Synthesis and Structure−Activity Relationships of 4-alkynyloxy Phenyl Sulfanyl, Sulfinyl, and Sulfonyl Alkyl Hydroxamates as Tumor Necrosis Factor-α Converting Enzyme and Matrix Metalloproteinase Inhibitors

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A series of 4-alkynyloxy phenyl sulfanyl, sulfinyl and sulfony alkyl and piperidine-4-carboxylic acid hydroxamides were synthesized. Their structure−activity relationships, against tumor necrosis factor-α (TACE) and matrix metalloproteinase (MMP) inhibitor activities, are presented by investigating the oxidation state on sulfur and altering the P1′ substituent. The sulfonyl derivatives **20**−**24** carrying a 4-butynyloxy moiety were selective TACE inhibitors over the MMPs tested. The sulfinyl derivatives showed a preference for a specific oxidation on sulfur as in compounds **25**−**28**. The selectivity over MMPs was also demonstrated in the sulfonyl series. The enhanced cellular activity was achieved upon incorporating a butynyloxy substituent in the piperidene series. Compounds **64** and **65** were potent inhibitors of TNF-α release in the mouse at 100 mg/kg po.

Introduction

Tumor necrosis factor α (TNF-α) converting enzyme (TACE, ADAM-17)[1−4] is a zinc-containing metalloproteinase that converts membrane-bound TNF-α to its soluble form. TNF-α exhibits a wide spectrum of biological activities in vitro and in vivo.[5] In inflammatory response, TNF-α initiates the up-regulation of adhesion molecules on endothelial cells, promotes migration of inflammatory cells, and triggers the local production of proinflammatory cytokines. In addition to this, Tracey et al.[6] showed that the intravenous administration of TNF-α in mice produced pathology similar to septic shock syndrome, causing vascular leakage, hypotension, and organ failure. TNF-α has also been implicated in the etiology of rheumatoid arthritis (RA), and agents that modulate TNF levels, such as Enbrel, a soluble TNF receptor, have been shown to be very effective in treating patients suffering from RA. Hence, small molecules that arrest the formation of soluble TNF-α by inhibiting TACE may be useful for the treatment of RA and other diseases mediated by TNF, including AIDS, graft rejection, diabetes, sepsis, and cancer.[7]

Another large family of closely related zinc-containing endopeptidases involved in the degradation of extracellular matrix and tissue remodeling are the matrix metalloproteinases (MMP's).[1−6,8−13] These enzymes are strictly controlled by endogenous MMP inhibitors such as α 2-macroglobulins and tissue inhibitors of MMPs (TIMPS). Overexpression of MMPs results in an imbalance between the activity of MMPs and TIMPS that can lead to various pathological disorders, including osteoarthritis (OA),[14a] angiogenesis,[14b] tumor metastasis,[15] artherosclerosis,[16] rheumatoid arthritis, emphysema, and central nervous system disorders. In our previous papers[17,18] we described the synthesis and optimization of α-sulfonyl hydroxamic acids, **1**, and *N*-substituted 4-aryl sulfonyl piperidine-4-hydroxamic acids, **2**, as novel and orally active matrix metalloproteinase inhibitors for the treatment of osteoarthritis (Figure 1).

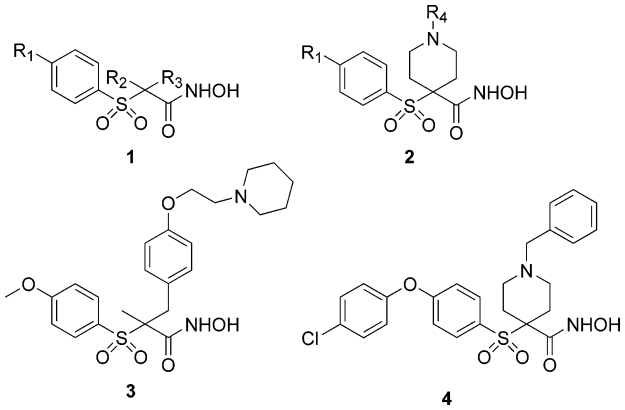

Figure 1. Structures of our previously reported MMP inhibitors.

These compounds exhibited excellent affinity for MMP-13. In particular, compounds **3** and **4** were found to be orally active in a short-term rabbit osteoarthritis model (Figure 1). It has been shown by an X-ray structure of compound **4**[18] bound to MMP-13 that the R_1 substituent of compounds of general structures **1** and **2** occupies the S1′ pocket of MMP-13. The different depths and shapes of the S1′ pockets of MMP-1, MMP-9, MMP-13, and TACE have been exploited by workers in this field to design MMP- or TACE-selective compounds.[19,20]

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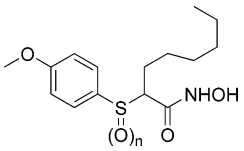
Table 1. In Vitro[a] IC_{50} (nM) Values of 2-(4-Methoxybenzene(sulfanyl, sulfinyl, and sulfonyl)octanoic Acid Hydroxamide



compd	*n*	MMP-1	MMP-9	MMP-13	TACE
9	0	9%[b]	67%[b]	55%[b]	87 ± 2
10	1-α[c]	1146 ± 14	186 ± 9	72 ± 6	30 ± 3
11	1-β[c]	1509 ± 12	148 ± 8	18 ± 3	375 ± 10
14	2	1310 ± 16	119 ± 6	12 ± 3	966 ± 6

[a] Inhibitor concentrations were run in triplicate. MMP and TACE IC_{50} determinations were calculated from a four-parameter logistic fit of the data within a single experiment. The final values given here are mean of the triplicate values of the sample. [b] Percent inhibition at 10 μM concentration, and the dose–response curves were not generated for compounds at <60% incubation at 10 μM concentration. [c] Stereochemistry at position 2 and 3; α = *RS* + *SR* for the faster moving isomer and the slower moving isomer β = *RR* + *SS* (SiO_2 gel coated plate, 250 μm, Analtech, Uniplate, 1:1 ethyl acetate:hexane as eluant).

The optimal MMP selectivity profile for a TACE inhibitor in the treatment of RA is unknown. Compounds that inhibit some MMPs as well as TACE may be more efficacious than an inhibitor of TACE alone, since MMPs are found to be overexpressed in RA joints. On the other hand, because both MMPs and TACE are involved in a number of normal physiological processes, selective inhibitors may present fewer side effects.[19a] It has been shown by Levin et al.[19] that the incorporation of a butynyloxy substituent at the P1′ position of anthranilic acid based inhibitors, as well as in other scaffolds, not only gives very potent inhibitors of isolated TACE enzyme but also increases activity in cells. The increase in TACE potency was rationalized due to the well fit match that exists between the S1′ pocket of the enzyme and the P1′ butynyloxy moiety. In all of our previous work on α-sulfonyl hydroxamic acid based MMP inhibitors, the inhibitor P1′ group was either an alkoxy or aryloxy moiety. During the course of our investigation of the SAR of the α-sulfonyl hydroxamate MMP/TACE inhibitors, we were interested in assessing the effect of the P1′ group and the sulfur oxidation state on the potency and selectivity of these compounds.

Chemistry

The octanoic acid hydroxamide derivatives **9**, **10**, **11**, and **14** (Table 1) were prepared starting from the reaction of 4-methoxy mercaptophenol **5** and 2-bromo ethyl octonoate **6** to give **7** (Scheme 1). The ester **7** was then hydrolyzed to the corresponding carboxylic acid **8**. This was then converted to hydroxamate **9** via the acid chloride and subsequent reaction with hydroxylamine hydrochloride/triethylamine. To prepare the sulfinyl derivatives **10** and **11**, compound **9** was oxidized with 30% hydrogen peroxide in methanol at room temperature. The resultant two diastereoisomers formed were separated by silica gel column chromatography.[21]

To prepare the corresponding sulfonyl derivative **14**, intermediate **7** was oxidized using oxone in methanol/THF at 0 °C and subsequently converted to hydroxamic acid **14** by the route depicted in Scheme 1. Compounds listed in Table 2 were prepared as shown in Scheme 1. Incorporation of the butynyloxy substituent at the P1′ position was achieved by reacting 4-hydroxythiophenol **15** with an appropriately substituted α-bromoethyl acetate, **16**, in chloroform solution at room temperature in the presence of triethylamine to yield **17**. This was O-alkylated with 1-bromo-2-butyne in the presence of K_2CO_3 in refluxing acetone. Subsequently, compound **18** was converted into the final products as described in Scheme 1.

Compounds **42**–**46** (Table 3) were prepared by reacting ethyl tetrahydro-4H-pyran-4-yl acetate **40a** (Y = O) or ethyl tetrahydro-4*H*-thiopyran-4-ylacetate **40b** (Y =S) or *tert*-butyl-4-(2-ethoxy-2-oxoethyl)-1-piperidinecarboxylate **40c** (Y = N-tBoc)[22] with 4-but-2-ynyloxybenzenesulfonyl fluoride in the presence of sodium bis(trimethylsilyl)amide at −78 to −15 °C (Scheme 2). Intermediate **41c** (where Y = N-tBoc) was reacted with ethanolic hydrogen chloride to yield **47** in almost quantitative yield, which was further utilized to prepare compounds **51**–**53** (Scheme 2).

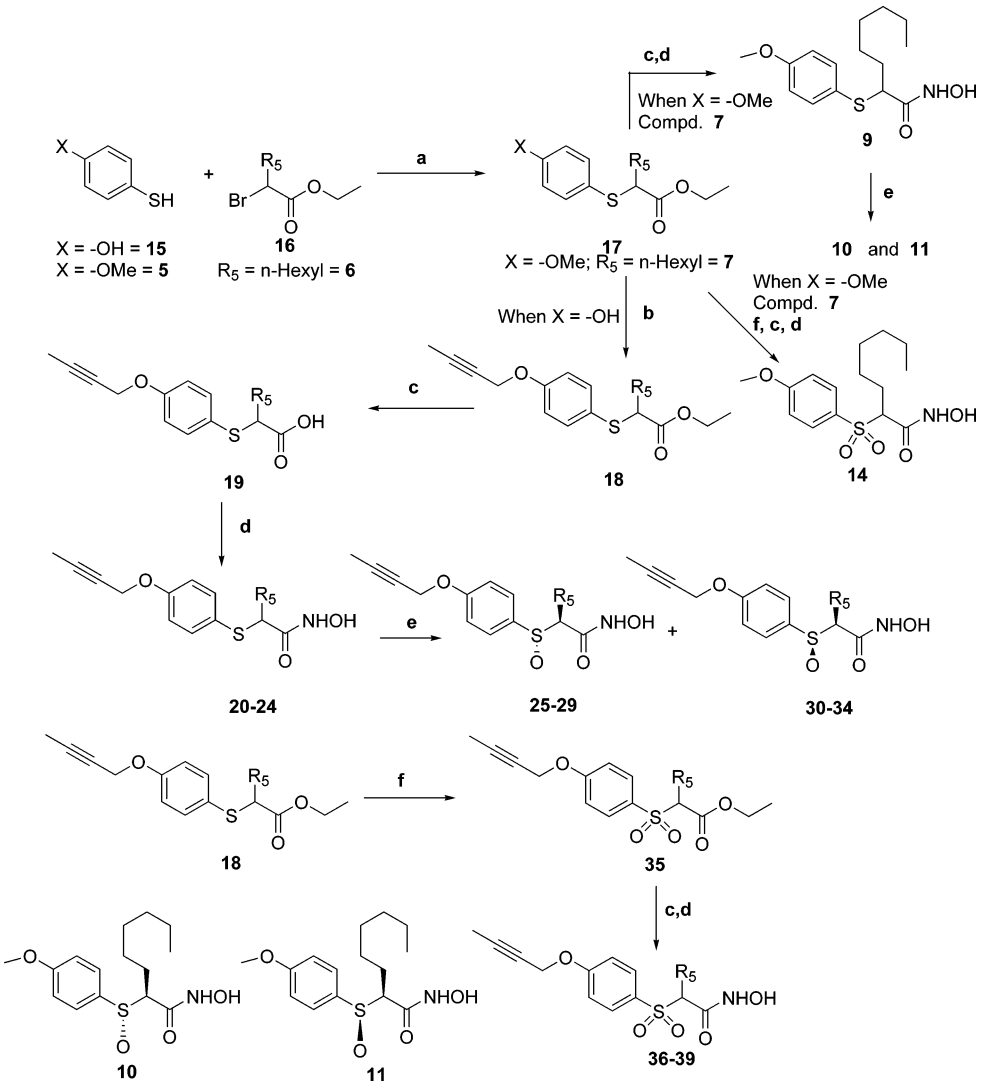
Intermediates **41a**, **41b**, and **41c** (where Y = O, S, or N-tBoc) were converted to hydroxamic acid derivatives **42**–**44**, as depicted in Scheme 2. Compound **44** (Y = N-tBoc) was converted to **46** via acid hydrolysis. Compound **43** (Y = S), when treated with 30% hydrogen peroxide in methanol at room temperature, yielded **45**. Compounds **58**–**66** were prepared from the intermediate **54** as shown in Scheme 3. To prepare compounds **59**, **62**, **64**, and **65** (Table 4) intermediate **54** was reacted with 1-bromo-2-butyne to yield **55**. (R_7 = CH_3). The latter was oxidized to the sulfone derivative **56** (R_7 =CH_3), which on reaction with *N*-substituted bis(2-chloroethyl)amine hydrochloride in the presence of K_2CO_3/18-crown-6 in boiling acetone yielded 4-(4-but-2-ynyloxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester **57** (R_7 = CH_3) in good yield. The ester obtained as above was subsequently converted to its corresponding carboxylic acid and then to the corresponding hydroxamic acid derivatives **59**, **62**, **64**, **65** (Scheme 3).

