ppm) as an internal reference with coupling constants (J) reported in hertz (Hz). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Electrospray (ES) mass spectra were recorded in positive or negative mode on a Micromass Platform spectrometer. Electron impact and high-resolution mass spectra were obtaned on a Finnigen MAT-90 spectrometer. Combustion analyses were obtained using a Perkin-Elmer series II 2400 CHNS/O analyzer. Chromatographic purifications were performed by flash chromatography using Baker 40 μm silica gel. Thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF 250 M prescored plates. The terms "concentrated" and "evaporated" refer to removal of solvents using a rotary evaporator at water aspirator pressure with a bath temperature equal to or less than 60 °C. Unless otherwise noted, reagents were obtained from commercial sources and were used without further purification.

***N*-Hydroxy-2-(4-methoxybenzenesulfonyl)-3-phenylpropionamide (28).** To a stirred solution of 4-methoxybenzenethiol (2.8 g, 20 mmol) and anhydrous K_2CO_3 (10 g, excess) in dry acetone (100 mL), α-bromoethyl acetate (3.3 g, 20 mmol) was added in a round-bottom flask. The reaction mixture was heated at reflux for 8 h with good stirring. At the end, the reaction mixture was cooled, the potassium salts were filtered off, and the reaction mixture was concentrated. The residue was extracted with chloroform and washed with 0.5 N NaOH solution. The organic layer was further washed well with water, dried over $MgSO_4$, filtered, and concentrated. (4-Methoxyphenylsulfanyl)acetic acid ethyl ester was isolated as pale-yellow oil. Yield: 4.4 g, 100%. MS, m/z: 227 $(M + H)^+$.

To a stirred solution of 60% 3-chloroperoxybenzoic acid (14.0 g, 40 mmol) in methylene chloride (100 mL) at 0 °C, (4-methoxyphenylsulfanyl)acetic acid ethyl ester (4.4 g, 20 mmol) in CH_2Cl_2 (15 mL) was added slowly. The reaction mixture turned cloudy and was stirred at room temperature for 6 h. The reaction mixture was then diluted with hexanes (300 mL) and stirred for 15 min. The solids were filtered off, and Na_2SO_3 solution was added to the organic layer, which was stirred for at least 3 h before the mixture was extracted with $CHCl_3$ and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated, and the colorless (4-methoxyphenylsulfonyl)acetic acid ethyl ester was isolated as an oil. Yield: 100%. MS, m/z: 259.1 $(M + H)^+$.

To a stirred solution of the (4-methoxybenzenesulfonyl)acetic acid ethyl ester (2.5 g, 10 mmol), benzyl bromide (1.8 g,10 mmol) and 18-crown-6 (500 mg) in acetone (250 mL) was added K_2CO_3 (10 g, excess). The mixture was refluxed for 24 h. At the end, the reaction mixture was filtered and the acetone layer was concentrated. The residue obtained was extracted with chloroform, washed well with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. The product obtained was purified by silica gel column chromatography, eluting with 30% ethyl acetate/hexane. The product 2-(4-methoxybenzenesulfonyl)-3-phenylpropionic acid ethyl ester was isolated as a low melting solid. Yield: 3.0 g, 86%. MS, m/z: 349 $(M + H)^+$.

To a stirred solution of 2-(4-methoxybenzenesulfonyl)-3-phenylpropionic acid ethyl ester (348 mg, 1 mmol) in methanol (25 mL), 10 N NaOH (10 mL) was added. The reaction mixture was stirred at room temperature for 48 h. At the end, the reaction mixture was concentrated and carefully neutralized with dilute HCl. The residue obtained was extracted with chloroform, washed well with water, dried, and concentrated. The product obtained was purified by silica gel column chromatography, eluting with ethyl acetate/methanol (95:5) to afford 2-(4-methoxybenzenesulfonyl)-3-phenylpropionic acid as a colorless oil. Yield: 250 mg, 89%. MS, m/z: 321 $(M + H)^+$.

To a stirred solution of 2-(4-methoxybenzenesulfonyl)-3-phenylpropionic acid (200 mg, 0.625 mmol) and DMF (2 drops) in CH_2Cl_2 (100 mL) at 0 °C, oxalyl chloride (1.0 g, 8 mmol) was added in a dropwise manner. After the addition, the reaction mixture was stirred at room temperature for 1 h. Simultaneously, in a separate flask a mixture of hydroxylamine hydrochloride (2.0 g, 29 mmol) and triethylamine (5 mL, excess) was stirred in THF/water (5:1, 30 mL) at 0 °C for 1 h. At the end of 1 h, the oxalyl chloride reaction mixture was concentrated and the pale-yellow residue was dissolved in 10 mL of CH_2Cl_2. The mixture was added slowly to the hydroxylamine at 0 °C. The reaction mixture was stirred at room temperature for 24 h and concentrated. The residue obtained was extracted with chloroform and washed well with water. The product obtained was purified by silica gel column chromatography and eluted with ethyl acetate. The *N*-hydroxy-2-(4-methoxybenzenesulfonyl)-3-phenylpropionamide was isolated as a brown solid. Yield: 71%. Mp 180 °C. MS, m/z: 336 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.2 (m, 1H), 3.8 (s, 3H), 4.0−4.2 (m, 2H), 7.0−8.0 (m, 9H). Anal. ($C_{16}H_{17}NO_5S$) C, H, N.

***N*-Hydroxy-2-(4-methoxybenzenesulfonyl)-2-methyl-3-phenylpropionamide (29).** To a stirred solution of 2-(4-methoxybenzenesulfonyl)-3-phenylpropionic acid ethyl ester (1.0 g, 3 mmol) (from example **28**), methyl iodide (1 mL, excess), and 18-crown-6 (500 mg) in acetone (250 mL), K_2CO_3 (10 g, excess) was added. The reaction mixture was refluxed for 24 h. At the end, the reaction mixture was filtered and the acetone layer was concentrated. The residue obtained was extracted with chloroform, washed well with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. The product obtained was purified by silica gel column chromatography by eluting it with 30% ethyl acetate/hexanes to afford 2-(4-methoxybenzenesulfonyl)-2-methyl-3-phenylpropionic acid ethyl ester as a colorless oil. Yield: 1.0 g, 98%. MS, m/z: 349 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-phenylpropionic acid ethyl ester (900 mg, 2.7 mmol), 850 mg (quantitative) of 2-(4-methoxybenzenesulfonyl)-2-methyl-3-phenylpropionic acid was isolated by following the procedure as outlined in example **28**. A colorless oil was obtained. MS, m/z: 335 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-phenylpropionic acid (900 mg, 2.7 mmol) and following the procedure as outlined in example **28**, 450 mg of *N*-hydroxy-2-(4-methoxybenzenesulfonyl)-2-methyl-3-phenylpropionamide was isolated as a brown solid. Yield: 48%. Mp 58 °C. MS, m/z: 350 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.4 (s, 3H), 3.1 (d, J = 9 Hz, 1H), 3.6 (d, J = 9 Hz, 1H), 3.9 (s, 3H), 6.8−7.8 (m, 9H). Anal. ($C_{17}H_{19}NO_5S$) C, H, N.

***N*-Hydroxy-2-(4-methoxybenzenesulfonyl)-3-naphthalen-2-ylpropionamide (30).** Following the procedure as outlined in example **28**, 2-(4-methoxybenzensulfonyl)-3-naphthalen-2-ylpropionic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)acetic acid ethyl ester (5.0

g, 20 mmol) and 2-bromomethylnaphthalene (4.4 g, 20 mmol). Yield: 7.2 g, 91%. Colorless oil. MS, *m/z*: 399 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-3-naphthalen-2-ylpropionoic acid ethyl ester (3.7 g, 9 mmol), 3.3 g (96%) of 2-(4-methoxybenzenesulfonyl)-3-naphthalen-2-ylpropionoic acid was isolated as a colorless oil by following the procedure as outlined in example **28**. MS, *m/z*: 369.1 $(M - H)^-$.

Starting from 2-(4-methoxybenzenesulfonyl)-3-naphthalen-2-ylpropionic acid (2.2 g, 5.9 mmol) and following the procedure as outlined in example **28**, 820 mg of *N*-hydroxy-2-(4-methoxybenzenesulfonyl)-3-naphthalen-2-ylpropionamide was isolated as a light-brown solid. Yield: 36%. Mp 161−163 °C. MS, *m/z*: 385.9 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.32 (d, $J = 7.0$ Hz, 1H), 3.69 (d, $J = 7.0$ Hz, 1H), 3.82 (s, 3H), 5.02 (s, 1H), 6.92−7.89 (m, 11H). Anal. ($C_{20}H_{19}NO_5S$) C, H, N.

***N*-Hydroxy-2-(4-methoxybenzenesulfonyl)-2-methyl-3-naphthalen-2-ylpropionamide (31).** To stirred solution of 4-methoxybenzenethiol (2.8 g, 20 mmol) and anhydrous K_2CO_3 (10 g, excess) in dry acetone (100 mL), ethyl 2-bromopropionate (3.6 g, 20 mmol) was added in a round-bottom flask, and the reaction mixture was heated at reflux for 8 h with good stirring. At the end, the reaction mixture was allowed to cool, the potassium salts were filtered off, and the reaction mixture was concentrated. The residue was extracted with chloroform and washed with water and 0.5 N NaOH solution. The organic layer was further washed well with water, dried over $MgSO_4$, filtered, and concentrated to afford 2-(4-methoxyphenylsulfanyl)propionic acid ethyl ester as a light-yellow oil. Yield: 4.5 g, 94%. MS, *m/z*: 241 $(M + H)^+$.

