Synthesis and Structure−Activity Relationship of N-Substituted 4-Arylsulfonylpiperidine-4-hydroxamic 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. In our preceding paper, we have reported on a series of novel and orally active *N*-hydroxy-α-phenylsulfonylacetamide derivatives. However, these compounds had two drawbacks (moderate selectivity and chirality issues). To circumvent these two problems, a series of novel and orally active N-substituted 4-benzenesulfonylpiperidine-4-carboxylic acid hydroxyamide derivatives have been synthesized. The present paper deals with the synthesis and SAR of these compounds. Among the several compounds synthesized, derivative **55** turned out to be a potent, selective, and an orally active MMP inhibitor in the clinically relevant advanced rabbit osteoarthritis model. Detailed pharmacokinetics and metabolism data are described.

Introduction

Inhibition of matrix metalloproteinases (MMPs) has been recognized as a major therapeutic target since the early 1980s. Initially these enzymes were thought to be involved in arthritis. Subsequently, cancer therapy emerged as the major focus.[1] Currently about 21 mammalian MMPs have been discovered and shown to be involved in osteoarthritis (OA), oncology, atherosclerosis, rheumatoid arthritis, emphysema, and central nervous system (CNS) disorders. These enzymes degrade extracellular matrix components, and they can be placed into subgroups based on their preference for specific matrix macromolecule substrates. Collagenases, one of the subgroups, are the most selective and efficient members of the MMP family at degrading native, fibrillar collagens. Three collagenases have been identified to date in humans: collagenase-1 (MMP-1), collagenase-2 (MMP-8), and collagenase-3 (MMP-13). The expression of all three collagenases and their[2,3] activity is up-regulated in human OA cartilage. Type II collagen is the preferred substrate for collagenase-3,[4,5] and this enzyme has been hypothesized to be the primary collagenase responsible for collagen degradation in articular cartilage.

These MMPs are strictly controlled by endogenous MMP inhibitors such as tissue inhibitors of metalloproteinases (TIMPs) and α_2-macroglobulins. Overexpression of these enzymes is implicated in various pathological disorders. [6] Because MMPs are involved in a number of normal physiological processes, selective inhibitors should present fewer side effects. Broad-spectrum MMPs in clinical trials for oncology have shown some musculoskeletal side effects that are hypothesized to be due to MMP-1 inhibition. Therefore, inhibitors that are selective against MMP-13 over MMP-1 may have therapeutic benefit in OA without incurring musculoskeletal side effects.[7]

In our preceding paper, we had disclosed a number of α-phenylsulfonylhydroxamic acids (Figure 1) as potent, selective, and orally active MMP inhibitors. After an extensive SAR study, compound **1a** (Figure 2) was selected for further studies. Even though **1a** has an excellent oral bioavailability (81% in rat) and is active in vivo, it (a) suffered from moderate selectivity and (b) presented an asymmetric center. In our preceding paper, we had shown that selectivity over MMP-1 can be achieved by having a suitable R_1 substituent on the molecule **1** (Figure 1). X-ray studies had shown that the R_1 substituents of related compounds occupy the S1′ pocket of the enzymes.[8] Hence, by having a proper R_1 substituent, selectivity can be achieved. To solve the chirality problem, initially several attempts were made to resolve the racemic mixture of **1a** by various chemical methods, and this proved to be very ineffective. However, the enantiomers of **1a** were separated by a preparative chiral HPLC column. As mentioned in our preceding paper, the dextro enantiomer was found to be 20 times more potent as an MMP-13 inhibitor than the levo enantiomer. However, separating the enantiomers by a chiral column HPLC is not very practical for large-quantity scale-up. Hence, to circumvent these problems, the general structure **1** was modified to a symmetrical molecule such as **2** (Figure 1) where the molecule becomes achiral and R_1 can be modified to achieve the selectivity over MMP-1. In this article, the detailed in vitro and in vivo data of these molecules will be presented. In our paradigm, these compounds were tested against another zinc-containing enzyme, namely, TNF-α converting enzyme (TACE). Inhibition of TACE