A similar sequence of reactions was carried out to prepare compounds **58**, **60**, **61**, and **63**, starting from the appropriately substituted derivatives. Compound **58** was further reacted with formalin and morpholine to yield **66** in good yield. Compounds **69** and **70** were prepared by the procedure outlined in Scheme 4. The key step for this tranformation was reaction of **67** with a diphenyl disulfide derivative in the presence of lithium diisopropylamide (LDA) at −78 °C.

Biology

All final hydroxamic acids were tested in vitro[23] for their ability to inhibit MMP-1, MMP-9, MMP-13, and TACE.[24] Inhibitors of MMP-9 are potentially valuable for arresting tumor metastasis,[25] while inhibiting MMP-13 may offer protection from the cartilage degradation associated with osteoarthritis.[26,17,18] As stated earlier, inhibitors of TACE are potentially valuable for the treatment of rheumatoid arthritis, Crohn's disease, and other inflammatory diseases.[27] After evaluating these compounds in a cell-free in vitro enzyme inhibition study, the most potent TACE active compounds were tested in an in vitro whole cell assay using human monocytic THP-1 cell.[28] In this assay, THP-1 cells were stimulated with lipopolysacharide (LPS) in the presence

Scheme 1. Preparation of Compounds **9**−**11**, **14**, **20**−**34**, and **36**−**39**[a]



[a] (a) $Et_3N/CHCl_3$/rt; (b) 1-bromo-2-butyne/K_2CO_3/acetone/reflux; (c) 1 N NaOH/THF/MeOH/H^+; (d) $(COCl)_2$/DMF/CH_2Cl_2/0 °C/$NH_2OH{\cdot}HCl/Et_3N$/THF; (e) H_2O_2/MeOH/rt; (f) oxone/MeOH/THF/0 °C−rt. Stereochemistry of the sulfinyl derivatives **10**, **11**, **25**−**34** reported here are only relative stereochemistry and the compounds are racemic. The less polar isomers (α) were assigned *SR* and the more polar isomers (*β*) *SS* stereochemistry.

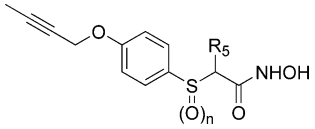
of the test compounds. After 4 and 24 h, soluble TNF-α was measured by an ELISA assay. The most potent inhibitors of TNF-α production were then tested in an in vivo lipopolysacharide (LPS) induced serum TNF-α model in mice. In this model the test compounds were administered to mice orally or ip. After 30 min, the animals were injected with LPS and 1 h later blood samples were drawn and TNF-α levels were measured and quantitated by ELISA.

Structure−Activity Relationships and Discussion

The in vitro potencies for a series of 2-(4-methoxybenzene sulfanyl, sulfinyl, and sulfonyl)octanoic acid hydroxamide derivatives **9**, **10**, **11**, and **14** are shown in Table 1. All four of these derivatives bear a methoxy group at the P1′ position. It is interesting to note that sulfanyl derivative **9** shows poor MMP inhibitory activity but good activity against isolated TACE enzyme. Contrary to this, the fully oxidized sulfone derivative**14** is a potent MMP-13 inhibitor and a poor TACE inhibitor. The partially oxidized sulfinyl derivatives **10** and **11** also show an interesting activity profile. The slower moving diastereoisomer, namely the *SS*,*RR* compounds **11**, shows potent MMP-13 activity and exhibit modest activity against TACE. However, the corresponding faster moving diastereoisomer, namely *SR*,*RS* compounds **10**, shows a reversal in potency. This isomer is almost 10 times more potent as a TACE inhibitor than **11**. Isomer **10** also shows good MMP-13 potency. This can be explained by modeling compounds **10** and **11** against TACE enzyme (Figures 2 and 3).[29] Compound **10** and **11** were both docked into the TACE protein structure via Monte Carlo simulation using the program FLO (1). For each ligand, 1000 cycles of Monte Carlo were performed. While most of the protein was held fixed during the docking, residues 348−350 as well as one crystal water (all others were removed from the structure prior to the simulation) were allowed to undergo movement subject to harmonic constraints; in addition, constraint bonds from His405, His409, and His415, respectively, to the Zn were specified.

The model for the more TACE active compound **10**, bound to TACE, shows the hydroxamate chelating the

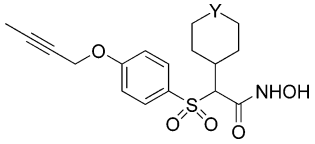
Table 2. In Vitro[a] IC_{50} (nM) Values of 2-Substituted-4-but-2-ynyloxyphenyl Sulfides, Sulfoxides, and Sulfones



compd	R_5	X[b]	*n*	MMP-1	MMP-9	MMP-13	TACE	THP (%)[c]
20	*n*-hexyl		0	>10 000	3000 ± 50	2000 ± 60	105 ± 5	5 ± 1
25	*n*-hexyl	α	1	3000 ± 70	1500 ± 60	900 ± 50	4 ± 1	67 ± 5
30	*n*-hexyl	*β*	1	3200 ± 80	1000 ± 40	150 ± 25	12 ± 3	35 ± 4
36	*n*-hexyl		2	>10 000	2500 ± 80	500 ± 30	75 ± 3	6 ± 4
21	isopropyl		0	>10 000	>10 000	>10 000	157 ± 5	13 ± 3
26	isopropyl	α + *β*	1	6480 ± 20	399 ± 6	216 ± 8	48 ± 3	29 ± 6
31	isopropyl		2	5141 ± 18	1262 ± 19	107 ± 5	17 ± 3	25 ± 6
22	phenyl		0	>10 000	>10 000	>10 000	50 ± 4	14 ± 5
27	phenyl	α	1	>10 000	>10 000	>10 000	28 ± 5	74 ± 5
32	phenyl	*β*	1	>10 000	>10 000	>10 000	74 ± 4	4 ± 2
37	phenyl		2	4567 ± 6	124 ± 5	68 ± 4	94 ± 6	68 ± 6
23	4-OMe-phenyl		0	>10 000	>10 000	>10 000	50 ± 3	3 ± 1
28	4-OMe-phenyl	α	1	>10 000	>10 000	>10 000	17 ± 4	13 ± 6
33	4-OMe-phenyl	*β*	1	>10 000	>10 000	>10 000	48 ± 2	12 ± 8
38	4-OMe-phenyl		2	>10 000	>10 000	3687 ± 20	201 ± 10	14 ± 7
24	cyclohexyl		0	>10 000	3000 ± 69	2000 ± 98	105 ± 5	5 ± 5
29 + **34**	cyclohexyl	α,*β*	1	1502 ± 20	336 ± 12	93 ± 8	52 ± 4	31 ± 6
39	cyclohexyl		2	>10 000	>10 000	708 ± 20	26 ± 4	39 ± 7

[a] Inhibitor concentrations were run in triplicate. MMP and TACE IC_{50} determinations were calculated from a four-parameter logistic fit of the data within a single experiment. The final values given here are mean of the triplicate values of the sample [b]Stereochemistry at position 2 and 3; α = *RS* + *SR* for the faster moving isomer and the slower moving isomer *β* = *RR* + *SS* (SiO_2 gel coated plate, 250 *μ*m, Analtech, Uniplate, 1:1 ethyl acetate:hexane as eluant). [c] Percent inhibition of TNF-α release at 3 *μ*M concentration of the inhibitors.

Table 3. In Vitro[a] IC_{50} (nM) Values of 2-Cycloalkyl Groups Having a Heteroatom-Substituted 4-But-2-ynyloxyphenyl Sulfone



compd	Y	MMP-1	MMP-9	MMP-13	TACE	THP (%)[b]
42	O	>10 000	>10 000	>10 000	51 ± 3	36 ± 3
43	S	>10 000	>10 000	>10 000	113 ± 6	15 ± 5
45	SdO	>10 000	>10 000	>10 000	39 ± 4	14 ± 6
46	NH	>10 000	>10 000	>10 000	299 ± 10	24 ± 5
44	N-tBoc	>10 000	>10 000	>10 000	190 ± 8	50 ± 3
51	N-acetyl	>10 000	>10 000	>10 000	119 ± 5	31 ± 3
52	N-COPh	>10 000	>10 000	>10 000	233 ± 10	28 ± 6
53	N-CO-cyclopropyl	>10 000	>10 000	>10 000	54 ± 4	71 ± 3

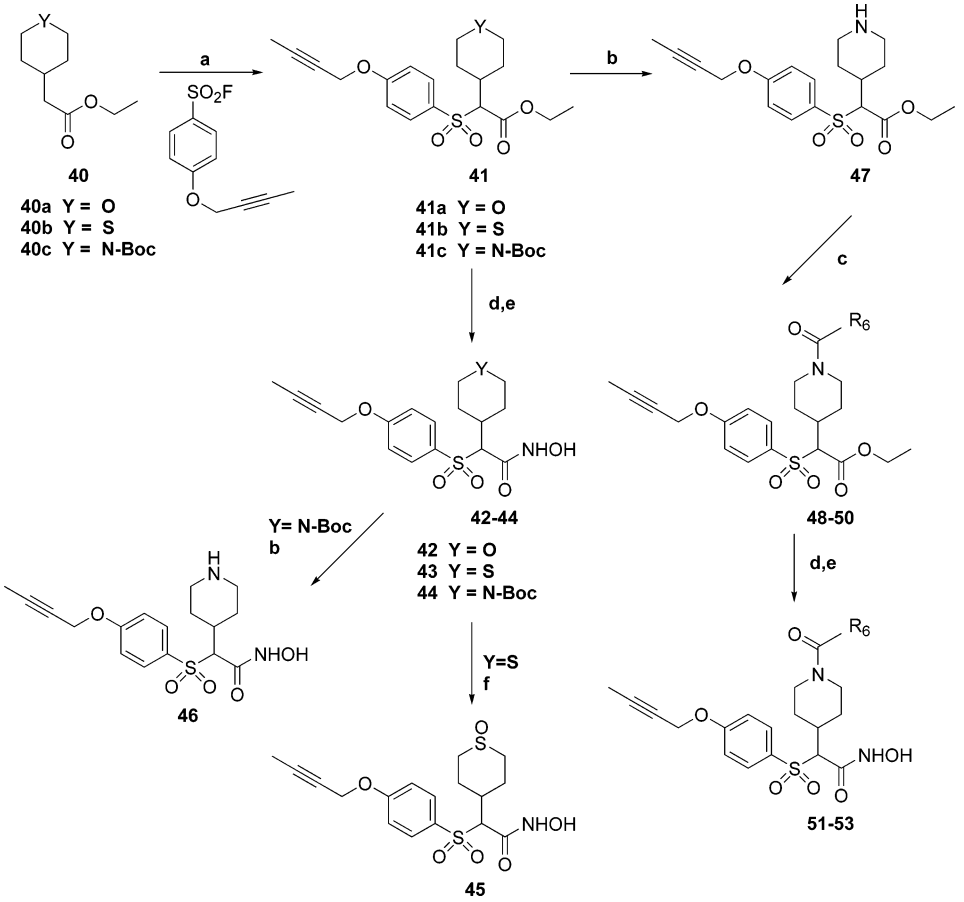
[a] Inhibitor concentrations were run in triplicate. MMP and TACE IC_{50} determinations were calculated from a four-parameter logistic fit of the data within a single experiment. The final values given here are mean of the triplicate values of the sample. [b] % Inhibition of TNF-α release at 3 *μ*M concentration of the inhibitors.

Zn, as expected (Figure 2). In addition, the sulfoxide is making a strong (very linear) hydrogen bond to the Gly348 amide nitrogen. In the model for the much less potent isomer **11**, this hydrogen bond is lacking (Figure 3). Furthermore, the phenyl ring is rotated, making less favorable interactions with the surface of the protein.

It is interesting to note that despite the fact that all these compounds bear a small methoxy substituent at the P1′ position, they all exhibit weak MMP-1 activity. Even though compounds **9** and **10** exhibited good TACE potency against isolated TACE enzyme, they turned out to be nearly active at 10 *μ*M concentration in the THP-1 whole cell assay. As mentioned earlier, it was shown by Levin et al.[19] that incorporation of a butynyloxy group as the P1′ substituent on the sulfonamide-based inhibitors not only increased the TACE potency but also improved the cell activity. Hence, in the present case, we decided to incorporate a butynyloxy substituent at the P1′ position of this class of molecules. The in vitro MMP/TACE activities of inhibitors bearing a butynyloxy P1′ moiety are tabulated in Table 2. Replacement of the methoxy functionality of compound **9** with a butynyloxy moiety (compound **20**) did not alter either MMP or TACE potency dramatically. However, in the case of the sulfinyl derivative **25** (faster moving diastereoisomer) the TACE in vitro potency improved dramatically and it exhibited a moderate cell activity.