To a stirred solution of 2-(4-methoxyphenylsulfanyl)propionic acid ethyl ester (2.41 g. 10 mmol) in methanol/THF (1:1, 100 mL) an aqueous solution of Oxone (10 g, excess, in 100 mL of water) was added at room temperature. The reaction mixture was stirred for 4 h and filtered. The filtrate was concentrated and extracted with ethyl acetae. The organic layer was ashed with water and dried over anhydrous $MgSO_4$. It was filtered and concentrated. The product was found to be 98% pure (by HPLC) and was taken to next step with out any purification. It was obtained as an oil. Yield: 2.5 g, 95%. MS, *m/z*: 273 $(M + H)^+$.

Following the procedure as outlined in example **28**, 2-(4-methoxybenzenesulfonyl)-2-methyl-3-naphthalen-2-ylpropionic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (5.4 g, 20 mmol) and 2-bromomethylnaphthalene (4.4 g, 20 mmol). Yield: 8.0 g, 97%. Colorless crystals. Mp 182−184 °C. MS, *m/z*: 413 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-naphthalen-2-ylpropionic acid ethyl ester (4.6 g, 11 mmol), 4.2 g (98%) of 2-(4-methoxybenzenesulfonyl)-2-methyl-3-naphthalen-2-ylpropionic acid was isolated as colorless crystals by following the procedure as outlined in example **28**. Mp 144−146 °C. MS, *m/z*: 384.9 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-naphthalen-2-ylpropionic acid (2.4 g, 6.2 mmol) and following the procedure as outlined in example **28**, 1.6 g of *N*-hydroxy-2-(4-methoxybenzenesulfonyl)-2-methyl-3-naphthalen-2-ylpropionamide was isolated as a light, colorless solid. Yield: 64%. Mp 185−187 °C. MS, *m/z*: 400.2 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 3H), 3.28 (d, $J = 8.0$ Hz, 1H), 3.81 (d, $J = 8$ Hz, 1H), 3.93 (s, 3H), 4.88 (bs, 1H), 7.02−7.92 (m, 11H). Anal. ($C_{21}H_{21}NO_5S$) C, H, N.

3-(Biphenyl-4-yl)-*N*-hydroxy-2-(4-methoxybenzenesulfonyl)-2-methylpropionamide (32). Following the procedure as outlined in example **31**, 3-(biphenyl-4-yl)-2-(4-methoxybenzenesulfonyl)-2-methylpropionic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (2.7 g,10 mmol) and 4-(chloromethyl)biphenyl (2.5 g, 12 mmol). Yield: 4.0 g, 91%. Colorless oil. MS, *m/z*: 438 $(M + H)^+$.

Starting from 3-(biphenyl-4-yl)-2-(4-methoxybenzenesulfonyl)-2-methylpropionic acid ethyl ester (3 g, 6.8 mmol), 2.5 g (89%) of 3-(biphenyl-4-yl)-2-(4-methoxybenzenesulfonyl)-2-methylpropionic acid was isolated as a colorless solid by following the procedure as outlined in example **28**. Mp 161 °C. MS, *m/z*: 411 $(M + H)^+$.

Starting from 3-(biphenyl-4-yl)-2-(4-methoxybenzenesulfonyl)-2-methylpropionic acid (2.0 g, 4.8 mmol) and following the procedure as outlined in example **28**, 1.2 g of 3-(biphenyl-4-yl)-*N*-hydroxy-2-(4-methoxybenzenesulfonyl)-2-methylpropionamide was isolated as a colorless solid. Yield: 58%. Mp 177 °C. MS, *m/z*: 426 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.4 (s, 3H), 3.2 (d, $J = 9$ Hz, 1H), 3.7 (d, $J = 9$ Hz, 1H), 3.9 (s, 3H), 7.0−7.8 (m, 13H), 9.7 (bs, 1H). Anal. ($C_{23}H_{23}NO_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-2,5-dimethylhex-4-enoic Acid Hydroxyamide (33). Following the procedure as outlined in example **31**, 2-(4-methoxybenzenesulfonyl)-2,5-dimethylhex-4-enoic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (1 g, 3.6 mmol) and isoprenyl bromide (1.0 g, 6 mmol). Yield: 1.0 g, 81%. Colorless oil. MS, *m/z*: 341 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2,5-dimethylhex-4-enoic acid ethyl ester (900 mg, 2.6 mmol), 800 mg (96%) of 2-(4-methoxybenzenesulfonyl)-2,5-dimethylhex-4-enoic acid was isolated as a semisolid by following the procedure as outlined in example **28**. MS, *m/z*: 313 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2,5-dimethylhex-4-enoic acid (1.0 g, 3.2 mmol) and following the procedure as outlined in example **28**, 700 mg of 2-(4-methoxybenzenesulfonyl)-2,5 dimethylhex-4-enoic acid hydroxyamide was isolated as a low-melting solid. Yield: 67%. MS, *m/z*: 328 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.3 (s, 3H), 1.5 (d, $J = 6.2$ Hz, 6H), 2.5−3.0 (m, 2H), 3.9 (s, 3H), 7.0 (d, $J = 11$ Hz, 2H), 7.8 (d, $J = 11$ Hz, 2H). Anal. ($C_{15}H_{21}NO_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-5-methyl-2-(3-methylbut-2-enyl)hex-4-enoic Acid Hydroxyamide (34). Following the procedure as outlined in example **28**, 2-(4-methoxybenzenesulfonyl)-5-methyl-2-(3-methylbut-2-enyl)hex-4-enoic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)acetic acid ethyl ester (5.0 g, 20 mmol) and isoprenyl bromide (6.0 g, 40 mmol). Yield: 7.0 g, 88%. Colorless oil. MS, *m/z*: 395 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-5-methyl-2-(3-methylbut-2-enyl)hex-4-enoic acid ethyl ester (3.5 g, 9 mmol), 3.3 g (97%) of 2-(4-methoxybenzenesulfonyl)-5-methyl-2-(3-methylbut-2-enyl)hex-4-enoic acid was isolated as a colorless oil by following the procedure as outlined in example **28**. MS, *m/z*: 365 $(M - H)^-$.

Starting from 2-(4-methoxybenzenesulfonyl)-5-methyl-2-(3-methylbut-2-enyl)hex-4-enoic acid (2.6 g, 7.0 mmol) and following the procedure as outlined in example **28**, 1.36 g of 2-(4-methoxybenzenesulfonyl)-5-methyl-2-(3-methylbut-2-enyl)hex-4-enoic acid hydroxyamide was isolated as a colorless solid. Yield: 67%. Mp 93−96 °C. MS, *m/z*: 383 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68 (s, 6H), 1.73 (s, 6H), 2.72 (m, 4H), 3.82 (s, 3H), 5.12 (m, 2H), 6.92 (d, $J = 8$ Hz, 2H), 7.33 (bs, 1H), 7.72 (d, $J = 8$ Hz, 2H), 9.71 (bs, 1H). Anal. ($C_{19}H_{27}NO_5S$) C, H, N.

2-Allyl-2-(4-methoxybenzenesulfonyl)pent-4-enoic Acid Hydroxyamide (35). Following the procedure as outlined in example **28**, 2-allyl-2-(4-methoxybenzenesulfonyl)pent-4-enoic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)acetic acid ethyl ester (3.0 g, 11.6 mmol) and allyl bromide (4 mL, excess). Yield: 3.6 g, 92%. Yellow oil. MS, *m/z*: 338 $(M + H)^+$.

2-Allyl-2-(4-methoxybenzenesulfonyl)pent-4-enoic acid was prepared starting from 2-allyl-2-(4-methoxybenzenesulfonyl)pent-4-enoic acid ethyl ester (2.2 g, 6.5 mmol) dissolved in methanol (50 mL) and 10 N NaOH (30 mL). The resulting reaction mixture was worked up as outlined in example **28**. Yield: 1.76 g, 87%. Yellowish oil. MS, *m/z*: 311 $(M + H)^+$.

Starting from 2-allyl-2-(4-methoxybenzenesulfonyl)pent-4-enoic acid (1.5 g, 4.8 mmol) and following the procedure as outlined in example **28**, 1.5 g of 2-allyl-2-(4-methoxybenzenesulfonyl)pent-4-enoic acid hydroxyamide was isolated as a colorless solid. Mp 114−116 °C. Yield: 99%. MS, *m/z*: 326 (M

+ H)$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (s, 1H), 2.70−2.80 (m,4H), 3.9 (s, 3H), 5.16−5.27 (m, 4H), 5.81−5.94 (m, 2H), 7.12 (d, J = 8 Hz, 2H). Anal. ($C_{15}H_{19}NO_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-2-methyl-5-phenylpent-4-enoic Acid Hydroxyamide (36). Following the procedure as outlined in example **28**, 2-(4-methoxybenzenesulfonyl)-2-methyl-5-phenylpent-4-enoic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (3.0 g, 11 mmol) and cinnamyl bromide (2.1 g, 11 mmol). Yield: 3.51 g, 82%. Colorless oil. MS, *m*/*z*: 389 (M + H)$^+$.