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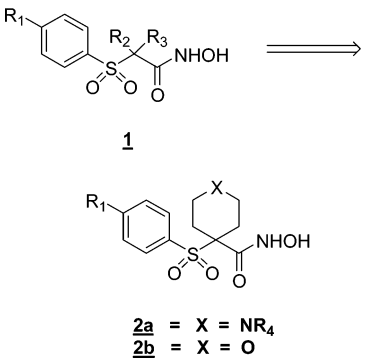


Figure 1.

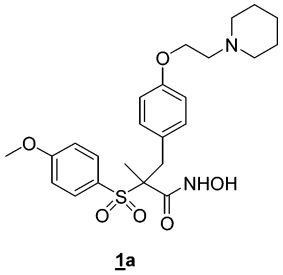


Figure 2.

may prove to be efficacious in the treatment of rheumatoid arthritis, Crohn's disease, and other inflammatory disorders.[9,10]

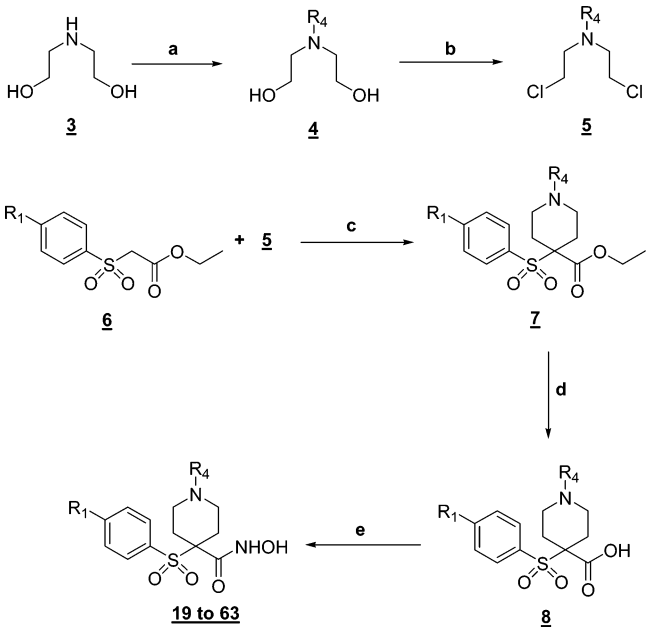
Chemistry

The corresponding 1-substituted 4-arylsulfonylpiperidine-4-carboxylic acid hydroxyamides were prepared starting from diethanolamine and appropriately substituted alkyl or substituted benzyl halides (Scheme 1). The N-substituted diethanolamine derivatives **4** were converted to the dichloro compounds using thionyl chloride in boiling toluene. The corresponding dichlorides **5** were reacted with substituted α-arylsulfonylacetic acid ethyl ester **6** derivatives in the presence of K_2CO_3/18-crown-6 in boiling acetone. The corresponding 1-substituted 4-arylsulfonylpiperidine-4-carboxylic acid ethyl esters **7** thus obtained were converted to the hydroxyamides **19**−**66** via their respective carboxylic acids **8**. Alternatively, this class of compounds can be prepared starting from *N*-^{t}Boc protected ethyl isonipecotate **9** and sulfonyl fluoride **10**.[11] The anion generated from **9** using LDA or lithium bis(trimethylsilyl)amide was reacted with sulfonyl fluoride **10** at −78 °C in THF. The corresponding 1-substituted 4-arylsulfonylpiperidine-4-carboxylic acid ethyl ester **11** obtained was converted to the hydroxamide **13** as outlined in Scheme 2. The ^{t}Boc group was removed, and compound **56** was obtained in 85% yield. The corresponding pyran derivative **18** was prepared by reacting 4-(4-butoxybenzenesulfonyl)acetic acid ethyl ester **14** with the commercially available 2-chloroethyl ether **15** (Scheme 3).