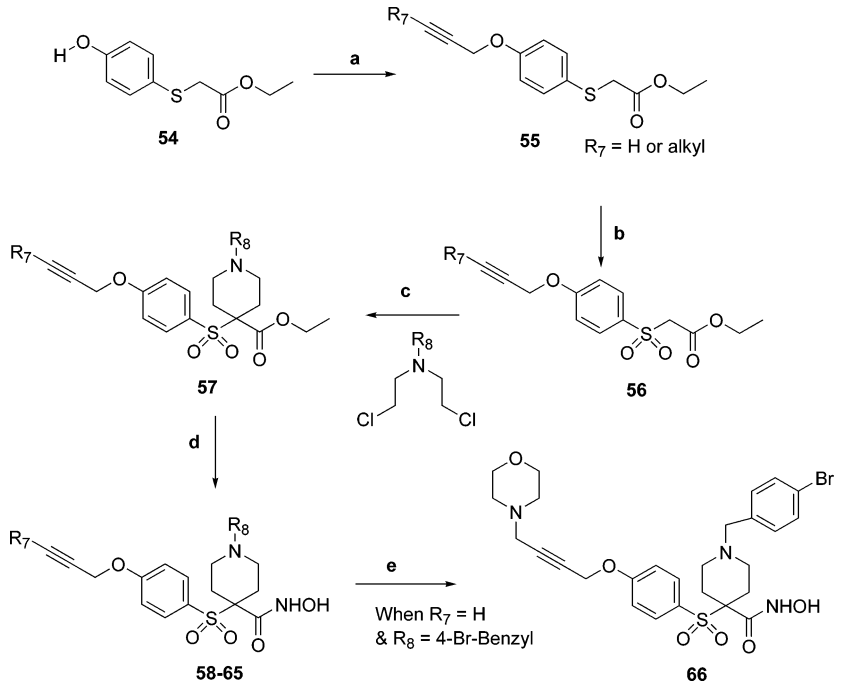
The slower moving sulfinyl derivative **30** had slightly reduced TACE potency both in vitro and in the whole cell when compared to its faster moving counterpart **25**. The corresponding sulfonyl derivative **36** is approximately 18 times less potent than **25** against TACE enzyme and exhibits poor MMP-13 inhibitory activity. The sulfanyl derivative **21** (R_5 = isopropyl) showed a very poor MMP activity and moderate inhibition of TACE enzyme. The sulfonyl derivative **31** shows good TACE inhibitory activity. A similar trend was observed when R_5 was cyclohexyl, as in compounds **24**, **29**, **34**,

Scheme 2. Preparation of Compounds **42**−**46** and **51**−**53**[a]



[a] (a) LDA/−78 °C; (b) HCl/EtOH/rt; (c) $Et_3N/CHCl_3/ClCOR_6$; (d) 1 N NaOH/THF/MeOH/H^+; (e) $(COCl)_2$/DMF/CH_2Cl_2/0 °C/NH_2OH·HCl/Et_3N/THF; (f) H_2O_2/MeOH/rt.

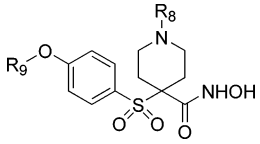
Scheme 3. Preparation of Compounds **58**−**66**[a]



[a] (a) Bromo-2-alkynes/K_2CO_3/acetone/reflux; (b) oxone/MeOH/THF/0 °C−rt; (c) acetone/K_2CO_3/18-crown-6/reflux (d) 1 N NaOH/THF/MeOH/H^+; $(COCl)_2$/DMF/CH_2Cl_2/0 °C/NH_2OH·HCl/Et_3N/THF; (e) formalin/morpholine/EtOH/H^+/reflux.

and **39**. When R_5 was phenyl or 4-methoxyphenyl, their corresponding sulfanyl derivatives (compounds **22** and **23**) were found to be highly selective TACE inhibitors. Also when R_5 = phenyl or 4-methoxyphenyl, the faster moving sulfinyl derivatives (compounds **28** and **22**) were found to be better TACE inhibitors than their corre-

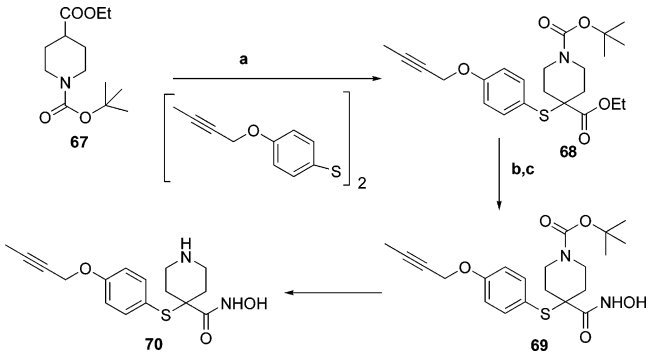
Table 4. In Vitro[a] IC_{50} Values of 1-Substituted-4-benzenesulfonylpiperidine-4-hydroxamic Acid Derivatives



compd	R_8	R_9	MMP-1	MMP-9	MMP-13	TACE	THP (%)[b]
70	4-bromobenzyl	Me	598 ± 14	10 ± 1	2.0 ± 1	72 ± 2	0
71	4-bromobenzyl	*n*-Bu	3963 ± 18	10 ± 1	5.0 ± 1	72 ± 2	6 ± 6
58	4-bromobenzyl	CH_2CCH	143 ± 13	6 ± 1	3.0 ± 1	98 ± 5	7 ± 3
59	4-bromobenzyl	CH_2CCCH_3	3372 ± 28	385 ± 6	155 ± 9	65 ± 3	46 ± 7
60	4-bromobenzyl	$CH_2CCCH_2CH_3$	51%[c]	41%[c]	40%[c]	188 ± 2	0
61	4-bromobenzyl	$CH_2CC(CH_2)_4CH_3$	33%[c]	59%[c]	60%[c]	393 ± 12	0
66	4-bromobenzyl	CH_2CCCH_2-morpholinyl	16%[c]	20%[c]	63%[c]	882 ± 23	0
62	benzyl	CH_2CCCH_3	2637 ± 6	148 ± 5	47 ± 3	90 ± 5	25 ± 4
63	benzyl	CH_2CCH	96 ± 3	18 ± 3	7.0 ± 1	69 ± 6	0
64	4-methoxybenzyl	CH_2CCCH_3	2573 ± 25	164 ± 8	40 ± 4	82 ± 6	68 ± 5
65	4-chlorobenzyl	CH_2CCCH_3	52%[c]	52%[c]	56%[a]	55 ± 2	66 ± 2
68			26%[c]	21%[c]	32%[c]	67%[c]	0
69			24%[c]	25%[c]	24%[c]	38%[c]	0
72	ethyl	CH_2CCCH_3	44%[c]	31%[c]	56%[c]	80 ± 4	35 ± 5

[a] Inhibitor concentrations were run in triplicate. MMP and TACE IC_{50} determinations were calculated from a four-parameter logistic fit of the data within a single experiment. The final values given here are mean of the triplicate values of the sample. [b] Percent inhibition of TNF-α release at 3 μM concentration of the inhibitors. [c] Percent inhibition at 10 μM concentration.

Scheme 4. Preparation of Compounds **69** and **70**[a]



[a] (a) LDA/−78 °C; (b) 10 N NaOH/THF:MeOH/rt/H^+; (c) $(COCl)_2$/DMF/CH_2Cl_2/0 °C/THF/Et_3N/NH_2OH·HCl.

sponding slower moving isomers (compounds **32** and **33**). To summarize the results in Table 2, the sulfanyl derivatives **20**−**24** exhibit good TACE in vitro activity and poor MMP inhibitory activity. In the case of the sulfinyl derivatives, the faster moving (*RS* or *SR*) isomers **25**−**28** showed better TACE activity than the corresponding slower moving *SS* or *RR* isomers. As can be seen in the Table 2, even though the faster moving sulfinyl derivatives are in general potent against cell-free TACE, they all show only moderate improvement in the THP-1 cell assay, when compared to their corresponding methoxy derivatives. Hence, in an effort to improve the THP cell activity by increasing the solubility of these molecules, several analogues (**42**−**46**, **51**−**53**) were prepared with an appended polar functionality. The in vitro activities of these molecules against TACE and MMP enzymes are tabulated in Table 3. One striking feature is that all of the compounds listed in Table 3 show poor MMP inhibitory activity and exhibit moderate TACE in vitro activity. Unfortunately, their THP-1 cell activity did not improve. In fact, except for compound **53**, all of the compounds listed in Table 3 show relatively weak cell activity. As

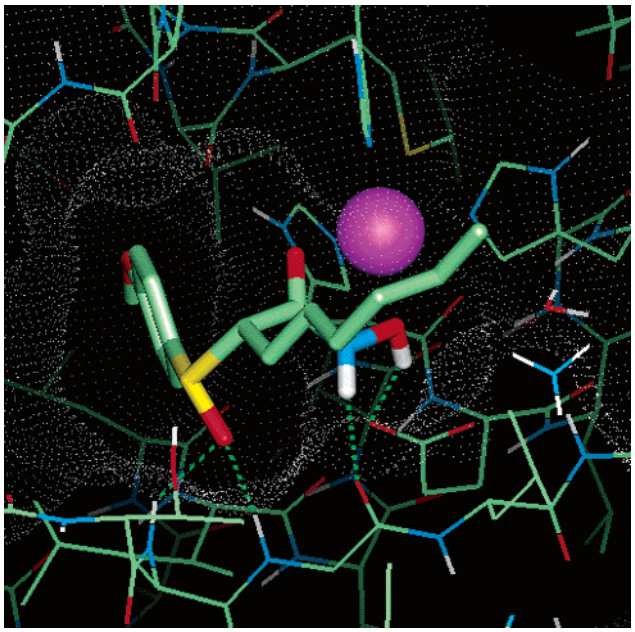


Figure 2. Models for compound **10** bound to the TACE protein. The molecular surface of the protein is shown in white, and atoms are colored by element. Zn is shown as a purple van der Waals sphere, and hydrogen bonds are depicted with bright green dashed lines. The figure was generated using Quanta (Accelrys, 2003, San Diego, CA).

we have mentioned before, MMP-13 inhibitor **4** (Figure 1) exhibited good in vitro and in vivo activity and had excellent oral bioavailability with an alkoxy and aryloxy P1′ substituent. Therefore, several alkynyloxy-substituted piperidine-4-carboxylic acid hydroxamide derivatives, **58**−**72**, were prepared. The in vitro potencies of these analogues against the MMP's and TACE enzymes are listed in Table 4. Compound **70** (R_8 = 4-bromobenzyl, R_9 = methyl) is a potent MMP-13 and MMP-9 inhibitor with a moderate selectivity over MMP-1 and moderate TACE enzyme inhibitory activity. Unfortunately, **70** does not show any THP-1 cell activity. Replacing the methoxy substituent with an *n*-butoxy or propargyl group at the P1′ position (compounds **71** and

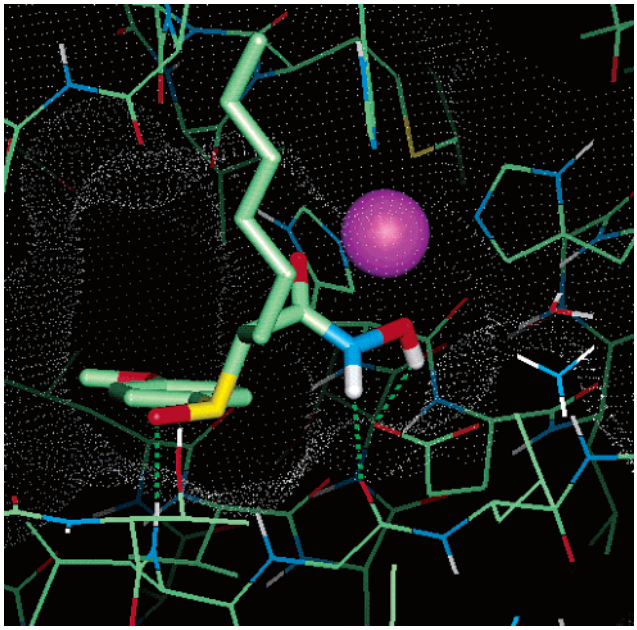


Figure 3. Models for compound **11** bound to the TACE protein. The molecular surface of the protein is shown in white, and atoms are colored by element. Zn is shown as a purple van der Waals sphere, and hydrogen bonds are depicted with bright green dashed lines. The figure was generated using Quanta (Accelrys, 2003, San Diego, CA).

58) increases MMP-13 selectivity over MMP-1 (only for compound **71**) but does not alter the TACE or MMP in vitro potency for both of these derivatives. However, incorporation of an *n*-butynyloxy group (compound **59**) at the P1′ position decreases potency against the MMP's without significantly diminishing TACE potency. Most importantly, this analogue shows enhanced THP-1 cell activity. Further extension of the *n*-butynyloxy group to five-carbon (**60**) or eight-carbon (**61**) analogues leads to a decrease in MMP and TACE potency. Incorporation of a basic amine functionality on the butynyloxy side chain (compound **66**) also led to a decrease in both TACE and MMP in vitro potency. The two compounds worth highlighting here are **64** and **65**. Both of these compounds show good selectivity over MMP-1 and are almost equipotent toward TACE enzyme. They also display good TNF-α release inhibition in the THP-1 cell cellular assay. To increase the basic nature of the amine, the *N*-ethyl compound **72** was prepared, and it exhibits mainly the TACE activity. This compound was cocrystallized with TACE enzyme (Figure 4). As anticipated, the hydroxamate chelates with the zinc atom, which is present at the active site and is surrounded by four histidine residues. The ethyl group is projecting in the solvent media. The butynyloxy moiety occupies the S1′ pocket. To investigate the effect of oxidation state on the sulfur of 1-substituted-4-benzene sulfonyl piperidine-4-hydroxamic acid derivatives **4** (Figure 1), compounds **69** and **70** have been prepared (Scheme 4). But these two compounds neither show MMP nor TACE activity in vitro.