2-(4-Methoxybenzenesulfonyl)-2-methyl-5-phenylpent-4-enoic acid was prepared starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-5-phenylpent-4-enoic acid ethyl ester (3.0 g, 11 mmol) dissolved in methanol (50 mL) and 10 N NaOH (30 mL). The resulting reaction mixture was worked up as outlined in example **28**. Yield: 1.9 g, 68%. Yellowish oil. MS, *m*/*z*: 361 (M + H)$^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-5-phenylpent-4-enoic acid (440 mg, 1.2 mmol) and following the procedure as outlined in example **28**, 420 mg of 2-(4-methoxybenzenesulfonyl)-2-methyl-5-phenylpent-4-enoic acid hydroxyamide was isolated as a colorless solid. Mp 162−164 °C. Yield: 92%. MS, *m*/*z*: 376 (M + H)$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 3H), 3.0−3.16 (m, 1H), 3.30 (d, J = 11 Hz, 2H), 3.92 (s, 3H), 5.9−6.1 (m, 1H), 6.53 (d, J = 11 Hz, 1H), 7.1−7.72 (m, 9H), 9.12 (bs,1H). Anal. ($C_{19}H_{21}NO_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-2-propylpentanoic Acid Hydroxyamide (37). 2-Allyl-2-(4-methoxybenzenesulfonyl)-pent-4-enoic acid hydroxyamide (326 mg, 1.0 mmol) (example **35**) was dissolved in methanol (50 mL) and hydrogenated over 10% Pd/C (100 mg) at room temperature under 49 psi for 4 h. At the end, the reaction mixture was filtered and methanol was removed. The resulting solid was crystallized from methanol. Yield: 250 mg, 75%. MS, *m*/*z*: 330 (M + H)$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, J = 4.0 Hz, 6H), 1.27−1.59 (m, 4H), 1.78−2.02 (m, 4H), 3.86 (s, 3H), 6.04 (bs, 1H), 6.97 (d, J = 9 Hz, 2H), 7.76 (d,J = 9 Hz, 2H). Anal. ($C_{15}H_{23}NO_5S$) C, H, N.

***N*-Hydroxy-2-(4-methoxybenzenesulfonyl)-3-methylbutyramide (38).** 2-(4-Methoxyphenylsulfanyl)-3-methylbutyric acid ethyl ester was prepared according to the general method as outlined in example **28**. Starting from ethyl 2-bromo-3-methylbutanoate (20.9 g, 100 mmol) and 4-methoxybenzenethiol (14.0 g, 100 mmol), 30 g of 2-(4-methoxyphenylsulfanyl)-3-methylbutyric acid ethyl ester was isolated. Yield: 99%. Light yellow oil. MS, *m*/*z*: 269 (M + H)$^+$.

Starting from 2-(4-methoxyphenylsulfanyl)-3-methylbutyric acid ethyl ester (2.68 g 10 mmol) and following the procedure as outlined in example **28** for oxidation, 3 g of 2-(4-methoxybenzenesulfonyl)-3-methylbutyric acid ethyl ester was isolated as a colorless solid. Yield: 99%. Mp 53 °C. MS, *m*/*z*: 273 (M + H)$^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-3-methylbutyric acid ethyl ester (3 g, 10 mmol), 2.7 g (96%) of 2-(4-methoxybenzenesulfonyl)-3-methylbutyric acid was isolated as a colorless solid by following the procedure as outlined in example **28**. Mp 96 °C. MS, *m*/*z*: 273 (M + H)$^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-3-methylbutyric acid (2.0 g, 7.34 mmol) and following the procedure as outlined in example **28**, 590 mg of *N*-hydroxy-2-(4-methoxybenzenesulfonyl)-3-methylbutyramide was isolated as a colorless solid. Mp 220 °C. Yield: 28%. MS, *m*/*z*: 288 (M + H)$^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88 (d, J = 6.7 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H), 2.09−2.20 (bs, 1H), 3.53 (d, J = 9, 1H), 7.12−7.17 (m, 2H), 7.74−7.79 (m, 2H). Anal. ($C_{12}H_{17}NO_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)hexanoic Acid Hydroxyamide (39). 2-(4-Methoxyphenylsulfanyl)hexanoic acid ethyl ester was prepared according to the general method as outlined in example **28**. Starting from ethyl 2-bromohexanoate (7 g, 32 mmol) and 4-methoxybenzenethiol (4.2 g, 30 mmol), 8.3 g of the product was isolated. Yield: 98%. Light-yellow oil. MS, *m*/*z*: 283 (M + H)$^+$.

Starting from 2-(4-methoxyphenylsulfanyl)hexanoic acid ethyl ester (2.8 g 10 mmol) and following the procedure as outlined in example **28**, 3 g of 2-(4-methoxybenzenesulfonyl)-hexanoic acid ethyl ester was isolated as a colorless solid. Yield: 95%. Mp 62 °C. MS, *m*/*z*: 314 (M + H)$^+$.

Starting from 2-(4-methoxybenzenesulfonyl)hexanoic acid ethyl ester (2 g, 6.3 mmol), 1.5 g (83%) of 2-(4-methoxybenzenesulfonyl)hexanoic acid was isolated as a colorless solid by following the procedure as outlined in example **28**. Mp 116 °C. MS, *m*/*z*: 287 (M + H)$^+$.

Starting from 2-(4-methoxybenzenesulfonyl)hexanoic acid (1.0 g, 3.1 mmol) and following the procedure as outlined in example **28**, 700 mg of 2-(4-methoxybenzenesulfonyl)hexanoic acid hydroxyamide was isolated as a colorless solid. Yield: 60%. Mp 130 °C. MS, *m*/*z*: 302 (M + H)$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.786 (t, J = 7.2 Hz, 3H), 1.1−1.3 (m, 4H), 1.6−1.8 (m, 2H), 3.7 (m, 1H), 3.9 (s, 3H),7.2 (d, J = 11 Hz, 2H), 7.8 (d, J = 11 Hz, 2H), 9.3 (s, 1H), 10.9 (s, 1H). Anal. ($C_{13}H_{19}NO_5S$) C, H, N.

3-Cyclohexyl-*N*-hydroxy-2-(4-methoxybenzenesulfonyl)-2-methylpropionamide (40). Following the procedure as outlined in example **31**, 3-cyclohexyl-2-(4-methoxybenzenesulfonyl)-2-methylpropionic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (2.7 g, 10 mmol) and bromomethylcyclohexane (1.8 g, 10 mmol). Yield: 3.5 g, 95%. Yellow oil. MS, *m*/*z*: 369 (M + H)$^+$.

Starting from 3-cyclohexyl-2-(4-methoxybenzenesulfonyl)-2-methylpropionic acid ethyl ester (3 g, 8.1 mmol), 2.5 g (90%) of 3-cyclohexyl-2-(4-methoxybenzenesulfonyl)-2-methylpropionic acid was isolated as colorless solid by following the procedure as outlined in example **28**. Mp 116 °C. MS, *m*/*z*: 341 (M + H)$^+$.

Starting from 3-cyclohexyl-2-(4-methoxybenzenesulfonyl)-2-methylpropionic acid (2.0 g, 5.8 mmol) and following the procedure as outlined in example **28**, 1.1 g of 3-cyclohexyl-*N*-hydroxy-2-(4-methoxybenzenesulfonyl)-2-methylpropionamide was isolated as colorless solid. Yield: 55%. Mp 58 °C. MS, *m*/*z*: 356 (M + H)$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4 (s, 3H), 2.3−1.0 (m, 13 H), 3.9 (s, 3H), 7.0 (d, 8.8 Hz, 2H), 7.69 (d, 9.0 Hz, 2H). Anal. ($C_{17}H_{25}NO_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)tetradecanoic Hydroxyamide (41). 2-(4-Methoxyphenylsulfanyl)tetradecanoic acid ethyl ester was prepared according to the general method as outlined in example **28**. Starting from the corresponding ethyl 2-bromomyristate (5.0 g, 14.9 mmol) and 4-methoxythiophenol (1.9 g, 13.4 mmol), 5.0 g of the product was isolated. Yield: 98%. Light-yellow oil. MS, *m*/*z*: 393 (M + H)$^+$.

Starting from 2-(4-methoxyphenylsulfanyl)tetradecanoic acid ethyl ester (3.9 g 10 mmol) and following the procedure as outlined in example **31**, 3.2 g of 2-(4-methoxybenzenesulfonyl)-tetradecanoic acid ethyl ester was isolated as a colorless solid. Yield: 76%. Oil. MS, *m*/*z*: 425 (M + H)$^+$.

Starting from 2-(4-methoxybenzenesulfonyl)tetradecanoic acid ethyl ester (2.5 g, 5.9 mmol), 2.0 g (85%) of 2-(4-methoxybenzenesulfonyl)tetradecanoic acid was isolated as a colorless solid by following the procedure as outlined in example **28**. Mp 82 °C. MS, *m*/*z*: 397 (M + H)$^+$.

Starting from 2-(4-methoxybenzene sulfonyl)tetradecanoic acid (1.14 g, 2.9 mmol) and following the procedure as outlined in example **28**, 670 mg of 2-(4-methoxybenzenesulfonyl)-tetradecanoic hydroxyamide was isolated as an off-white solid. Yield: 57%. Mp 114 °C. MS, *m*/*z*: 414 (M + H)$^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, J = 7 Hz, 3H), 1.16−1.27 (m, 20 H), 1.66 (m, 2H), 3.62−3.70 (m, 1H), 3.87 (s, 3H), 7.12 (d, J = 15 Hz, 2H), 7.73 (d, J = 15 Hz, 2H). Anal. ($C_{21}H_{35}NO_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-2-prop-2-ynylpent-4-ynoic Acid Hydroxyamide (42). 2-(4-Methoxybenzenesulfonyl)-2-prop-2-ynylpent-4-ynoic acid *tert*-butyl ester was prepared according to the procedure as outlined in example **28**. Starting from 2-(4-methoxybenzenesulfonyl)acetic acid *tert*-butyl ester (2.0 g, 7.0 mmol) and propargyl bromide (1.77 g,

15 mmol), 1.9 g of the product was isolated. Yield: 75%. White solid. Mp 113−115 °C. MS, *m/z*: 362.1 $(M + H)^+$.