Table 5. In Vivo % Inhibition of TNF-α Induced by LPS for Compounds **64** and **65** at 100 mg/kg po

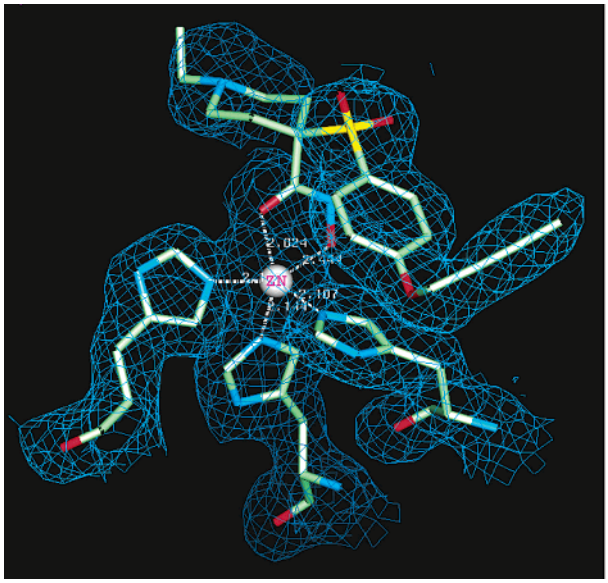
compd	at 1 h	at 12 h
64	91 ± 5	24 ± 6
65	61 ± 8	23 ± 9
TMI-1[a]	80 ± 4	NA

[a] For the structure of TMI-1, see ref 30. TMI-1 was dosed at 10 mg/kg po.

The most potent TACE compounds in terms of their in vitro activity and THP cell activity were tested at 100 mg/kg po in a mouse model of LPS-stimulated production of TNF-α. As indicated in Table 5, compounds **64** and **65** were found to be potent inhibitors of TNF-α production over a period of 12 h. However, when the dose was decreased to 10 mg/kg po, these compounds failed to inhibit LPS-induced TNF-α production in mice. In these experiments, TMI-1 was used as the standard.[30] It is evident from the Table 5 that compounds **64** and **65** were found to be less potent than TMI-1.

Conclusion

In summary, we have synthesized a series of 4-alkynyloxybenzene sulfonyl, sulfinyl, and sulfonyl hydroxamic acid derivatives, which are potent inhibitors of MMPs and TACE. It has been observed that both the



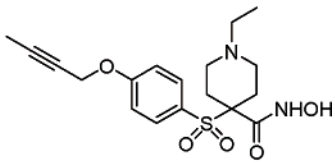


Figure 4. X-ray crystal structure of the TACE−compound **72** complex at 2.1 Å: $2F_o - F_c$ electron density map contoured at 1σ.

oxidation state on the sulfur and the choice of P1′ substituent dictate the potency, the selectivity, and to some extent the cellular activity in this class of molecules. The sulfanyl derivatives in general tend to offer greater TACE selectivity and the sulfonyl derivatives tend to have greater MMP inhibition. In the case of sulfinyl derivatives, the stereochemistry on the sulfur−oxygen bond steers the selectivity and potency either toward MMP or TACE selectivity. The presence of a buytynyloxy moiety at the P1′ position boosts the TACE in vitro and THP-1 cell activity.

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 (δ) 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 obtained on a Finnigen MAT-90 spectrometer. Combustion analyses were obtained using Perkin-Elmer Series II 2400 CHNS/O analyzer. The combustion analysis was conducted on the free base. 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. The stereochemistry of the sulfinyl derivatives reported in this paper is only relative stereochemistry. The sulfinyl compounds reported in this paper are racemic. The less polar isomers (α) were given *SR* stereochemistry and the more polar isomers (β) were given *SS* stereochemistry. All the compounds reported in this paper gave satisfactory spectral and microanalysis data.

Example 9. Preparation of 2-(4-Methoxybenzenesulfanyl)octanoic Acid Hydroxyamide 9. Step 1. To a stirred solution of 4-methoxythiophenol (6.0 g, 43 mmol) and triethylamine (20 mL, excess) in chloroform (200 mL) was added ethyl 2-bromooctanoate (11.8 g, 47.3 mmol) slowly in chloroform solution at room temperature. After the addition, the reaction mixture was stirred at room temperature for 1 h and quenched with water. The reaction mixture was washed well with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was pure enough for further transformations. Yield: 7.24 g, 57%, clear oil; MS: 311.2 $(M + H)^+$.

Step 2. To a stirred solution of 2-(4-methoxybenzenesulfanyl)octanoic acid ethyl ester (3.1 g, 10 mmol) in methanol:THF (1:1, 100 mL) was added 1 N NaOH (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 5 h and concentrated. To the residue was added ice cold water and the mixture was acidified with concentrated hydrochloric acid. 2-(4-Methoxybenzenesulfanyl)octanoic acid separated out as semisolid. This was extracted with chloroform, washed well with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was taken to the next step without any purification. Yield: 2.55 g, 90%. MS: 283 $(M + H)^+$.

Step 3. To a stirred solution of methylene chloride/DMF (150 mL/1 mL) and 2-(4-methoxybenzenesulfanyl)octanoic acid (4.25 g, 15 mmol) was added oxalyl chloride (3.24 g, 24.0 mmol) in methylene chloride (10 mL) dropwise at 0 °C. After the addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The acid chloride thus formed was concentrated to remove excess oxalyl chloride and redissolved in CH_2Cl_2 (30 mL). In a separate flask, hydroxylamine hydrochloride (3.78 g, 60 mmol) was dissolved in water (20 mL) and triethylamine (60 g, 60 mmol) was added. The reaction mixture was further diluted with acetonitrile (100 mL) and stirred at 0 °C for 1 h. The acid chloride was dissolved in methylene chloride (30 mL) and slowly added into the hydroxylamine/triethylamine mixture. After the addition was complete, reaction mixture was brought to room temperature and stirred for 24 h. The reaction mixture was concentrated and the residue was extracted with chloroform, washed well with water, and dried over anhydrous Na_2SO_4. The product was purified by silica gel column chromatography by eluting it with 50% ethyl acetate/hexane. 2-(4-Methoxybenzenesulfanyl)octanoic acid hydroxyamide was isolated as white solid. Yield: 3.6 g 76%.

Examples 10 and 11. Preparation of (2*S)-*N*-Hydroxy-2-[(*R**)-(4-methoxyphenyl)sulfinyl]octanamide 10 and (2*S**)-*N*-Hydroxy-2-[(*S**)-(4-methoxyphenyl)sulfinyl]octanamide 11.** To a stirred solution of 2-(4-methoxybenzenesulfanyl)octanoic acid hydroxyamide **9** (1.48 g, 4 mmol) in methanol/THF (3:1, 100 mL) was added 30% hydrogen peroxide (10 mL). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then quenched with water (200 mL), $NaHSO_3$ solution (10%, 30 mL) was added, and the mixture stirred for 1 h. The reaction mixture was extracted with chloroform and washed well with water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The separated semisolid was purified by silica gel column chromatography by eluting it with 50% ethyl acetate/hexane. The less polar isomer, namely, (2*S**)-*N*-hydroxy-2-[(*R**)-(4-methoxyphenyl)sulfinyl]octanamide **10**, was separated as white solid. Yield: 450 mg, 71%.

The more polar isomer, namely, (2*S**)-*N*-hydroxy-2-[(*S**)-(4-methoxyphenyl)sulfinyl]octanamide **11**, was separated as white solid. Yield: 360 mg, 57%.

Example 14. Preparation of 2-(4-Methoxybenzenesulfonyl)octanoic Acid Hydroxyamide 14. Step 1. To a stirred solution of 2-(4-Methoxybenzenesulfanyl)octanoic acid ethyl ester (3.11 g, 10 mmol) in methanol/THF (3:1, 200 mL) at 0 °C was added slowly Oxone (20 g, excess) dissolved in water (100 mL). The reaction mixture was stirred at room temperature for 5 h and filtered. The filtrate was concentrated and extracted with chloroform, washed well with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product, 2-(4-methoxybenzenesulfonyl)octanoic acid ethyl ester was taken to next step without any purification. Yield: 3.0 g, 87%. MS: $(M + H)^+$ 343.

Step 2. 2-(4-Methoxybenzenesulfonyl)octanoic acid was prepared according to the procedure outlined in example 9, step 2. Starting from 2-(4-methoxybenzenesulfonyl)octanoic acid ethyl ester (1.7 g, 5 mmol), 2-(4-methoxybenzenesulfonyl)-octanoic acid was isolated as a semisolid. Yield: 1.1 g, 70%. MS: 315 $(M + H)^+$.

Step 3. 2-(4-Methoxybenzenesulfonyl)octanoic acid hydroxamide was prepared according to the procedure outlined in example 9, step 3. Starting from 2-(4-methoxybenzenesulfonyl)octanoic acid (945 mg, 3 mmol) 2-(4-methoxybenzenesulfonyl)octanoic acid hydroxamide was purified by silica gel column chromatography by eluting it with 50% ethyl acetate/hexane to give a white solid. Yield: 700 mg, 71%.

Example 36. Preparation of 2-(4-But-2-ynyloxybenzenelsulfonyl)octanoic Acid Hydroxamide 36. Step 1. 2-(4-Hydroxyphenylsulfanyl)octanoic acid ethyl ester was prepared according to the general method outlined in example 9, step 1. Starting from 4-mercaptophenol (12.6 g 100 mmol) and 2-bromoethyl octonoate (25.2 g 100 mmol), 25 g of 2-(4-hydroxyphenylsulfanyl)octanoic acid ethyl ester was isolated as a colorless liquid. Yield: 84%. MS: 297 $(M + H)^+$.

Step 2. To a stirred solution of 2-(4-hydroxyphenylsulfanyl)-octanoic acid ethyl ester (13.6 g, 46 mmol) and anhydrous K_2-

CO_3 (30 g) in acetone (200 mL)was added 1-bromo-2-butyne (6.23 g, 47 mmol) slowly. The reaction mixture was refluxed for 6 h, cooled to room temperature, filtered, and concentrated. The residue was extracted with chloroform, washed well with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue obtained, namely, 2-(4-but-2-ynyloxyphenylsulfanyl)octanoic acid ethyl ester, was pure enough and taken to the next step without purification. Yield: 13.78 g, 86%, white oil. MS: 349.0 $(M + H)^+$.

Step 3. 2-(4-But-2-ynyloxybenzenesulfonyl)octanoic acid ethyl ester was prepared according to the general method outlined in example 14, step 1. Starting from 2-(4-but-2-ynyloxyphenylsulfanyl)octanoic acid ethyl ester (7.26 g, 21 mmol), 6.78 g of product was isolated. Yield: 85%), yellow oil. MS: 381.2 $(M + H)^+$.

Step 4. 2-(4-But-2-ynyloxybenzenesulfonyl)octanoic acid was prepared starting from 2-(4-but-2-ynyloxybenzenesulfonyl)octanoic acid ethyl ester (6.52 g, 17 mmol) dissolved in THF:methanol (100:50 mL) and 10 N NaOH (10 mL). The resulting reaction mixture was worked up as outlined in example 9, step 2. Yield: 2.42 g, 42%, colorless gum. MS: 352.9 $(M + H)^+$.

Step 5. Starting from 2-(4-but-2-ynyloxybenzenesulfonyl)-octanoic acid (2.21 g, 6 mmol) and following the procedure outlined in example 9, step 3, 270 mg of 2-(4-but-2-ynyloxybenzenesulfonyl)octanoic acid hydroxamide was isolated as a amber gum. Yield: 42%.

Example 20. Preparation of 2-(4-But-2-ynyloxyphenylsulfanyl)octanoic Acid Hydroxamide 20. Step 1. 2-(4-But-2-ynyloxyphenylsulfanyl)octanoic acid was prepared according to the general method outlined in example 9, step 2. Starting from 2-(4-but-2-ynyloxyphenylsulfanyl)octanoic acid ethyl ester (4.77 g, 13.7 mmol), 4.16 g of product was isolated. Yield: 96%. MS: 321.0 $(M + H)^+$.

Step 2. Starting from 2-(4-but-2-ynyloxyphenylsulfanyl)-octanoic acid (4.12 g, 12.9 mmol) and following the procedure outlined in example 9, step 3, 2.23 g of 2-(4-but-2-ynyloxyphenylsulfanyl)octanoic acid hydroxamide was isolated as a white solid. Yield: 73%.

Examples 25 and 30. Preparation of (*S*)-2-[(*R*)-4-But-2-ynyloxyphenylsulfinyl)octanoic Acid Hydroxamide 25 and (*S*)-2-[(*S*)-4-But-2-ynyloxyphenylsulfinyl)octanoic Acid Hydroxamide 30. 2-(4-But-2-ynyloxyphenylsulfanyl)-octanoic acid hydroxamide (prepared in example **20**, step 2) (1.78 g, 5 mmol) was dissolved in methanol (50 mL), and H_2O_2 (30%, 10 mL) was added. The reaction mixture was stirred at room temperature for 96 h and quenched with an ice-cold solution of $NaHSO_3$ solution. The reaction mixture was concentrated under reduced pressure and the residue was extracted with chloroform. Examination of the reaction mixture showed the formation of two diastereoisomers, and they were separated by silica gel column chromatography by eluting with 50:50 ethyl acetate:hexane. The faster moving isomer, namely, (*S*)-2-[(*R*)-4-but-2-ynyloxyphenylsulfinyl)octanoic acid hydroxamide, was isolated as a white solid. Yield: 210 mg, 24%.

The more polar isomer, namely, (*S*)-2-[(*S*)-4-but-2-ynyloxyphenylsulfinyl)octanoic acid hydroxamide, was isolated as a white solid. Yield: 0.356 g, 40%.

Example 21. Preparation of 2-{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-isopropyl-*N*-hydroxyacetamide 21. Step 1. Ethyl isopropyl [4-(hydroxyphenyl)sulfanyl]acetate was prepared according to the general method outlined in example 9, step 1, starting from ethyl 2-bromoisovalerate (2.09 g, 10 mmol) and 4-mercaptophenol (1.26 g, 10.0 mmol). The product was pure enough and taken for further transformations. Yield: 2.5 g, 99%, yellow oil. MS: 255 $(M + H)^+$.

Step 2. Ethyl-{[4-(2-butynyloxy)phenyl]sulfanyl}(isopropyl) acetate was prepared according to the general method outlined in example 36, step 2, starting from ethyl isopropyl [4-(hydroxyphenyl)sulfanyl]acetate (2.54 g, 10 mmol) and 4-bromo-2-butyne (1.34, 10 mmol). Yield: 3.0 g, 99%, yellow oil. MS (EI): 307 $(M + H)^+$.

Step 3. {[4-(2-Butynyloxy)phenyl]sulfanyl}(isopropyl)acetic acid was prepared according to the general method outlined in example 9, step 2, starting from ethyl-{[4-(2-butynyloxy)-phenyl]sulfanyl}(isopropyl) acetate (3.06 g, 10 mmol). Yield: 2.7 g, 99%, yellow oil. MS: 277 $(M - H)^-$.

Step 4. Starting from {[4-(2-butynyloxy)phenyl]sulfanyl}-(isopropyl)acetic acid (1.39 g, 5 mmol) and following the procedure outlined in example 9, step 3, 800 mg of 2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-isopropyl-*N*-hydroxyacetamide was isolated as a white powder. Yield: 54%.

Example 26. Preparation of (*S*)-2-[(*R*)-4-But-2-ynyloxyphenylsulfinyl)-2-isopropyl-*N*-hydroxyacetamide and (*S*)-2-[(*S*)-4-But-2-ynyloxyphenylsulfinyl)-2-isopropyl-*N*-hydroxyacetamide 26 (Mixture). Starting from 2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-isopropyl-*N*-hydroxyacetamide (1.45 g, 5 mmol) and following the procedure outlined in example 10, 123 mg of (*S*)-2-[(*R*)-4-but-2-ynyloxyphenylsulfinyl)-2-isopropyl-*N*-hydroxyacetamide **26** was isolated as a white solid. The two diastereoisomers could not be separated by silica gel column chromatography by eluting with 50:50 ethyl acetate: hexane. Yield: 255 mg, 16%.

Example 31. Preparation of 2-[4-(2-Butynyloxy)phenyl]sulfonyl}-2-isopropyl-*N*-hydroxyacetamide 31. Step 1. Starting from Ethyl-{[4-(2-butynyloxy)phenyl]sulfanyl}(isopropyl) acetate (1.530 g, 5 mmol) and following the procedure outlined in example 14, step 1, ethyl-{[4-(2-butynyloxy)phenyl]-sulfonyl}(isopropyl) acetate was isolated as oil. Yield: 1.3 g, 77%. MS: 339 $(M + H)^+$.

Step 2. Starting from ethyl-{[4-(2-butynyloxy)phenyl]sulfonyl}(isopropyl) acetate (1.69 g, 5 mmol) and following the procedure outlined in example 9, step 2, {[4-(2-butynyloxy)-phenyl]sulfonyl}(isopropyl)acetic acid was isolated as a semi-solid. Yield: 1.25 g, 81%. MS: 309 $(M - H)^-$.

Step 3. Starting from {[4-(2-butynyloxy)phenyl]sulfonyl}-(isopropyl)acetic acid (308 mg, 1 mmol) and following the procedure outlined in example 9, step 3, 2-{[4-(2-butynyloxy)-phenyl]sulfonyl}-2-isopropyl-*N*-hydroxyacetamide was isolated as a white solid. Yield: 159 mg, 49%.

Example 22. Preparation of 2-{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-phenyl-*N*-hydroxyacetamide. Step 1. Ethyl phenyl [4-(hydroxyphenyl)sulfanyl]acetate was prepared according to the general method outlined in example 9, step 1, starting from ethyl 2-bromophenylacetate (2.42 g, 10 mmol) and 4-mercaptophenol (1.26 g, 10.0 mmol). The product was pure enough and taken for further transformations. Yield: 2.7 g, 93%, yellow oil. MS: 289 $(M + H)^+$.

Step 2. Ethyl-{[4-(2-butynyloxy)phenyl]sulfanyl}(phenyl) acetate was prepared according to the general method outlined in example 36, step 2, starting from ethyl phenyl [4-(hydroxyphenyl)sulfanyl]acetate (2.88 g, 10 mmol) and 4-bromo-2-butyne (1.34, 10 mmol). Yield: 3.2 g, 94%, yellow oil. MS(EI): 341 $(M + H)^+$.

Step 3. {[4-(2-Butynyloxy)phenyl]sulfanyl}(phenyl)acetic acid was prepared according to the general method outlined in example 9, step 2, starting from ethyl-{[4-(2-butynyloxy)-phenyl]sulfanyl}(phenyl) acetate (3.4 g, 10 mmol). Yield: 3.0 g, 88%, yellow oil. MS: 311 $(M-H)^-$.

Step 4. Starting from {[4-(2-butynyloxy)phenyl]sulfanyl}-(phenyl)acetic acid (3.12 g, 10 mmol) and following the procedure outlined in example 9, step 3, 3.0 g of 2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-phenyl-*N*-hydroxyacetamide was isolated as a white powder.

Examples 27 and 32. Preparation of (*S*)-2-[(*R*)-4-but-2-ynyloxyphenylsulfinyl)-2-phenyl-*N*-hydroxyacetamide 27 and (*S*)-2-[(*S*)-4-but-2-ynyloxyphenylsulfinyl)-2-phenyl-*N*-hydroxyacetamide 32. Starting from 2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-phenyl-*N*-hydroxyacetamide (1.5 g, 4.5 mmol) and following the procedure outlined in example 10, 400 mg of (*S*)-2-[(*R*)-4-but-2-ynyloxyphenylsulfinyl)-2-phenyl-*N*-hydroxyacetamide **27** was isolated as a white solid. The two diastereoisomers were separated by silica gel column chromatography by eluting with 50:50 ethyl acetate:hexane. The faster moving isomer was **27**. Yield: 51%.

The slow moving isomer, namely, (*S*)-2-[(*S*)-4-but-2-ynyloxyphenylsulfinyl)-2-phenyl-*N*-hydroxyacetamide **32,** was isolated as white solid. Mp: 55 °C. Yield: 300 mg, 38%.

Example 37. Preparation of 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-2-phenyl-*N*-hydroxyacetamide 37. Step 1. Ethyl-{[4-(2-butynyloxy)phenyl]sulfonyl}(phenyl) acetate was prepared according to the general method outlined in example 14, step 1, starting from ethyl-{[4-(2-butynyloxy)phenyl]-sulfanyl}(phenyl) acetate (3.4 g, 10 mmol), and 3.0 g of the product was isolated as a yellow oil. Yield: 80%. MS (EI): 373 $(M + H)^+$.

Step 2. {[4-(2-Butynyloxy)phenyl]sulfonyl}(phenyl)acetic acid was prepared according to the general method outlined in example 9, step 2, starting from ethyl-{[4-(2-butynyloxy)-phenyl]sulfonyl}(phenyl) acetate (3.73 g, 10 mmol), and 3.0 g of the acid was isolated as a yellow oil. Yield: 87%. MS: 344 $(M - H)^-$.

Step 3. Starting from {[4-(2-butynyloxy)phenyl]sulfonyl}-(phenyl)acetic acid (3.45 g, 10 mmol) and following the procedure outlined in example 9, step 3, 2.2 g of 2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-phenyl-*N*-hydroxyacetamide was isolated as a white powder. Yield: 61%.

Example 23. Preparation of 2-{[4-(2-Butynyloxy)phenyl]sulfanyl}-*N*-hydroxy-2-(4-methoxyphenyl)acetamide 23. Step 1. Starting from ethyl bromo (4-methoxyphenyl) acetate (16.5 g, 60.4 mmol) and 4-mercaptophenol (7.63 g, 60.4 mmol) and following the procedure outlined in example 9, step 1, ethyl [(4-hydroxyphenyl)sulfanyl](4-methoxyphenyl) acetate was isolated as a yellow oil (15.82 g). Yield: 82%. MS: 317.2 $(M - H)^-$.

Step 2. Ethyl {[4-(2-butynyloxy)phenyl]sulfanyl}(4-methoxyphenyl) acetate was prepared according to the general method outlined in example 36, step 2, starting from ethyl [(4-hydroxyphenyl)sulfanyl](4-methoxyphenyl) acetate (15.82 g, 49.7 mmol) and 4-bromo-2-butyne (4.79 mL, 54.7 mmol). Yield: 17.66 g, 96%, yellow oil. MS (EI): 370.1 $(M + H)^+$.

Step 3. {[4-(2-Butynyloxy)phenyl]sulfanyl}(4-methoxyphenyl)acetic acid was prepared according to the general method outlined in example 9, step 2 (the hydrolysis was carried out at room temperature for 24 h), starting from ethyl {[4-(2-butynyloxy)phenyl]sulfanyl}(4-methoxyphenyl) acetate (10 g, 27 mmol). Yield: 5.78 g, 63%, yellow oil. MS: 341.2 $(M - H)^-$.

Step 4. Starting from {[4-(2-butynyloxy)phenyl]sulfanyl}-(4-methoxyphenyl)acetic acid (5.59 g, 16.3 mmol) and following the procedure outlined in example 9, step 3, 450 mg of 2-{[4-(2-butynyloxy)phenyl]sulfanyl}-*N*-hydroxy-2-(4-methoxyphenyl) acetamide was isolated as a white solid. Yield: 8%.

Examples 28 and 33. Preparation of (*S*)-2-[(*R*)-4-But-2-ynyloxyphenylsulfinyl)-2-(4-methoxyphenyl)-*N*-hydroxyacetamide 28 and (*S*)-2-[(*S*)-4-but-2-ynyloxyphenylsulfinyl)-2-(4-methoxyphenyl)-*N*-hydroxyacetamide 33. Starting from 2-{[4-(2-butynyloxy)phenyl]sulfanyl}-*N*-hydroxy-2-(4-methoxyphenyl)acetamide (prepared in example 76) (340 mg, 0.95 mmol) and following the procedure outlined in example 7 gave a mixture of two diastereoisomers that was separated by silica gel column chromatography by eluting with 50:50 ethyl acetate:hexane. The faster moving isomer, namely, (*S*)-2-[(*R*)-4-but-2-ynyloxyphenylsulfinyl)-2-(4-methoxyphenyl)-*N*-hydroxyaceta mide **28**, was isolated as a white powder. Yield: 49.0 mg, 14%.

The slower moving isomer, namely, (*S*)-2-[(*S*)-4-but-2-ynyloxyphenylsulfinyl)-2-(4-methoxyphenyl)-*N*-hydroxyacetamide **33**, was isolated as a white powder. Mp: 134 °C. Yield: 39 mg, 10%.

Example 38. Preparation of 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-*N*-hydroxy-2-(4-methoxyphenyl)acetamide 38. Step 1. Ethyl-{[4-(2-butynyloxy)phenyl]sulfonyl}(4-methoxyphenyl) acetate was prepared according to the general method outlined in example 14, step 1, starting from ethyl-{[4-(2-butynyloxy)(phenyl)]sulfanyl}(4-methoxyphenyl) acetate (3.7 g, 10 mmol). Yellow oil. Yield: 3.2 g, 86%. MS (EI): 403 $(M + H)^+$.

Step 2. {[4-(2-Butynyloxy)phenyl]sulfonyl}(4-methoxyphenyl)acetic acid was prepared according to the general method outlined in example 9, step 2, starting from ethyl-{[4-(2-butynyloxy)phenyl]sulfonyl}(4-methoxyphenyl) acetate (4.02 g, 10 mmol), and 3.3 g of the acid was isolated as a yellow oil. Yield: 88%. MS: 373 $(M-H)^-$.

Step 3. Starting from {[4-(2-butynyloxy)phenyl]sulfonyl}-(4-methoxyphenyl)acetic acid (3.73 g, 10 mmol) and following the procedure outlined in example 9, step 3, 1.8 g of 2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-phenyl-*N*-hydroxyacetamide was isolated as a white powder. Yield: 46%.