2-(4-Methoxybenzenesulfonyl)-2-prop-2-ynylpent-4-ynoic acid was prepared according to the procedure as outlined in example **28**. To a stirred solution of 2-(4-methoxybenzenesulfonyl)-2-prop-2-ynylpent-4-ynoic acid *tert*-butyl ester (1.70 g, 4.7 mmol) in CH_2Cl_2 (100 mL) trifluoroacetic acid (20 mL) was added at room temperature. The reaction mixture was stirred at room temperature for 24 h. At the end, the reaction mixture was concentrated and extracted with chloroform, washed well with water, and dried over anhydrous $MgSO_4$. The organic layer was concentrated, and the separated white solid was crystallized from aqueous methanol. An amount of 1.30 g of 2-(4-methoxybenzenesulfonyl)-2-prop-2-ynylpent-4-ynoic acid was isolated as a white solid. Yield: 90%. Mp 156 °C. MS, *m/z*: 305.1 $(M - H)^-$.

2-(4-Methoxybenzenesulfonyl)-2-prop-2-ynylpent-4-ynoic acid hydroxyamide was prepared according to the method as outlined in example **28**. Starting from (4-methoxybenzenesulfonyl)-2-prop-2-ynylpent-4-ynoic acid (0.25 g, 0.81 mmol) and hydroxylamine hydrochloride (0.70 g, 10 mmol), 0.22 g of the product was isolated. Yield: 85%. White solid. Mp 156 °C. MS, *m/z*: 321.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.00−2.13 (m, 2H), 3.00−3.30 (m, 4H), 3.90(s, 3H), 7.01 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 9.0 Hz, 2H), 8.76 (brs, 1H), 10.65 (brs, 1H). Anal. ($C_{15}H_{15}NO_5S$) C, H, N.

***N*-Hydroxy-2-(4-methoxybenzenesulfonyl)-2-methyl-3-pyridin-3-ylpropionamide (43).** To a stirred solution of 2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (2.7 g, 10 mmol), 3-picolyl chloride hydrochloride (3.2 g, 20 mmol), and triethylbenzylammonium chloride (1 g) in methylene chloride (400 mL), 10 N NaOH (30 mL) was added. The reaction was continued at room temp for 48 h. At the end, the organic layer was separated and washed well with water. The organic layer was dried, filtered, and concentrated. The crude product obtained was purified by silica gel column chromatography. The column was eluted with 50% ethyl acetate/hexane.

2-(4-Methoxybenzensulfonyl)-2-methyl-3-pyridin-3-ylpropionic acid ethyl ester was isolated as a brown oil. Yield: 3.0 g, 82%. MS, *m/z*: 364 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-pyridin-3-ylpropionic acid ethyl ester (2.5 g, 6.8 mmol), 1.8 g (79%) of 2-(4-methoxybenzenesulfonyl)-2-methyl-3-pyridin-3-ylpropionic acid was isolated as a colorless solid by following the procedure as outlined in example **28**. Mp 58 °C. MS, *m/z*: 336 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-pyridin-3-ylpropionic acid (410 mg, 1 mmol) and following the procedure as outlined in example **28**, 225 mg of *N*-hydroxy-2-(4-methoxybenzenesulfonyl)-2-methyl-3-pyridin-3-ylpropionamide was isolated as a colorless solid. Yield: 52%. Mp 98 °C. MS, *m/z*: 351 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.4 (s, 3H), 3.1 (d, J = 9.0, 1H), 3.65 (d, J = 9.1, 1H), 3.9 (s, 3H), 7−8.5 (m, 8H). Anal. ($C_{16}H_{18}N_2O_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhex-4-enoic Acid Hydroxyamide (44). Following the procedure as outlined in example **28**, 2-(4-methoxybenzenesulfonyl)-5-methylhex-4-enoic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)acetic acid ethyl ester (6.0 g, 23 mmol) and isoprenyl bromide (3.0 g, 20 mmol). Yield: 6.52 g, 86%. Colorless oil. MS, *m/z*: 327 $(M + H)^+$.

Following the procedure as outlined in example **43**, 2-(4-methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhex-4-enoic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)-5-methylhex-4-enoic acid ethyl ester (6.0 g, 23 mmol) and 3-picolyl chloride hydrochloride (2.1 g, 13 mmol). Yield: 4.14 g, 81%. Brown oil. MS, *m/z*: 418 $(M + H)^+$.

2-(4-Methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhex-4-enoic acid was prepared starting from 2-(4-methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhex-4-enoic acid ethyl ester (4.0 g, 9.5 mmol) dissolved in methanol (50 mL) and 10 N NaOH (30 mL). The resulting reaction mixture was worked up as outlined in example **28**. Yield: 3.2 g, 87%. Ivory solid. Mp 117−119 °C. MS, *m/z*: 390 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhex-4-enoic acid (2.1 g, 5.4 mmol) and following the procedure as outlined in example **28**, 1.82 g of 2-(4-methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhex-4-enoic acid hydroxyamide was isolated as a colorless solid. Yield: 82%. Mp 89−92 °C. MS, *m/z*: 405 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (s, 3H), 1.76 (s, 3H), 2.62−2.78 (m, 2H), 3.3 (d, J = 4.0 Hz, 1H), 3.63 (d, J = 4.0 Hz, 1H), 3.82 (s, 3H), 5.26 (m, 1H), 7.12−7.88 (m, 6H), 8.27−8.33 (m, 2H). Anal. ($C_{20}H_{24}N_2O_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-4-methyl-2-pyridin-3-ylmethylpentanoic Acid Hydroxyamide (45). Following the procedure as outlined in example **28**, 2-(4-methoxybenzenesulfonyl)-4-methylpentanoic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)acetic acid ethyl ester (5.0 g, 20 mmol) and 1-bromo-2-methylpropane (2.6 g, 20 mmol). Yield: 6.0 g, 95%. Colorless oil. MS, *m/z*: 315 $(M + H)^+$.

Following the procedure as outlined in example **43**, 2-(4-methoxybenzenesulfonyl)-4-methyl-2-pyridin-3-ylmethylpenanoic acid ethyl ester was prepared, starting from 2-[(4-methoxybenzenesulfonyl)-4-methyl pentanoic acid ethyl ester (3.1 g, 10 mmol) and 3-picolyl chloride hydrochloride (1.8 g, 11 mmol). Yield: 3.0 g, 75%. Colorless oil. MS, *m/z*: 406 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-4-methyl-2-pyridin-3-ylmethylpentanoic acid ethyl ester (1.2 g, 2.9 mmol), 1.0 g (91%) of 2-(4-methoxybenzenesulfonyl)-4-methyl-2-pyridin-3-ylmethylpentanoic acid was isolated as colorless crystals by following the procedure as outlined in example **28**. Mp 188−186 °C. MS, *m/z*: 378 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-4-methyl-2-pyridin-3-ylmethylpentanoic acid (800 mg, 2.1 mmol) and following the procedure as outlined in example **28**, 180 mg of 2-(4-methoxybenzenesulfonyl)-4-methyl-2-pyridin-3-ylmethylpentanoic acid hydroxyamide was isolated as a colorless solid. Yield: 21%. Mp 78 °C. MS, *m/z*: 393.4 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.65 (d, 6.3 Hz, 3H), 0.89 (d, J = 6.2 Hz, 3H), 1.7 (m, 1H), 2.06 (m, 2H), 3.85 (s, 3H), 6.8−8.5 (m, 10H). Anal. ($C_{19}H_{24}N_2O_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhexanoic Acid Hydroxyamide (46). Following the procedure as outlined in example **28**, 2-(4-methoxybenzenesulfonyl)-5-hexanoic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)acetic acid ethyl ester (10.0 g, 39 mmol) and 1-bromo-3-methylbutane (6.0 g, 40 mmol). Yield: 8.5 g, 62%. Colorless oil. MS, *m/z*: 329 $(M + H)^+$.

Following the procedure as outlined in example **43**, 2-(4-methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhexanoic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)-5-methylhexanoic acid ethyl ester (6.0 g, 18 mmol) and picolyl chloride hydrochloride (4.1 g, 25 mmol). Yield: 4.5 g, 60%. Brown oil. MS, *m/z*: 420 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhexanoic acid ethyl ester (3.0 g, 7.1 mmol), 2.6 g (92%) of 2-(4-methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhexanoic acid was isolated as a colorless solid by following the procedure as outlined in example **28**. Mp 173 °C. MS, *m/z*: 392 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhexanoic acid (1.0 g, 2.5 mmol) and following the procedure as outlined in example **28**, 800 mg of 2-(4-methoxybenzenesulfonyl)-5-methyl-2-pyridin-3-ylmethylhexanoic acid hydroxyamide was isolated as a colorless solid. The hydrochloride was prepared by passing hydrogen chloride gas through a methanol solution of the hydroxyamide. Yield: 72%. Mp 62 °C (HCl salt). MS, *m/z*: 408 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (m, 6H), 1.2−2.0 (m, 5H), 3.5 (brq, 2H), 7.1−8.8 (m, 8H), 11.1 (brs,1H). Anal. ($C_{20}H_{26}N_2O_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-2-pyridin-3-ylmethylhexanoic Acid Hydroxyamide (47). (4-Methoxyphenylsulfanyl)acetic acid *tert*-butyl ester was prepared according to the

general method as outlined in example **28**. Starting from the corresponding 1-bromo *tert*-butylacetate (5.3 g, 27 mmol) and 4-methoxybenzenethiol (3.7 g, 27 mmol), 6.4 g of the product was isolated. Yield: 98%. Light-yellow oil. MS, *m*/*z*: 255 (M + H)$^+$.