Example 24. Preparation of 2-{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-cyclohexyl-*N*-hydroxyacetamide 24. Step 1. To a solution of cyclohexylacetic acid (10 g, 70 mmol), in 100 mL of CCl_4 was added red phosphorus (6.32 g, 204 mmol). The mixture was heated to reflux and bromine (70.7 mL, 1.38 mmol) was added over 3 h dropwise through the condenser via an addition funnel. The reaction was heated at reflux for 5 h before it was quenched slowly with water and then washed with 10% Na_2SO_4, water, and then into $NaHCO_3$. The sodium bicarbonate solution was made acidic using 1 N HCl. The solid was collected, and the aqueous filtrate was extracted into $CHCl_3$ and washed with saturated Na_2HSO_4 solution and then with water. The organic layer was dried over Na_2SO_4, filtered, concentrated, and combined with solid collected earlier to provide 3.22 g of 2-bromo cyclohexylacetic acid as a white solid. Yield: 21%. MS: 219.1 $(M - H)^-$.

Step 2. Ethyl cyclohexyl [4-(hydroxyphenyl)sulfanyl]acetic acid was prepared according to the general method outlined in example 9, step 1, starting from 2-bromo cyclohexylacetic acid (3.08 g, 13.9 mmol) and 4-mercaptophenol (2 g, 14.2 mmol). The product was pure enough and taken for further transformations. Yield: 3.10 g, 84%, yellow oil. MS: 265 $(M + H)^+$.

Step 3. To a solution of ethyl cyclohexyl [4-(hydroxyphenyl)-sulfanyl]acetic acid (3.1 g, 11.65 mmol) in 100 mL of ethanol was added 1 mL of sulfuric acid. The mixture was heated at reflux overnight and then concentrated, extracted with methylene chloride, and washed first with saturated $NaHCO_3$ solution and then with water. The organic layer was dried over Na_2SO_4, filtered over Magnesol, and concentrated to provide 1.22 g of ethyl cyclohexyl [4-(hydroxyphenyl)sulfanyl] acetate as a yellow oil. Yield: 35%. MS: 295.4 $(M + H)^+$.

Step 4. Ethyl-{[4-(2-butynyloxy)phenyl]sulfanyl}(cyclohexyl) acetate was prepared according to the general method outlined in example 36, step 2, starting from ethyl cyclohexyl [4-(hydroxyphenyl)sulfanyl] acetate (1 g, 3.4 mmol) and 4-bromo-2-butyne (0.32 mL, 3.7 mmol). Yield: 1.25 g, 100%, yellow oil. MS (EI): 346.1 $(M + H)^+$.

Step 5. {[4-(2-Butynyloxy)phenyl]sulfanyl}(cyclohexyl)acetic acid was prepared according to the general method outlined in example 9, step 2, starting from ethyl-{[4-(2-butynyloxy)-phenyl]sulfanyl}(cyclohexyl) acetate (1.2 g, 3.47 mmol). Yield: 1.19 g, 100%, yellow oil. MS: 317.4 $(M-H)^-$.

Step 6. Starting from {[4-(2-butynyloxy)phenyl]sulfanyl}(cyclohexyl)acetic acid and following the procedure outlined in example 9, step 3, 672 mg of 2-{[4-(2-butynyloxy)phenyl]-sulfanyl}-2-cyclohexyl-*N*-hydroxyacetamide was isolated as a white powder. Yield: 75%.

Examples 29 and 34. Preparation of (*S* or *R*)-2-[(*S* or *R*)-4-But-2-ynyloxyphenylsulfinyl)-2-cyclohexyl-*N*-hydroxyacetamides 29 and 34. Starting from 2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-cyclohexyl-*N*-hydroxyacetamide (580 mg, 1.74 mmol) and following the procedure outlined in example 10, 230 mg of 2-{[4-(2-butynyloxy)phenyl]sulfinyl}-2-cyclohexyl-*N*-hydroxyacetamide was isolated as a white solid. Yield: 38%.

Example 39. Preparation of 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-2-cyclohexyl-*N*-hydroxyacetamide 39. To a stirred solution of 2-{[4-(2-butynyloxy)phenyl]sulfinyl}-2-cyclohexyl-*N*-hydroxyacetamide (180 mg, 0.52 mmol) in MeOH/THF at room temperature, oxone (5.0 g, excess) was added in water (20 mL). The reaction mixture was stirred at room temperature for 6 h and filtered. The methanol−THF layer

was concentrated and extracted with chloroform. The organic layer was washed well with water, dried, filtered, and concentrated. The product was purified by silica gel column chromatography by eluting with 4:1 ethyl acetate: hexane, and 2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-cyclohexyl-*N*-hydroxyacetamide was isolated as a white solid. Yield: 45 mg, 24%.

Example 44. Preparation of *tert*-Butyl 4-[1-{[4-(2-Butynyloxy)phenyl]sulfonyl}-2-(hydroxyamino)-2-oxoethyl]-1-piperidinecarboxylate 44. *tert*-Butyl 4-(2-ethoxy-2-oxoethyl)-1-piperidinecarboxylate **40c** was made according to the literature procedure from Ashwood et al.[22] in two steps starting from *N*-*tert*-butoxycarbonyl-4-piperidone. Yield: 4.69 g, 95% (over two steps), clear oil. MS: 272.2 $(M + H)^+$.

Step 1. *tert*-Butyl 4-(1-{[4-(2-Butynyloxy)phenyl]sulfonyl}-2-ethoxy-2-oxoethyl)-1-piperidinecarboxylate 41c. Sodium bis(trimethylsilyl)amide (7.05 g, 38 mmol) was added to a dried flask under nitrogen. THF (100 mL) was added slowly and the temperature was lowered to −15 °C. *tert*-Butyl 4-(2-ethoxy-2-oxoethyl)-1-piperidinecarboxylate (4.6 g, 16.97 mmol) and 4-but-2-ynyl oxybenzenesulfonyl fluoride (preparation given below) (4.08 g, 17.9 mmol) were combined in THF (50 mL) and added dropwise to the mixture, the temperature of the reaction being maintained below −15 °C. The mixture stirred at −10 °C for 1.5 h before it was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and then dried over Na_2SO_4, filtered, and concentrated. *tert*-Butyl 4-(1-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-ethoxy-2-oxoethyl)-1-piperidinecarboxylate was isolated using silica gel column chromatography by eluting with 20:80 ethyl acetate:hexane solution. Yield: 3.74 g, 46%, clear gel. MS: 480.2 $(M + H)^+$.

Step 2. [1-(*tert*-Butoxycarbonyl)-4-piperidinyl]{[4-(2-butynyloxy)phenyl]sulfonyl}acetic acid was prepared according to the general method outlined in example 9, step 2, starting from *tert*-butyl-4-(1-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-ethoxy-2-oxoethyl)-1-piperidinecarboxylate (2.5 g, 5.2 mmol). Yield: 1.85 g, 79, low-melting yellow solid. MS: 450.3 $(M - H)^-$.

Step 3. Starting from [1-(*tert*-butoxycarbonyl)-4-piperidinyl]-{[4-(2-butynyloxy)phenyl]sulfonyl}acetic acid (1.75 g, 3.88 mmol) and following the procedure outlined in example 9, step 3, 283 mg of *tert*-butyl 4-[1-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(hydroxyamino)-2-oxoethyl]-1-piperidinecarboxylate was isolated as a white solid. Yield: 16%.

Preparation of 4-But-2-ynyloxybenzenesulfonyl Fluoride. To a stirred solution of 4-but-2-ynyloxybenzenesulfonyl chloride (2.0 g, 8.18 mmol) in acetonitrile (10 mL) was added a fused potassium fluoride−calcium fluoride mixture and the reaction stirred at 50 °C for 4 h. The reaction mixture was concentrated, dissolved in dichloromethane, and passed through a pad of Celite. The organic layer was concentrated to obtain 1.5 g (80%) of the product as a white solid.[31]

Example 46. Preparation of 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-*N*-hydroxy-2-(4-piperidinyl)acetamide HCl. 46. *tert*-butyl 4-[1-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(hydroxy amino)-2-oxoethyl]-1-piperidinecarboxylate (160 mg, 0.34 mmol) was dissolved in methanolic HCl (50 mL) and allowed to stir at room temperature for 1 h. The mixture was concentrated and the separated solid was triturated with dichloromethane and filtered. After overnight drying at 60 °C, 80 mg of 2-{[4-(2-butynyloxy)phenyl]sulfonyl}-*N*-hydroxy-2-(4-piperidinyl)acetamide was isolated as a pink powder. Yield: 59%.

Example 52. Preparation of 2-(1-Benzoyl-4-piperidinyl)-2-{[4-(2-butynyloxy)phenyl]sulfonyl}-*N*-hydroxyacetamide 52. Step 1. Ethyl (1-Benzoyl-4-piperidinyl){[4-(2-butynyloxy)phenyl]sulfonyl}acetate. To a solution of ethyl {[4-(2-butynyloxy)phenyl]sulfonyl}(4-piperidinyl)acetate (2 g, 4.8 mmol) in methylene chloride (100 mL) in an ice water bath was added triethylamine (1.34 mL, 9.6 mmol). Benzoyl chloride (0.56 mL, 4.8 mmol) was added dropwise to keep the temperature at 0 °C. The mixture was warmed to room temperature and stirred overnight before it was concentrated. The residue was extracted with chloroform and washed twice with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Ethyl (1-benzoyl-4-piperidinyl){[4-(2-butynyloxy)phenyl]sulfonyl}acetate was isolated using silica gel column chromatography by eluting with 50:50 ethyl acetate: hexane. Mp: 120 °C. Yield: 1.8 g, 72% yellow solid. MS: 484.1 $(M + H)^+$.

Step 2. (1-Benzoyl-4-piperidinyl){[4-(2-butynyloxy)phenyl]-sulfonyl}acetic acid was prepared according to the general method outlined in example 9, step 2, starting from ethyl (1-benzoyl-4-piperidinyl){[4-(2-butynyloxy)phenyl]sulfonyl}acetate (1.39 g, 2.88 mmol). Mp: 90 °C. Yield: 1.3 g, 99%, white solid. MS: 456.1 $(M + H)^+$.

Step 3. Starting from (1-benzoyl-4-piperidinyl){[4-(2-butynyloxy)phenyl]sulfonyl}acetic acid (1.22 g, 2.68 mmol) and following the procedure outlined in example 9, step 3, 860 mg of 2-(1-benzoyl-4-piperidinyl)-2-{[4-(2-butynyloxy)phenyl]sulfonyl}-*N*-hydroxyacetamide was isolated as a white powder. Yield: 68%.

Example 51. Preparation of 2-(1-Acetyl-4-piperidinyl)-2-{[4-(2-butynyloxy)phenyl]sulfonyl}-*N*-hydroxyacetamide 51. Step 1. Ethyl (1-acetyl-4-piperidinyl){[4-(2-butynyloxy)phenyl]sulfonyl}acetate was prepared according to the general method outlined in example 52, step 1, starting from ethyl {[4-(2-butynyloxy)phenyl]sulfonyl}(4-piperidinyl)acetate (1.5 g, 3.61 mmol) and acetyl chloride (0.26 mL, 3.61 mmol). Yield: 1.35 g, 89%, yellow oil. MS: 422 $(M + H)^+$.

Step 2. (1-Acetyl-4-piperidinyl){[4-(2-butynyloxy)phenyl]-sulfonyl}acetic acid was prepared according to the general method outlined in example 52, step 2, starting from ethyl (1-acetyl-4-piperidinyl){[4-(2-butynyloxy)phenyl]sulfonyl}-acetate (1.23 g, 2.92 mmol). Yield: 400 mg, 35%, white gel. MS: 391.9 $(M - H)^-$.

Step 3. Starting from (1-acetyl-4-piperidinyl){[4-(2-butynyloxy)phenyl]sulfonyl}acetic acid (290 mg, 0.74 mmol) and following the procedure outlined in example 9, step 3, 60 mg of 2-(1-acetyl-4-piperidinyl)-2-{[4-(2-butynyloxy)phenyl]sulfonyl}-*N*-hydroxyacetamide was isolated as an off white powder. Yield: 20%.

Example 42. Preparation of 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-*N*-hydroxy-2-tetrahydro-2*H*-pyran-4-ylacetamide 42. Step 1. Ethyltetrahydro-4*H*-pyran-4-ylideneacetate was prepared from tetrahydropyran-4-one (9.0 g 90 mmol) and ethyl diethylphosphonoacetate (20.16 g, 90 mmol) in DMF/K_2CO_3 at 80 °C as a colorless oil. Yield: 16.3 g, 96%. MS: 171 $(M + H)^+$.

Step 2. Ethyl tetrahydro-4*H*-pyran-4-ylacetate was prepared from ethyl tetrahydro-4*H*-pyran-4-ylideneacetate (16.0 g, 94 mmol) and Pd/NH_4COOH at 80 °C as a colorless oil. Yield: 16.3 g, quantitaive). MS: 173.2 $(M + H)^+$.

Step 3. 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}(tetrahydro-2H-pyran-4-yl)ethyl acetate was prepared according to the general method outlined in example 44, step 1. Starting from ethyl tetrahydro-4*H*-pyran-4-ylacetate (4.0 g, 23.3 mmol) and 4-but-2-ynyloxybenzenesulfonyl fluoride (7.1 g, 26.0 mmol), 7 0 g of product was isolated as a yellow oil. Product was purified by silica gel column chromatography by eluting with 50:50 ethyl acetate:hexane. Yield: 89%. MS: 381 $(M + H)^+$.