2-(4-Methoxybenzenesulfonyl)acetic acid *tert*-butyl ester was prepared according to the general method as outlined in example **31**. Starting from 2-(4-methoxybenzenesulfanyl)acetic acid *tert*-butyl ester (5.0 g, 20 mmol) and 3-chloroperoxybenzoic acid 57% (12.0 g, 40 mmol), 5.3 g of the product was isolated. Yield: 92%. Waxy solid. MS, *m*/*z*: 287.1 (M + H)$^+$.

2-(4-Methoxybenzenesulfonyl)pyridin-3-ylpropionic acid *tert*-butyl ester was prepared according to the procedure as outlined in example **43**. Starting from 2-(4-methoxybenzenesulfonyl)acetic acid *tert*-butyl ester (20.0 g, 70.0 mmol) and 3-picolyl chloride (7.28 g, 44.4 mmol), 10.5 g of the product was isolated by silica gel chromatography (50% ethyl acetate/hexane). Yield: 63%. White solid. Mp 93−94 °C. MS, *m*/*z*: 378.0 (M + H)$^+$.

2-(4-Methoxybenzenesulfonyl)-2-pyridin-3-ylmethylhexanoic acid *tert*-butyl ester was prepared according to the procedure as outlined in example **28**. Starting from 2-(4-methoxybenzenesulfonyl)pyridin-3-ylpropionic acid *tert*-butyl ester (2.0 g, 5.3 mmol) and *n*-butyl bromide (0.73 g, 5.3 mmol), 1.20 g of the product was isolated. Yield: 52%. Yellowish gum. MS, *m*/*z*: 434.3 (M + H)$^+$.

A mixture of the 2-(4-methoxybenzenesulfonyl)-2-pyridin-3-ylmethylhexanoic acid *tert*-butyl ester (1.1 g, 2.5 mmol) in methylene chloride/TFA (1:1) was stirred at room temperature for about 2 h. The solvents were then evaporated, and the 2-(4-methoxybenzenesulfonyl)-2-pyridin-3-ylmethylhexanoic acid was purified by silica gel chromatography (30% methanol/methylene chloride). Yield: 0.90 g, 94%. White solid. Mp 70° C. MS, *m*/*z*: 376.1 (M − H)$^-$.

2-(4-Methoxybenzenesulfonyl)-2-pyridin-3-ylmethylhexanoic acid hydroxyamide was prepared according to the method as outlined in example **28**. Starting from 2-(4-methoxybenzenesulfonyl)-2-pyridin-3-ylmethylhexanoic acid (0.31 g, 0.81 mmol) and hydroxylamine hydrochloride (0.70 g, 10 mmol), 0.13 g of the product was isolated. Yield: 37%. pale-yellowish solid. Mp 65 °C. MS, *m*/*z*: 392.9 (M + H)$^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80 (t, J = 7.2 Hz, 3H), 1.10−1.25 (m, 2H), 1.25−1.50 (m, 2H), 1.70−2.00 (m, 2H), 3.53 (d, J = 14.4 Hz, 1H), 3.62 (d, J = 14.4 Hz, 1H), 3.88 (s, 3H), 7.15 (d, J = 8.9 Hz, 2H), 7.71 (d, J = 8.9 Hz, 2H), 7.90−8.00 (m, 1H), 8.40−8.45 (m, 1H), 8.70−8.85 (m, 2H), 11.0 (brs, 1H). Anal. ($C_{19}H_{24}N_2O_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-2-pyridin-3-ylmethyldecanoic Acid Hydroxyamide (48). Starting from 2-(4-methoxybenzenesulfonyl)acetic acid ethyl ester (7.5 g, 29 mmol) and 1-bromooctane (6.7 g, 35 mmol), 8 g of the monooctylated compound 2-(4-methoxybenzenesulfonyl)decanoic acid ethyl ester was isolated by following the procedure outlined in example **28**. Yield: 8.0 g, 74%. MS, *m*/*z*: 370 (M + H)$^+$.

Following the procedure as outlined in example **43**, 2-(4-methoxybenzenesulfonyl)-2-pyridin-3-ylmethyldecanoic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)decanoic acid ethyl ester (8.0 g, 21.6 mmol) and 3-picolyl chloride hydrochloride (4.1 g, 25 mmol). Yield: 6.5 g, 68%. Brown oil. MS, *m*/*z*: 462 (M + H)$^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-pyridin-3-ylmethyldecanoic acid ethyl ester (5.0 g, 11 mmol), 4.5 g (91%) of 2-(4-methoxybenzenesulfonyl)-2-pyridin-3-ylmethyldecanoic acid was isolated as a colorless solid by following the procedure as outlined in example **28**. Mp 159 °C. MS, *m*/*z*: 434 (M + H)$^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-pyridin-3-ylmethyldecanoic acid (2.5 g, 5.7 mmol) and following the procedure as outlined in example **28**, 1.4 g of 2-(4-methoxybenzenesulfonyl)-2-pyridin-3-ylmethyldecanoic acid hydroxyamide was isolated as a colorless solid. Yield: 50%. Mp 62 °C. MS, *m*/*z*: 448 (M + H)$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J = 6.9 Hz, 3H), 1.25−2.17 (m, 14 H), 3.3 (d, J = 14 Hz, 1H), 3.5 (d, J = 14 Hz, 1H), 3.9 (s, 3H), 6.8−8.6 (m, 8H). Anal. ($C_{23}H_{32}N_2O_5S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-2-pyridin-3-ylmethylpent-4-ynoic Acid Hydroxyamide (49). 2-(4-Methoxybenzenesulfonyl)-2-pyridin-3-ylmethylpent-4-ynoic acid *tert*-butyl ester was prepared according to the procedure as outlined in example **28**. Starting from 2-(4-methoxybenzenesulfonyl)-pyridin-3-ylpropionic acid *tert*-butyl ester (3.77 g, 10 mmol) and propargyl bromide (1.74 g, 13 mmol), 2.50 g of the product was isolated. Yield: 60%. Yellowish solid. Mp 132−133 °C. MS, *m*/*z*: 416.0 (M + H)$^+$.

2-(4-Methoxybenzenesulfonyl)-2-pyridin-3-ylmethylpent-4-ynoic acid was prepared according to the procedure as outlined in example **47**. Starting from 2-(4-methoxybenzenesulfonyl)-2-pyridin-3-ylmethylpent-4-ynoic acid *tert*-butyl ester (2. 0 g, 4.8 mmol), 1.2 g of the product was isolated. Yield: 69%. White solid. Mp 119−121 °C. MS, *m*/*z*: 358.1 (M − H)$^-$.

2-(4-Methoxybenzenesulfonyl)-2-pyridin-3-ylmethylpent-4-ynoic acid hydroxyamide was prepared according to the method as outlined in example **28**. Starting from 2-(4-methoxybenzenesulfonyl)-2-pyridin-3-ylmethylpent-4-ynoic acid (0.29 g, 0.81 mmol) and hydroxylamine hydrochloride (0.70 g, 10 mmol), 0.065 g of the product was isolated. Yield: 25%. Off-white solid. Mp 70 °C. MS, *m*/*z*: 375.0 (M + H)$^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (brs, 1H), 2.90−3.00 (m, 2H), 3.55 (d, J = 13.8 Hz, 1H), 3.67 (d, J = 13.8 Hz, 1H), 3.89 (s, 3H), 7.18 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.80−7.89 (m, 1H), 8.35−8.40 (m, 1H), 8.70−8.80 (m, 2H), 11.1 (brs, 1H). Anal. ($C_{18}H_{18}N_2O_5S$) C, H, N.

***N*-Hydroxy-2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl]propionamide (50).** Following the procedure as outlined in example **31**, 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl]propionic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (2.7 g, 10 mmol) and the 4-(2-piperidin-1-ylethoxy)benzyl chloride (2.9 g, 10 mmol). Yield: 4.8 g, 98%. Brown oil. MS, *m*/*z*: 490 (M + H)$^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl]propionic acid ethyl ester (4.0 g, 7.9 mmol), 3.5 g (yield: 94%) of 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl]propionic acid was isolated as colorless crystals by following the procedure as outlined in example **28**. Mp 106 °C. MS, *m*/*z*: 462.5 (M + H)$^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl]propionic acid (2.0 g, 4.2 mmol) and following the procedure as outlined in example **28**, 1 g of *N*-hydroxy-2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl]propionamide was isolated as a colorless solid. Yield: 1 g, 48%. Mp 98 °C. MS, *m*/*z*: 477 (M + H)$^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2 (s, 3H), 3.5−1.5 (m, 16 H), 3.9 (s, 3H), 4.4 (m, 1H), 6.5−7.8 (m, 8H), 10.8 (bs, 1H). Anal. ($C_{24}H_{32}N_2O_6S$) C, H, N.

2-[4-(2-Azepan-1-ylethoxy)benzyl]-2-(4-methoxybenzenesulfonyl)propionic acid Hydroxyamide (51). Following the procedure as outlined in example **31**, 2-[4-(2-azepan-1-ylethoxy)benzyl]-2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (2.7 g, 10 mmol) and the 1-[2-(4-chloromethylphenoxy)ethyl]azepane (3.03 g, 10 mmol). Yield: 4.5 g, 90%. Brown oil. MS, *m*/*z*: 504 (M + H)$^+$.