Step 4. 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}(tetrahydro-2*H*-pyran-4-yl)acetic acid was prepared according to the general method outlined in example 9, step 2. Starting from 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}(tetrahydro-2*H*-pyran-4-yl)ethyl acetate (7.0 g, 18.4 mmol), 6.1 g of product was isolated. Yield: quantitative. MS: 351.4 $(M - H)^+$.

Step 5. 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-*N*-hydroxy-2-tetrahydro-2*H*-pyran-4-ylacetamide was prepared according to the general method outlined in example 9, step 3. Starting from 2-{[4-(2-butynyloxy)phenyl]sulfonyl}(tetrahydro-2*H*-pyran-4-yl)acetic acid (4.0 g, 11.4 mmol), 3.4 g of the product was isolated. The product was purified by silica gel column chromatography by eluting with 75:25 ethyl acetate:hexane. Yield: 84%, white solid.

Example 43. Preparation of 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-*N*-hydroxy-2-tetrahydro-2*H*-thiopyran-4-ylacetamide 43. Step 1. Ethyl tetrahydro-4*H*-thiopyran-4-ylideneacetate was prepared from tetrahydrothiopyran-4-one (10.0

g 86 mmol) and ethyl diethylphosphonoacetate (21.2 g, 95 mmol) in DMF/K_2CO_3 at 80 °C as a colorless oil. Yield. 15.4 g, 96%. MS: 187 $(M + H)^+$.

Step 2. Ethyl tetrahydro-4*H*-thiopyran-4-ylacetate was prepared from ethyl tetrahydro-4*H*-thiopyran-4-ylideneacetate (8.0 g, 43 mmol), $NaBH_4$ (8.2 g, 5equiv), and $NiCl_2$ (5.0 g) at 0 °C for 1 h as a colorless oil. Yield: 8.1 g (quantitaive). MS: 189 $(M + H)^+$.

Step 3. 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}(tetrahydro-4*H*-thiopyran-4-yl)ethyl acetate was prepared according to the general method outlined in example 44, step 1. Starting from ethyl tetrahydro-4*H*-thiopyran-4-ylacetate (5.0 g, 26.6 mmol) and 4-but-2-ynyloxybenzenesulfonyl fluoride (5.5 g, 26.0 mmol), 9.3 g of product was isolated as a yellow oil. Product was purified by silica gel column chromatography by eluting with 50:50 ethyl acetate:hexane. Yield: 88%. MS: 398 $(M + H)^+$.

Step 4. 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}(tetrahydro-4*H*-thiopyran-4-yl)acetic acid was prepared according to the general method outlined in example 9, step 2. Starting from 2-{[4-(2-butynyloxy)phenyl]sulfonyl}(tetrahydro-4*H*-thiopyran-4-yl)ethyl acetate (7.0 g, 17.7 mmol), 6.8 g of product was isolated as a white solid. Mp: 141−143 °C Yield: quantitative. MS: 370 $(M - H)^+$.

Step 5. 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-*N*-hydroxy-2-tetrahydro-4*H*-thiopyran-4-ylacetamide was prepared according to the general method outlined in example 9, step 3. Starting from 2-{[4-(2-butynyloxy)phenyl]sulfonyl}(tetrahydro-4*H*-thiopyran-4-yl)acetic acid (4.5 g, 12.2 mmol), 4.6 g of the product was isolated. The product was purified by silica gel column chromatography by eluting with 1:1 ethyl acetate: hexane. White solid. Yield: 98%.

Example 45. Preparation of 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-*N*-hydroxy-2-(1-oxidotetrahydro-4*H*-thiopyran-4-yl)acetamide 45. 2-{[4-(2-Butynyloxy)phenyl]sulfonyl}-*N*-hydroxy-2-(1-oxidotetrahydro-4*H*-thiopyran-4-yl)acetamide was prepared, starting from 2-{[4-(2-butyn-yloxy)-phenyl]sulfonyl}-*N*-hydroxy-2-tetrahydro-4*H*-thiopyran-4-ylacetamide (0.6 g, 1.6 mmol) and following the procedure outlined in example 10, to give 510 mg of the product isolated as a white solid after being crystallizing from methanol. Yield: 80%.

Example 59. Preparation of 1-(4-Bromobenzyl)-4-(4-but-2-ynyxoybenzenesulfonyl)piperdine-4-carboxylic Acid Hydroxyamide 59. Step 1. A mixture of K_2CO_3 (15 g, excess), (4-hydroxyphenylsulfanyl)acetic acid ethyl ester (5 g, 23.6 mmol), and 1-bromo-2-butyne (9.34 g, 35.4 mmol) was refluxed with stirring for 8 h. The reaction mixture was then cooled to room temperature and filtered. The filtrate was concentrated and extracted with chloroform. The chloroform layer was washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. The product obtained was taken to the next step with out purification. Yield: 6.0 g, 96%, yellow oil. MS (EI): 265.0 (M + H).

Step 2. To a stirred solution of (4-but-2-ynyloxyphenylsulfanyl)acetic acid ethyl ester (101 g, 381 mmol) in MeOH:THF (3:1) (1000 mL) was added oxone (670.0 g, excess) in water (1000 mL) at room temperature. The reaction mixture was stirred at room temperature for 8 h. The reaction mixture was then diluted with chloroform (600 mL) and filtered. The organic layer was separated and washed once with a saturated solution of $NaHSO_3$ (400 mL). The chloroform layer was washed well with water, dried, and concentrated. The oily product was dissolved in MeOH (100 mL), and hexane (600 mL) was added. The separated colorless solid was filtered and washed with hexane. Yield: 108 g, 96%. Mp: 91−93 °C. MS: 297 $(M + H)^+$.

Step 3. A stirred mixture of anhydrous K_2CO_3 (10 g, excess), 18-crown-6 (1 g), tetrabutylammonium bromide (1.0 g), (4-but-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester (2.8 g, 9.46 mmol), and (4-bromobenzyl)bis(2-chloroethyl)amine[18] (4.9 g, 14.2 mmol) in anhydrous acetone (200 mL) was refluxed for 24 h. The reaction mixture was then cooled and filtered and the filtrate was concentrated. The crude product was extracted with chloroform, washed well with water, dried, and concentrated. The brown material was purified by column chromatography on silica gel by eluting with 50:50 ethyl acetate: hexane. Yield: 1.36 g, 27%, brown oil. MS: 534 $(M + H)^+$.

Step 4. 1-(4-Bromobenzyl)-4-(4-but-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid was prepared starting from 1-(4-bromobenzyl)-4-(4-but-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid ethyl ester (1.36 g, 2.54 mmol) dissolved in THF:methanol (100:50 mL) and 10 N NaOH (15 mL). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then concentrated and residue was cooled and neutralized with concentrated HCl. The separated solid was extracted with chloroform:methanol (3:1) (300 mL) and washed with water. The chloroform layer was dried and concentrated. The product was crystallized from methanol. Yield: 800 mg, 62%, off-white solid. Mp: 197 °C. MS: 507.9 $(M + H)^+$.

Step 5. To a stirred solution of 1-(4-bromobenzyl)-4-(4-but-2-ynyxoybenzenesulfonyl)piperdine-4-carboxylic acid (750 mg, 1.5 mmol) and DMF (1 mL) in CH_2Cl_2 (100 mL) was added oxalyl chloride (508 mg, 4.0 mmol) in methylene chloride (2 mL) dropwise at 0 °C. After the addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The acid chloride thus formed was concentrated to remove excess oxalyl chloride and redissolved in CH_2Cl_2 (30 mL). In a separate flask, hydroxylamine hydrochloride (690 mg, 10 mmol) was dissolved in DMF (10 mL), and triethylamine (10 g, 10 mmol) was added. The reaction mixture was further diluted with acetonitrile (25 mL) and stirred at 0 °C. The acid chloride was slowly added into the hydroxylamine, and after the addition was complete, the reaction mixture was brought to room temperature and stirred for 24 h. The reaction mixture was concentrated and the residue was extracted with chloroform, washed well with water, and dried over anhydrous Na_2SO_4. The product was purified by silica gel column chromatography by eluting it with 10:90 methanol:ethyl acetate to give 270 mg of 1-(4-bromobenzyl)-4-(4-but-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid hydroxyamide as the hydrochloride salt, a white powder. Yield: 52%.

Example 58. Preparation of 1-(4-Bromobenzyl)-4-(4-prop-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic Acid Hydroxyamide 58. Step 1. (4-Prop-2-ynyloxyphenylsulfanyl)acetic acid ethyl ester was prepared according to the general method outlined in example 59, step 1. Starting from (4-hydroxyphenylsulfanyl)acetic acid ethyl ester (2.12 g, 10 mmol) and propargyl bromide (1.8 g, 15mol), 2.4 g of the product was isolated. Yield: 96%, amber oil. MS: 251$(M + H)^+$.

Step 2. (4-Prop-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester was prepared according to the general method outlined in example 59, step 2. Starting from (4-prop-2-ynyloxyphenylsulfanyl)acetic acid ethyl ester (2.5 g, 10 mmol), 2.8 g of (4-prop-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester was isolated. Yield: 99%, brown oil. MS: 283 $(M + H)^+$.

Step 3. 1-(4-Bromobenzyl)-4-(4-prop-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example 59, step 3. Starting from (4-prop-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester (21.62 g, 76.7 mmol) and (4-bromobenzyl)bis(2-chloroethyl)amine (31.9 g, 92 mmol), 23 g of the ester derivative was isolated. Yield: 58%, yellow oil. MS: 521.9 $(M + H)^+$.

Step 4. 1-(4-Bromobenzyl)-4-(4-prop-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid was prepared, starting from 1-(4-bromobenzyl)-4-(4-prop-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid ethyl ester (5 g, 9.59 mmol) dissolved in THF:methanol (150:50 mL) and 10 N NaOH (15 mL). The resulting reaction mixture was worked up as outlined in example 59, step 4. Yield: 3.4 g, 72%, brown low-melting solid. MS: 491.9 $(M - H)^-$.

Step 5. Starting from 1-(4-bromobenzyl)-4-(4-prop-2-ynyloxybenzenesulfonyl)-piperdine-4-carboxylic acid (3 g, 6.1 mmol) and following the procedure outlined in example 59, step 5, 580 mg of 1-(4-bromobenzyl)-4-(4-prop-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid hydroxyamide was isolated as the HCl salt, an off-white powder. Yield: 18%.

Example 60. Preparation of 1-(4-Bromobenzyl)-4-(4-pent-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic Acid Hydroxyamide 60. Step 1. (4-Pent-2-ynyloxyphenylsulfanyl)acetic acid ethyl ester was prepared according to the general method outlined in example 59, step 1. Starting from (4-hydroxyphenylsulfanyl)acetic acid ethyl ester (5 g, 30 mmol) and 2-pentynyl chloride (3.7 g, 36.6 mmol), 7.15 g of the product was isolated. Yield: 7.15 g, 86%, brown oil. MS (EI): 278 $(M + H)^+$.

Step 2. (4-Pent-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester was prepared according to the general method outlined in example 59, step 2. Starting from (4-pent-2-ynyloxyphenylsulfanyl)acetic acid ethyl ester (7.04 g, 25.3 mmol) and oxone (25 g), (4-pent-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester was isolated. Yield: 8 g, 99%, yellow oil. MS: 310.9 $(M + H)^+$.

Step 3. 1-(4-Bromobenzyl)-4-(4-pent-2-ynyloxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example 59, step 3. Starting from (4-pent-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester (4 g, 12.9 mmol) and (4-bromobenzyl)bis(2-chloroethyl)amine (5.83 g, 16.8 mmol), 2.85 g of the product was isolated. Yield: 31%, low melting white solid. MS: 549.9 $(M + H)^+$.

Step 4. 1-(4-Bromobenzyl)-4-(4-pent-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid was prepared starting from 1-(4-bromobenzyl)-4-(4-pent-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid ethyl ester (2.64 g 4.8 mmol) dissolved in THF:methanol (100:50 mL) and 10 N NaOH (10 mL). The resulting reaction mixture was worked up as outlined in example 59, step 4. Yield: 1.6 g, 65%, off white solid. Mp: 217 °C. MS: 521.9 $(M + H)^+$.

Step 5. Starting from 1-(4-bromobenzyl)-4-(4-pent-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid (1.55 g, 2.98 mmol) and following the procedure outlined in example 59, step 5, 200 mg of 1-(4-bromobenzyl)-4-(4-pent-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid hydroxyamide was isolated as the HCl salt, a yellow solid. Yield: 12%.

Example 61. Preparation of 1-(4-Bromobenzyl)-4-(4-oct-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic Acid Hydroxyamide 61. Step 1. (4-Oct-2-ynyloxyphenylsulfanyl)acetic acid ethyl ester was prepared according to the general method outlined in example 59, step 1. Starting from (4-hydroxyphenylsulfanyl)acetic acid ethyl ester (5 g, 30 mmol) and 1-bromo-2-octyne (6.9 g, 36.6 mmol), 8.9 g of (4-oct-2-ynyloxyphenylsulfanyl)acetic acid ethyl ester was isolated. Yield: 8.9 g, 92%, yellow oil. MS (EI): 320 $(M + H)^+$.