Starting from 2-[4-(2-azepan-1-ylethoxy)benzyl]-2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (4.0 g, 7.9 mmol), 3.5 g (yield: 94%) of 2-[4-(2-azepan-1-ylethoxy)-benzyl]-2-(4-methoxybenzenesulfonyl)propionic acid was isolated as a semisolid by following the procedure as outlined in example **28**. MS, *m*/*z*: 476 (M + H)$^+$.

Starting from 2-[4-(2-azepan-1-ylethoxy)benzyl]-2-(4-methoxybenzenesulfonyl)propionic acid (2.0 g, 4.2 mmol) and following the procedure as outlined in example **28**, 1 g of 2-[4-(2-azepan-1-ylethoxy)benzyl]-2-(4-methoxybenzenesulfonyl)propionic acid hydroxyamide was isolated as a colorless solid. Yield: 1.8 g, 87%. Mp 68°C. MS, *m*/*z*: 491 (M + H)$^+$. ^{1}H

NMR (300 MHz, $CDCl_3$): δ 1.23 (s, 3H), 3.5−1.7 (m, 18 H), 3.8 (s, 3H), 4.2 (m, 1H), 6.4−7.89 (m, 8H), 10.9 (brs, 1H). Anal. ($C_{25}H_{34}N_2O_6S$) C, H, N.

***N*-Hydroxy-2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diisopropylaminoethoxy)phenyl]propionamide (52).** Following the procedure as outlined in example **31**, 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diisopropylaminoethoxy)phenyl]propionic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)-propionic acid ethyl ester (5.4 g, 20 mmol) and the 4-(2-*N*,*N*-diisopropylaminoethoxy)benzyl chloride (6.1 g, 20 mmol). Yield: 8.9 g, 88%. Yellow oil. MS, *m*/*z*: 506.5 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diisopropylaminoethoxy)phenyl]propionic acid ethyl ester (4.0 g, 7.9 mmol), 3.5 g (yield: 92%) of 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diisopropylaminoethoxy)-phenyl]propionic acid was isolated as colorless crystals by following the procedure as outlined in example **28**. Mp 68 °C. MS, *m*/*z*: 478.6 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diisopropylaminoethoxy)phenyl]propionic acid (2.0 g, 4.1 mmol) and following the procedure as outlined in example **28**, 1 g of 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diisopropylaminoethoxy)phenyl]propionamide was isolated as a colorless solid. Yield: 1 g, 49%. Mp 98 °C (HCl salt). MS, *m*/*z*: 493 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2 (s, 3H), 1.3 (d,6H), 1.4 (d,6H), 3.5−1.5 (m, 6 H), 3.9 (s, 3H), 4.4 (s, 2H), 6.5−7.8 (m, 8H), 10.8 (brs, 1H). Anal. ($C_{25}H_{36}N_2O_6S$) C, H, N.

***N*-Hydroxy-2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionamide (53).** Following the procedure as outlined in example **31**, 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (5.4 g, 20 mmol) and the 4-(2-*N*,*N*-diethylaminoethoxy)benzyl chloride (5.5 g, 20 mmol). Yield: 8.5 g, 89%. Brown oil. MS, *m*/*z*: 478.6 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionic acid ethyl ester (3.5 g, 7.7 mmol), 3.0 g (yield: 85%) of 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]-propionic acid was isolated as colorless crystals by following the procedure as outlined in example **28**. Mp 96−98 °C. MS, *m*/*z*: 450.5 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionic acid (2.0 g, 4.4 mmol) and following the procedure as outlined in example **28**, 1 g of 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionamide was isolated as a colorless solid. Yield: 1 g, 48%. Mp 56−59°C (HCl Salt). MS, *m*/*z*: 465.5 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1 (t, 6H), 1.3 (s, 3H), 3.2−3.9 (m, 8 H), 3.9 (s, 3H), 4.3 (s, 2H), 6.5−7.8 (m, 8H), 10.8 (bs, 1H). Anal. ($C_{23}H_{32}N_2O_6S\cdot$HCl) C, H, N.

3-(4-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propoxy}-phenyl)-*N*-hydroxy-2-(4-methoxybenzenesulfonyl)-2-methylpropionamide (54). Following the procedure as outlined in example **31**, 3-(4-{3-[4-(3-chlorophenyl)piperazin-1-yl]propoxy}phenyl)-2-(4-methoxybenzenesulfonyl)-2-methyl-propionic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (2.72 g, 10 mmol) and the 1-[2-(4-chloromethylphenoxy)ethyl]-4-(3-chlorophenyl)piperazine (4.2 g, 11 mmol). Yield: 5.5 g, 89%. Brown oil. MS, *m*/*z*: 616 $(M + H)^+$.

Starting from 3-(4-{3-[4-(3-chlorophenyl)piperazin-1-yl]-propoxy}phenyl)-2-(4-methoxybenzenesulfonyl)-2-methylpropionic acid ethyl ester (4.0 g, 6.5 mmol), 3.0 g (yield: 78%) of 3-(4-{3-[4-(3-chlorophenyl)piperazin-1-yl]-propoxy}phenyl)-2-(4-methoxybenzenesulfonyl)-2-methylpropionic acid was isolated as colorless crystals by following the procedure as outlined in example **28**. Mp 196 °C. MS, *m*/*z*: 588.1 $(M + H)^+$.

Starting from 3-(4-{3-[4-(3-chlorophenyl)piperazin-1-yl]-propoxy}phenyl)-2-(4-methoxybenzenesulfonyl)-2-methylpropionic acid (3.0 g, 5.1 mmol) and following the procedure as outlined in example **28**, 1.8 g of 3-(4-{3-[4-(3-chlorophenyl)-piperazin-1-yl]propoxy}phenyl)-*N*-hydroxy-2-(4-methoxybenzenesulfonyl)-2-methylpropionamide was isolated as pale-yellow solid. Yield: 1.8 g, 55%. Mp 122°C (HCl salt). MS, *m*/*z*: 640 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2 (s, 3H), 3.4−1.5 (m, 14 H), 3.9 (s, 3H), 4.5 (m, 2H), 6.5−8.2 (m, 12H), 10.3 (brs, 1H). Anal. ($C_{30}H_{36}ClN_3O_6S$) C, H, N.

2-(4-Methoxybenzenesulfonyl)-2-methyl-3-[4-(2-morpholin-4-ylethoxy)phenyl]propionic Hydroxyamide Hydrochloride (55). Following the procedure as outlined in example **31**, 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-morpholin-1-ylethoxy)phenyl]propionic acid ethyl ester was prepared, starting from 2-(4-methoxybenzenesulfonyl)propionic acid ethyl ester (4.0 g, 15 mmol) and 4-(morpholin-1-ylethoxy)-benzyl chloride hydrochloride (2.9 g, 10 mmol). Yield: 4.8 g, 98%. Brown oil. MS, *m*/*z*: 492 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-morpholin-1-ylethoxy)phenyl]propionic acid ethyl ester (4.0 g, 8.1 mmol), 3.2 g (yield: 84%) of 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-morpholin-1-ylethoxy)phenyl]propionic acid was isolated as colorless crystals by following the procedure as outlined in example **28**. Mp 171 °C. MS, *m*/*z*: 464 $(M + H)^+$.

Starting from 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-morpholin-1-ylethoxy)phenyl]propionic acid (4.0 g, 8.6 mmol) and following the procedure as outlined in example **28**, 2.5 g of 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-morpholin-1-ylethoxy)phenyl]propionic hydroxyamide was isolated as colorless solid. The hydrochloride salt was prepared by reacting the free base with methanolic hydrogen chloride at 0 °C. Yield: 2.5 g, 60%. Mp 98°C. MS, *m*/*z*: 479 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): 1.36 (s, 3H), 3.8−12.6 (m, 16 H), 3.9 (s, 3H), 4.1−4.3 (m, 1H), 6.6 (d, $J = 8$ Hz, 2H), 6.96 (d, $J = 9$ Hz, 2H), 7.1 (d, $J = 8$ Hz, 2H), 7.84 (d, $J = 9$ Hz, 2H), 10.8 (brs, 1H). Anal. ($C_{23}H_{30}N_2O_7S$) C, H, N.

***N*-Hydroxy-2-(4-ethoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionamide (56).** To a stirred solution of 4-hydroxythiophenol (12.6 g, 100 mmol) and triethylamine (15.0 g, 150 mmol) in chloroform (400 mL) 2-bromo ethylpropionate (18. 2 g, 100 mmol) was added dropwise. The reaction mixture was refluxed for 1 h and cooled to room temperature. The reaction mixture was washed with water, dried, and concentrated. 2-(4-Hydroxyphenylsulfanyl)-propionic acid ethyl ester was isolated as a colorless oil. Yield: 22.0 g, 99%, MS, *m*/*z*: 227 $(M + H)^+$.

To stirred solution of 2-(4-hydroxyphenylsulfanyl)propionic acid ethyl ester (11.3 g, 50 mmol) and K_2CO_3 (50 g, excess) in acetone (300 mL) ethyl iodide (20 mL, excess) was added. The mixture was refluxed for 8 h. At the end, reaction mixture was filtered and concentrated. The residue obtained was extracted with chloroform and washed well with water. It was dried and concentrated. The product 2-(4-ethoxyphenylsulfanyl)propionic acid ethyl ester was isolated as a colorless oil. Yield: 12.0 g, 98%. MS, *m*/*z*: 255 $(M + H)$.

2-(4-Ethoxyphenylsulfanyl)propionic acid ethyl ester was converted to 2-(4-ethoxyphenylsulfonyl)propionic acid ethyl ester by following the procedure as described in example **31**.