Step 2. (4-Oct-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester was prepared according to the general method outlined in example 59, step 2. Starting from (4-oct-2-ynyloxyphenylsulfanyl)acetic acid ethyl ester (8.8 g, 27.5 mmol), 8.45 g of (4-oct-2-ynyloxyphenylsulfonyl)acetic acid ethyl ester was isolated. Yield: 87%, yellow oil. MS (EI): 352 $(M + H)^+$.

Step 3. 1-(4-Bromobenzyl)-4-(4-oct-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example 59, step 3. Starting from (4-oct-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester (4 g, 11.4 mmol) and (4-bromobenzyl)bis(2-chloroethyl)-amine (5.13 g, 14.8 mmol), 1.47 g of 1-(4-bromobenzyl)-4-(4-oct-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid ethyl ester was isolated.Yield: 22%, yellow solid. MS: 591.9 $(M + H)^+$.

Step 4. 1-(4-Bromobenzyl)-4-(4-oct-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid was prepared starting from 1-(4-bromobenzyl)-4-(4-oct-2-ynyloxybenzenesulfonyl)-piperdine-4-carboxylic acid ethyl ester (1.36 g, 2.3 mmol) dissolved in THF:methanol (50:50 mL) and 10 N NaOH (10 mL). The resulting reaction mixture was worked up as outlined in example 59, step 4. Yield: 660 mg, 51%, off white solid; mp 199 °C. MS: 562 $(M + H)^+$.

Step 5. Starting from 1-(4-bromobenzyl)-4-(4-oct-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid (570 mg, 1.01 mmol) and following the procedure outlined in example 59, step 5, 100 mg of 1-(4-bromobenzyl)-4-(4-oct-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid hydroxyamide was isolated as the hydrochloride salt, a white powder. Yield: 17%.

Example 66. Preparation of 1-(4-Bromobenzyl)-4-[4-(4-morpholin-4-ylbut-2-ynyloxy)benzenesulfonyl]piperdine-4-carboxylic Acid Hydroxyamide 66. Step 1. To a stirred solution of morpholine (1.68 g, 19.2 mmol) diluted in dioxane (100 mL) was added acetic acid (5 mL). The reaction fumed and stirred for 5 min. 1-(4-Bromobenzyl)-4-(4-prop-2-ynyloxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (5.0 g, 9.6 mmol), paraformaldehyde (0.29 g, 9.6 mmol), and the copper(I)chloride (0.35 g) were added to the piperidine solution. The reaction turned green and was heated at reflux for 1 h, turning brown. It was then concentrated, diluted in ice water, brought to pH 8 with NH_4OH, and extracted with $CHCl_3$. The organic layer was washed four times with water, dried over Na_2SO_4, and then concentrated. The product, 1-(4-bromobenzyl)-4-[4-(4-morpholin-4-ylbut-2-ynyloxy)benzenesulfonyl]piperidine-4-carboxylic acid ethyl ester was purified by silica gel column chromatography by eluting it with 5:95 methanol:chloroform solution. Yield: 3.0 g, 50%, colorless solid. Mp: 110 °C. MS: 311 $(M + 2H)^{2+}$, 621 $(M + H)^+$.

Step 2. 1-(4-Bromobenzyl)-4-[4-(4-morpholin-4-ylbut-2-ynyloxy)benzenesulfonyl]piperidine-4-carboxylic acid was prepared starting from 1-(4-bromobenzyl)-4-[4-(4-morpholin-4-ylbut-2-ynyloxy)benzenesulfonyl]piperidine-4-carboxylic acid ethyl ester (2.87 g, 4.6 mmol) dissolved in THF:methanol (3:1, 150 mL) and 10 N NaOH (10 mL). The resulting reaction mixture was worked up as outlined in example 59, step 4. Yield: 2.26 g, 83%, white powder. Mp: 198 °C. MS: 593.1 $(M + H)^+$.

Step 3. Starting from 1-(4-bromobenzyl)-4-[4-(4-morpholin-4-ylbut-2-ynyloxy)benzenesulfonyl]piperidine-4-carboxylic acid (2.1 g, 3.55 mmol) and following the procedure outlined in example 59, step 5, 1.8 g of 1-(4-bromobenzyl)-4-[4-(4-morpholin-4-ylbut-2-ynyloxy)benzenesulfonyl]piperidine-4-carboxylic acid hydroxyamide was isolated as the hydrochloride salt, a white solid. Yield: 80%.

Example 62. Preparation of 1-Benzyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic Acid Hydroxyamide 62. Step 1. 1-Benzyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example 59, step 3, starting from (4-but-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester (2 g, 6.73 mmol) and bis(2-chloroethyl)benzylamine (2.3 g, 8.8 mmol). Yield: 3.33 g, 99%, yellow oil. MS: 455.9 $(M + H)^+$.

Step 2. 1-Benzyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid was prepared starting from 1-benzyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid ethyl ester (3 g, 6.6 mmol) dissolved in THF:methanol (3:1, 150 mL) and 10 N NaOH (15 mL). The resulting reaction mixture was worked up as outlined in example 59, step 4. Yield: 1.65 g, 59%, off white powder. Mp: 191 °C. MS: 428 $(M + H)^+$.

Step 3. Starting from 1-benzyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid (1.55 g, 3.63 mmol) and following the procedure outlined in example 59, step 5, 1.08 g of 1-benzyl-4-(4-but-2-ynyloxybenzenesulfonyl)piperdine-4-carboxylic acid hydroxyamide was isolated as the hydrochloride salt, an off-white powder. Yield: 62%.

Example 64. Preparation of 4-(4-But-2-ynyloxybenzenesulfonyl)-1-(4-methoxybenzyl)piperdine-4-carboxylic Acid Hydroxyamide 64. Step 1. 4-(4-But-2-ynyloxybenzenesulfonyl)-1-(4-methoxybenzyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example 59, step 3. Starting from (4-but-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester (2 g, 6.73 mmol) and bis(2-chloroethyl)(4-methoxybenzyl)amine (2.61 g, 8.75 mmol) and following the procedure outlined in example 59, step 3, 2.5 g of the product was isolated. Yield: 2 77%, yellow oil. MS: 486 $(M + H)^+$.

Step 2. 4-(4-But-2-ynyloxybenzenesulfonyl)-1-(4-methoxybenzyl)piperdine-4-carboxylic acid was prepared starting from 4-(4-but-2-ynyloxybenzenesulfonyl)-1-(4-methoxybenzyl)piperdine-4-carboxylic acid ethyl ester (2.5 g, 5.15 mmol) dissolved

in THF:methanol (3:1, 200 mL) and 10 N NaOH (15 mL). The resulting reaction mixture was worked up as outlined in example 59, step 4. Yield: 1.26 g, 54%, off white solid. Mp: 223 °C. MS: 458 $(M + H)^+$.

Step 3. Starting from 4-(4-but-2-ynyloxybenzenesulfonyl)-1-(4-methoxybenzyl)piperdine-4-carboxylic acid (1 g, 2.19 mmol) and following the procedure outlined in example 59, step 5, 350 mg of 4-(4-but-2-ynyloxybenzenesulfonyl)-1-(4-methoxybenzyl)piperdine-4-carboxylic acid hydroxyamide was isolated as the hydrochloride salt, an off-white solid. Yield: 31%.

Example 65. Preparation of 4-(4-But-2-ynyloxybenzenesulfonyl)-1-(4-chlorobenzyl)piperdine-4-carboxylic Acid Hydroxyamide 65. Step 1. 4-(4-But-2-ynyloxybenzenesulfonyl)-1-(4-chlorobenzyl)piperdine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example 59, step 3. Starting from (4-but-2-ynyloxybenzenesulfonyl)acetic acid ethyl ester (4 g, 13.5 mmol) and (4-chlorobenzyl)bis(2-chloroethyl)amine (4.9 g, 16.2 mmol). Yield: 3.5 g, 53%, white crystals. Mp: 91.8 °C. MS: 490 $(M + H)^+$.

Step 2. 4-(4-But-2-ynyloxybenzenesulfonyl)-1-(4-chlorobenzyl)piperdine-4-carboxylic acid was prepared starting from 4-(4-but-2-ynyloxybenzenesulfonyl)-1-(4-chlorobenzyl)piperdine-4-carboxylic acid ethyl ester (3.14 g, 6.42 mmol) dissolved in THF:methanol 3:1 (100 mL) and 10 N NaOH (10 mL). The resulting reaction mixture was worked up as outlined in example 59, step 4. Yield: 2.37 g, 80%, white solid. Mp: 205 °C. MS: 461.9 $(M + H)^+$.

Step 3. Starting from 4-(4-but-2-ynyloxybenzenesulfonyl)-1-(4-chlorobenzyl)piperdine-4-carboxylic acid (2.31 g, 5.01 mmol) and following the procedure outlined in example 5, step 5, 790 mg of 4-(4-but-2-ynyloxybenzenesulfonyl)-1-(4-chlorobenzyl)piperdine-4-carboxylic acid hydroxyamide was isolated as the hydrochloride salt, a yellow solid. Yield: 31%.

Example 69. Preparation of 4-(4-But-2-ynyloxyphenylsulfanyl)-4-hydroxycarbamoylpiperidine-1-carboxylic Acid *tert*-Butyl Ester 69. Step 1. To a solution of triphenylphosphine (24.7 g, 94.2 mmol) and dimethylformamide (0.6 mL) in dichloromethane (25 mL) was added a solution of 4-but-2-ynyloxyphenylsulfonyl chloride (7.69 g, 31.4 mmol) in dichloromethane dropwise over 30 min. After an additional 2 h, 1 N aqueous hydrochloric acid (20 mL) and water was added. The organic layer was separated and concentrated in vacuo. Aqueous sodium hydroxide (1 N, 50 mL) was added and the solid removed by filtration. The aqueous phase was washed with diethyl ether (3×), treated with 1 N aqueous hydrochloric acid (50 mL), and extracted with ether (3×). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated to give the thiol as an oil (3.77 g). This material was dissolved in dimethyl sulfoxide (40 mL), and concentrated hydrochloric acid was added (2 mL). After 18 h, diethyl ether was added and the organic phase was washed with water (5×) and dried over anhydrous magnesium sulfate. Concentration in vacuo gave a yellow solid which was filtered through silica gel with hexane:ethyl acetate to give bis(4-but-2-ynyloxyphenyl) disulfide as a yellow solid (3.0 g, 80%).

Step 2. To a solution of *N*-Boc-isonipecotic acid (0.62 g, 2.7 mmol) in tetrahydrofuran (20 mL) at −78 °C was added *tert*-butyllithium (3.4 mL, 1.7M in hexane, 5.7 mmol). After 10 min at −78 °C, the yellow solution was warmed to 0 °C in an ice bath. After 30 min the colorless solution was cooled to −78 °C, whereupon bis(4-but-2-ynyloxyphenyl) disulfide(1.0 g, 2.8 mmol) was added as a solution in tetrahydrofuran (6 mL). The reaction mixture was allowed to warm to 25 °C. After 1.5 h, ethyl acetate was added, followed by 6 mL of 1 N aqueous hydrochloric acid in 20 mL of water. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Chromatography on silica gel (methanol/methylene chloride) gave the product (0.55 g).

Step 3. Dimethylformamide (0.163 mL) was added to a solution of oxalyl chloride (1.06 mL of a 2.0 M solution in dichloromethane) in dichloromethane (2 mL) at 0 °C. After 15 min a solution of the acid (500 mg, 1.23 mmol) in dimethylformamide (5 mL) was added and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction mixture was added to a mixture of hydroxylamine hydrochloride (0.737 g), triethylamine (2.22 mL), water (5.7 mL), and tetrahydrofuran (22.8 mL) that had been stirring at 0 °C for 15 min. The reaction was held at 0 °C for 18 h, diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate (3×), dried over potassium carbonate, and concentrated in vacuo to give 480 mg (92% yield) of 4-(4-but-2-ynyloxyphenylsulfanyl)-4-hydroxycarbamoylpiperidine-1-carboxylic acid *tert*-butyl ester.

Example 70. Preparation of 4-(4-But-2-ynyloxyphenylsulfanyl)piperidine-4-carboxylic Acid Hydroxyamide 70. 4-(4-But-2-ynyloxyphenylsulfanyl)-4-hydroxycarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester, prepared by the method outlined in example 68, step 3 (0.175 g, 0.4 mmol), was treated with 4 N hydrochloric acid in dioxane (5 mL) at 25 °C for 1 h and 15 min. The reaction mixture was concentrated in vacuo, diethyl ether was added, and the resulting precipitate was isolated by filtration to give 4-(4-but-2-ynyloxyphenylsulfanyl)piperidine-4-carboxylic acid hydroxyamide as a white solid. Yield: 0.12 g, 93%.

Example 72. Preparation of 4-(4-But-2-ynyloxybenzenesulfonyl)-1-ethylpiperdine-4-carboxylic Acid Hydroxyamide HCl (72). Starting from 4-(4-but-2-ynyloxybenzenesulfonyl)-1-ethylpiperdine-4-carboxylic acid (3.65 g, 10 mmol) and following the procedure outlined in example 59, step 5, 2.5 g of 4-(e4-but-2-ynyloxybenzenesulfonyl)-1-ethylpiperdine-4-carboxylic acid hydroxyamide was isolated as the hydrochloride salt, a yellow solid. Yield: 60%.

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Supporting Information Available: The spectral data (mass and NMR) and the microanalysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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