Following the procedure as outlined in example **31**, 2-(4-ethoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionic acid ethyl ester was prepared, starting from 2-(4-ethoxybenzenesulfonyl)propionic acid ethyl ester (3.5 g, 12.2 mmol) and the 4-(2-*N*,*N*-diethylaminoethoxy)-benzyl chloride (3.5 g, 12.2 mmol). Yield: 4.8 g, 80%. Brown oil. MS, *m*/*z*: 492.6 $(M + H)^+$.

Starting from 2-(4-ethoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionic acid ethyl ester (4.0 g, 8.1 mmol), 3.2 g (yield: 80%) of 2-(4-ethoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionic acid was isolated as a colorless semisolid by following the procedure as outlined in example **28**. MS, *m*/*z*: 464.5 $(M + H)^+$.

Starting from 2-(4-ethoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionic acid (2.0 g, 4.3 mmol) and following the procedure as outlined in example **28**, 1.2 g

of 2-(4-ethoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionamide was isolated as a colorless low-melting solid. Yield: 1.2 g, 57% (HCl salt). MS, *m*/*z*: 478.5 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (t, 3H), 1.1 (t, 6H), 1.3 (s,3H), 3.2−3.9 (m, 8 H), 3.9 (s, 3H), 4.3 (s, 2H), 6.5−7.8 (m, 8H), 10.8 (brs, 1H). Anal. ($C_{24}H_{34}N_2O_6S$·HCl) C, H, N.

***N*-Hydroxy-2-(4-*n*-butoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl]propionamide (57).** Following the procedure as outlined in example **31**, 2-(4-*n*-butoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-ylethoxy)-phenyl]propionic acid ethyl ester was prepared, starting from 2-(4-*n*-butoxybenzenesulfonyl)propionic acid ethyl ester (3.1 g, 10 mmol) (prepared from 2-(4-hydroxyphenylsulfanyl)propionic acid ethyl ester and *n*-butylbromide following the procedure outlined in example **56**) and the 4-(2-piperidin-1-ylethoxy)-benzyl chloride (3.0 g, 10.1 mmol). Yield: 4.5 g, 84%. Brown oil. MS, *m*/*z*: 532.7 $(M + H)^+$.

Starting from 2-(4-*n*-butoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl]propionic acid ethyl ester (5.0 g, 9.4 mmol), 4.2 g (yield: 88%) of 2-(4-*n*-butoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl]propionic acid was isolated as a colorless solid by following the procedure as outlined in example **28**. MS, *m*/*z*: 504.6 $(M + H)^+$

Starting from 2-(4-*n*-butoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl]propionic acid (3.0 g, 5.9 mmol) and following the procedure as outlined in example **28**, 1.3 g of 2-(4-*n*-butoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidine-1-ylethoxy)phenyl]propionamide was isolated as a colorless solid. Mp 65° C. Yield: 1.3 g, 42% (HCl salt). MS, *m*/*z*: 478.5 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (t, 3H), 1.2 (s, 3H), 1.3−1.9 (m,10H), 2.8−4.5 (m, 12 H), 6.8−7.8 (m, 8H), 10.8 (bs, 1H). Anal. ($C_{27}H_{38}N_2O_6S$·HCl) C, H, N.

3-[4-(2-Diethylaminoethoxy)phenyl]-2-(4-furan-2-yl-benzenesulfonyl)-*N*-hydroxy-2-methylpropionamide (58). To a stirred solution of 4-bromothiophenol (19.0 g, 100 mmol) and triethylamine (15.0 g, 150 mmol) in chloroform (400 mL) 2-bromo ethylpropionate (18. 2 g, 100 mmol) was added dropwise. The reaction mixture was refluxed for 1 h and cooled to room temperature. The reaction mixture was washed with water, dried, and concentrated. 2-(4-Bromophenylsulfanyl)-propionic acid ethyl ester was isolated as colorless oil. Yield: 28.0 g, 99%, MS, *m*/*z*: 290 (M + H).

2-(4-Bromophenylsulfanyl)propionic acid ethyl ester was converted to 2-(4-bromophenylsulfonyl)propionic acid ethyl ester by following the procedure as described in example **31**.

A mixture of 2-(4-bromophenylsulfonyl)propionic acid ethyl ester (6.4 g, 20 mmol), 2-(tributylstannyl)furan (7.5 g, 21 mmol) and $(Ph_3P)_4Pd$ (500 mg) was refluxed in degassed tolune (250 mL) for 8 h. At the end, the reaction mixture was filtered through Celite and concentrated. The product was purified by silica gel column chromatography by eluting it with 50% ethyl acetate/hexane. Colorless oil. Yield: 5.9 g, 95%, MS, *m*/*z*: 309 $(M + H)^+$.

Following the procedure as outlined in example **31**, 2-(4-(2-furanylbenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionic acid ethyl ester was prepared, starting from (3.08 g, 10.0 mmol) of 2-(4-(2-furanylbenzenesulfonyl)propionic acid ethyl ester and the 4-(2-*N*,*N*-diethylaminoethoxy)benzyl chloride (3.5 g, 12.2 mmol). Yield: 5.0 g, 97%. Brown oil. MS, *m*/*z*: 514.6 $(M + H)^+$.

Starting from 2-(4-(2-furanylbenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionic acid ethyl ester (5.1 g, 10.0 mmol), 3.8 g (yield: 78%) of 2-(4-(2-furanylbenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)-phenyl]propionic acid was isolated as a colorless solid by following the procedure as outlined in example **28**. Mp 58 °C. MS, *m*/*z*: 486.5 $(M + H)^+$.

Starting from 2-(4-(2-furanylbenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionic acid (5.0 g, 10.3 mmol) and following the procedure as outlined in example **28**, 1.2 g of 2-(4-ethoxybenzenesulfonyl)-2-methyl-3-[4-(2-*N*,*N*-diethylaminoethoxy)phenyl]propionamide was isolated as colorless low-melting solid. Yield: 3.2 g, 62% (HCl salt). MS, *m*/*z*: 502 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 6H), 1.4 (s, 2H), 2.8 (q,4H), 3.0 (t, 2 H), 4.1 (t, 2H), 6.5−8.0 (m, 7H). Anal. ($C_{26}H_{32}N_2O_6S$·HCl) C, H, N.

5-Methyl-2-(3-methylbut-2-enyl)-2-(toluene-4-sulfonyl)-hex-4-enoic Acid Hydroxyamide (60). 5-Methyl-2-(3-methylbut-2-enyl)-2-(toluene-4-sulfonylhex-4-enoic acid ethyl ester was prepared according to the general method as outlined in example **28**, starting from ethyl α-(*p*-tolylsulfonyl)acetate (2.9 g, 10.9 mmol) and 4-bromo-2-methylbutene (3.42 g, 23 mmol). Yield: 4.6 g. Tan oil. MS, *m*/*z*: 379.2 $(M + H)^+$.

5-Methyl-2-(3-methylbut-2-enyl)-2-(toluene-4-sulfonyl)hex-4-enoic acid was prepared according to the general method as outlined in example **28**, starting from 5-methyl-2-(3-methylbut-2-enyl)-2-(toluene-4-sulfonylhex-4-enoic acid ethyl ester (4.5 g, 11 mmol), ethanol (15 mL), and 10 N sodium hydroxide.

Starting from 5-methyl-2-(3-methylbut-2-enyl)-2-(toluene-4-sulfonyl)hex-4-enoic acid (4.1 g, 11 mmol) and following the procedure as outlined in example **28**, 1.07 g of 5-methyl-2-(3-methylbut-2-enyl)-2-(toluene-4-sulfonyl)hex-4-enoic acid hydroxyamide was isolated as a colorless solid. Yield: 30%. Mp 108−110 °C. MS, *m*/*z*: 366.2 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.49 (s, 6H), 1.62 (s, 6H), 2.41 (s, 3H), 2.53−2.63 (m, 4H), 5.00−5.05 (t, 2H), 7.40−7.43 (d, 2H), 7.59−7.62 (d, 2H), 9.04 (s, 1H), 10.80 (s, 1H). Anal. ($C_{19}H_{27}NO_4S$) C, H, N.

***N*-Hydroxy-2-(4-methoxyphenylmethanesulfonyl)-2-methyl-3-phenylpropionic Acid Hydroxamide (61).** A mixture of 4-methoxybenzylmercaptan (7.0 g, 45 mmol), ethyl 2-bromopropionate (8.2 g, 46 mmol), and powdered oven-dried potassium carbonate (10 g, 72 mmol) in 150 mL of acetone was heated at reflux for 18 h. The mixture was cooled and filtered, and the filtrate was concentrated. The residue was taken up in 150 mL of methylene chloride, washed with water (150 mL), dried over anhydrous sodium sulfate, and evaporated to yield 12 g (99%) of a colorless liquid. MS, *m*/*z*: 255.1 $(M + H)^+$. This product is used without further purification.

To an ice-cold (5 °C) solution of 2-(4-methoxyphenylmethanesulfanyl)propionic acid ethyl ester (5.7 g, 21 mmol) in 100 mL of CH_2Cl_2 was added portionwise *m*-chloroperbenzoic acid (7.2 g, 40 mmol), and the mixture was stirred for 1 h. The reaction mixture was diluted with hexanes (500 mL) and stirred at 25 °C for 30 min at room temperature. The mixture was filtered, and the organic layer was treated with saturated aqueous sodium bisulfite (200 mL). The hexanes solution containing the product was washed with water, dried (Na_2SO_4), and concentrated. Yield: 5.5 g, 91%. Colorless oil. MS, *m*/*z*: 287.1 $(M + H)^+$.

Following the procedure as outlined in example **28**, 2-(4-methoxyphenylmethanesulfonyl)-2-methyl-3-phenylpropionic acid ethyl ester was prepared, starting from 2-(4-methoxyphenylmethanesulfonyl)propionic acid ethyl ester (2 g, 7 mmol) and benzyl bromide (1.3 g, 7.7 mmol). Yield: 3.0 g, 100%. Low-melting solid. MS, *m*/*z*: 377 $(M + H)^+$.

2-(4-Methoxyphenylmethanesulfonyl)-2-methyl-3-phenylpropionic acid was prepared starting from 2-(4-methoxyphenylmethanesulfonyl)-2-methyl-3-phenylpropionic acid ethyl ester (3.5 g, 9.0 mmol) dissolved in methanol (50 mL) and 10 N NaOH (30 mL). The resulting reaction mixture was worked up as outlined in example **28**. Yield: 930 mg, 31%. Colorless solid. Mp 106−108 °C. MS, *m*/*z*: 347 $(M - H)^+$.

Starting from 2-(4-methoxyphenylmethanesulfonyl)-2-methyl-3-phenylpropionic acid (2.7 g, 7.0 mmol) and following the procedure as outlined in example **28**, 266 mg of *N*-hydroxy-2-(4-methoxyphenylmethanesulfonyl)-2-methyl-3-phenylpropionic acid hydroxamide was isolated as light colorless solid. Yield: 10%. Mp 58−59 °C. MS, *m*/*z*: 364.2 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.28 (s, 3H), 2.84−2.88 (d, 1H), 3.75 (s, 3H), 3.81−3.86 (d, 1H), 4.59−4.63 (d, 1H), 4.69−4.74 (d, 1H), 6.94−6.98 (d, 2H), 7.19 (m, 2H), 7.29−7.33 (d, 4H), 9.24 (s, 1H), 10.88 (s, 1H). Anal. ($C_{18}H_{21}NO_5S$) C, H, N.

***N*-Hydroxy-2-methyl-2-(octane-1-sulfonyl)-3-phenylpropionamide (62).** 2-(Octane-1-sulfonyl)propionic acid ethyl ester was prepared according to the general method as outlined in example **31**, starting from 2-(octane-1-sulfonyl)propionic acid ethyl ester (6.39 g, 26 mmol) and sodium peroxymono-

persulfate (64 g, 104 mmol). Yield: 6.2 g, 86%. Colorless liquid. MS, *m/z*: 279 $(M + H)^+$.

2-Methyl-2-(octane-1-sulfonyl)-3-phenylpropionic acid ethyl ester was prepared according to the general method as outline in example **28**, starting from 2-(octane-1-sulfonyl)propionic acid ethyl ester (2.78 g, 10 mmol) and benzyl bromide (1.72 g, 10 mmol) to give 2.5 g (40% yield) of the product as a colorless oil. MS, *m/z*: 369 $(M + H)^+$.

2-Methyl-2-(octane-1-sulfonyl)-3-phenylpropionic acid was prepared according to the general method as outline in example **28**, starting from 2-methyl-2-(octane-1-sulfonyl)-3-phenylpropionic acid ethyl ester (3.68 g, 10 mmol), ethanol (15 mL), and 10 N sodium hydroxide (15 mL). Yield: 2.8 g, 82%. Colorless oil. MS, *m/z*: 357 $(M + NH_3)^+$.

Starting from 2-methyl-2-(octane-1-sulfonyl)-3-phenylpropionic acid (2.5 g, 7.0 mmol) and following the procedure as outlined in example **28**, 641 mg of *N*-hydroxy-2-methyl-2-(octane-1-sulfonyl)-3-phenylpropionamide was isolated as an amber-colored oil. Yield: 25%. MS, *m/z*: 356.0 $(M + H)^+$. Anal. ($C_{18}H_{29}NO_4S$) C, H, N.

2-(Octane-1-sulfonyl)-3-[4-(2-piperidinylethoxy)phenyl]-propionic Acid Hydroxamide (63). 2-(Octane-1-sulfonyl)-3-[4-(2-piperidin-ylethoxy)phenyl]propionic acid ethyl ester was prepared according to the general method as outlined in example **31**, starting from 2-(octane-1-sulfonyl)propionic acid ethyl ester (5.0 g, 18 mmol) and 1-[2-(4-chloromethylphenoxy)-ethyl]piperidine (5.6 g, 19.7 mmol). Yield: 8.9 g, 96%. Amber oil. MS, *m/z*: 495 $(M + H)^+$.

2-(Octane-1-sulfonyl)-3-[4-(2-piperidinylethoxy)phenyl]propionic acid was prepared according to the general method as outlined in example **28**, starting from 2-(octane-1-sulfonyl)-3-[4-(2-piperidinylethoxy)phenyl]propionic acid ethyl ester (8.9 g, 18 mmol), ethanol (25 mL), and 10 N sodium hydroxide (25 mL). Yield: 6.0 g, 72%.

Starting from 2-(octane-1-sulfonyl)-3-[4-(2-piperidinylethoxy)phenyl]propionic acid (3.6 g, 7.7 mmol) and following the procedure as outlined in example **28**, 3.3 g of 2-(octane-1-sulfonyl)-3-[4-(2-piperidinylethoxy)phenyl]propionic acid hydroxyamide was isolated as a tan solid. Yield: 89%. Mp 69−70 °C. MS, *m/z*: 483.2 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.687 (t, 3H), 1.27−1.69 (m, 15H), 2.73 (d, 1H), 3.51 (s, 3H), 3.67 (d, 1H), 6.88 (d, 2H), 7.10 (d, 2H), 9.16 (s, 1H), 10.70 (s, 1H). Anal. ($C_{25}H_{42}N_2O_5S$) C, H, N.

2-Methyl-3-phenyl-2-(thiophene-2-sulfonyl)propion-ic Acid Hydroxamide (64). 2-Methyl-3-phenyl-2-(thiophene-2-sulfonyl)propionic acid ethyl ester was prepared according to the general method as outlined in example **29**, starting from 2-(thiophen-2-sulfonyl)propionic acid ethyl ester (3.0 g, 12 mmol) and benzyl bromide (2.48 g, 15 mmol). Yield: 5.2 g. Tan oil. MS, *m/z*: 339.1 $(M + H)^+$.

2-Methyl-3-phenyl-2-(thiophene-2-sulfonyl)propionic acid was prepared according to the general method as outlined in example **28**, starting from 2-methyl-3-phenyl-2-(thiophen-2-sulfonyl)propionic acid ethyl ester (5.0 g, 15 mmol), ethanol (30 mL), and 10 N sodium hydroxide (10 mL). Yield: 5.6 g, MS, *m/z*: 310.0 $(M + H)^+$.

Starting from 2-methyl-3-phenyl-2-(thiophene-2-sulfonyl)-propionic acid (5.0 g, 16 mmol) and following the procedure as outlined in example **28**, 1.8 g of 2-methyl-3-phenyl-2-(thiophene-2-sulfonyl)propionic acid hydroxyamide was isolated as a colorless solid. Yield: 40%. Mp 116−117 °C. MS, *m/z*: 325.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (s, 3H), 3.33 (d, 1H), 3.69 (d 1H), 7.18−7.30 (m, 5H), 7.74 (m, 1H), 8.22 (m, 1H), 9.13 (s, 1H), 10.80 (s, 1H). Anal. ($C_{14}H_{15}NO_4S_2$) C, H, N.

2-Methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl-2-(thio-phene-2-sulfonyl)propionic Acid Hydroxamide (65). 2-Methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl-2-(thiophene-2-sulfonyl)propionic acid ethyl ester was prepared acording to the general method as outlined in example **31**, starting from 2-(thiophene-2-sulfonyl)propionic acid ethyl ester (prepared from 2-mercaptothiophene and 2-bromopropionic acid ethyl ester) (4.4 g, 17.7 mmol) and 1-[2-(4-chloromethylphenoxy)-ethyl]piperidine (5.3 g, 19.5 mmol). Yield: 96%. Semisolid. MS, *m/z*: 466 $(M + H)^+$.

2-Methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl-2-(thiophene-2-sulfonyl)propionic acid was prepared acording to the general method as outlined in example **28**, starting from 2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl-2-sulfonyl)propionic acid ethyl ester (9.8 g, 20 mmol) dissolved in ethanol (20 mL) and 10 N sodium hydroxide (20 mL). The resulting mixture was worked up as outline in example **1**. Yield: 4.5 g, 49%. White solid. Mp 170−172 °C. MS, *m/z*: 436.3 $(M - H)^-$.

Starting from 2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl-2-(thiophene-2-sulfonyl)propionic acid (3.6 g, 8.0 mmol) and following the procedure as outlined in example **28**, 345 mg of 2-methyl-3-[4-(2-piperidin-1-ylethoxy)phenyl-2-(thiophene-2-sulfonyl)propionic acid hydroxyamide was isolated as light colorless solid. Yield: 10%. Mp 115−118 °C. MS, *m/z*: 451.2 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (s, 3H), 1.66−1.78 (m, 6H), 2.85 (d, 1H), 2.96−3.99 (m, 4H), 3.39−3.47 (m, 2H), 3.55 (d, 1H), 4.32 (m, 2H), 6.73 (d 1H), 6.91 (d, 2H), 7.01−7.20 (m, 3H), 7.31−7.33 (m, 1H), 7.69−7.72 (m, 1H), 7.83−7.84 (m, 1H), 8.07−8.08 (dd, 1H), 8.17 (dd, 1H), 9.0 (s, 1H), 10.0 (s, 1H), 10.78 (s, 1H). Anal. ($C_{21}H_{28}N_2O_5S_2$) C, H, N.

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