Biology

All final hydroxamic acid derivatives were tested in vitro[12] for their ability to inhibit MMP-1, MMP-9, MMP-13, and TACE.[13] As mentioned earlier, MMP-9 inhibitors may potentially be valuable for stopping the tumor metastasis,[14] while inhibiting MMP-13 can offer protection from the cartilage degradation associated with osteoarthritis.[7] Inhibitors of TACE are potentially valuable for the treatment of rheumatoid arthritis and other inflammatory diseases.[9] As mentioned in our preceding paper, the most active and selective compounds from the enzyme inhibition study were put into a bioactivity in vivo model known as dialysis implant assay[15] and tested against Novartis compound CGS-27023 (Figure 3). The most active compounds in this assay were advanced into an in vivo efficacy model known as the sponge-wrapped cartilage model[16] and compared with the Roche-Bio Science compound RS-130830 (Figure 3). Those compounds with good in vivo activity in the sponge-wrapped cartilage model were taken to a clinically more relevant model known as the anterior cruciate ligament model. This will be discussed in detail in the latter part of this paper.

Scheme 1. Method A: General Method To Prepare Compounds **19**−**63**

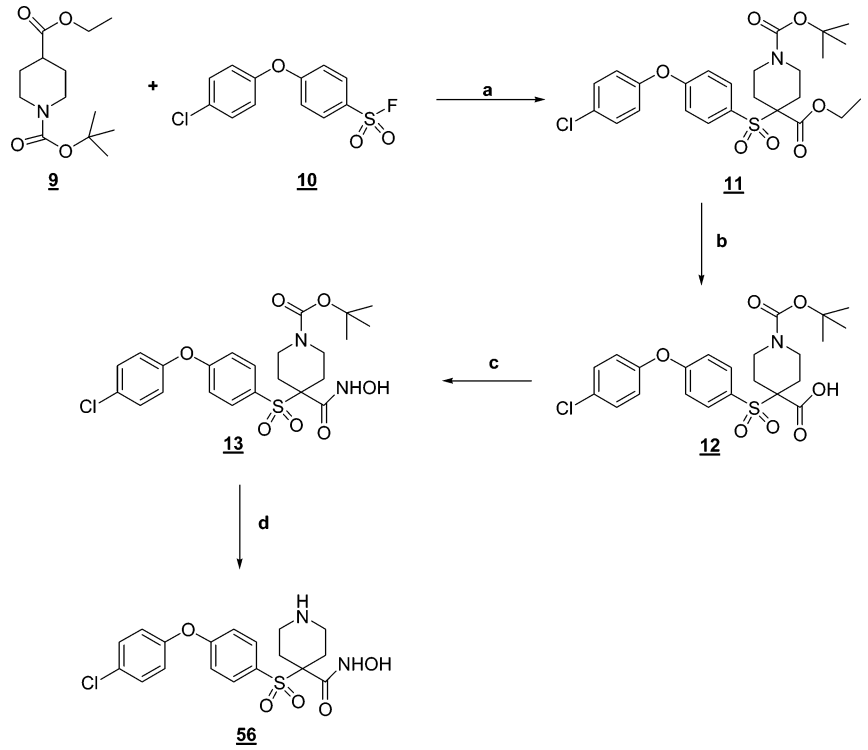


[a] (a) R_4Br, K_2CO_3, acetone, reflux; (b) toluene, $SOCl_2$, 100 °C; (c) K_2CO_3, 18-crown-6, acetone, reflux; (d) 10 N NaOH, THF, MeOH, room temp, and H^+; (e) $(COCl)_2$, DMF, CH_2Cl_2, $NH_2OH{\cdot}HCl$, Et_2N.

Structure−Acivity Relationships and Discussion

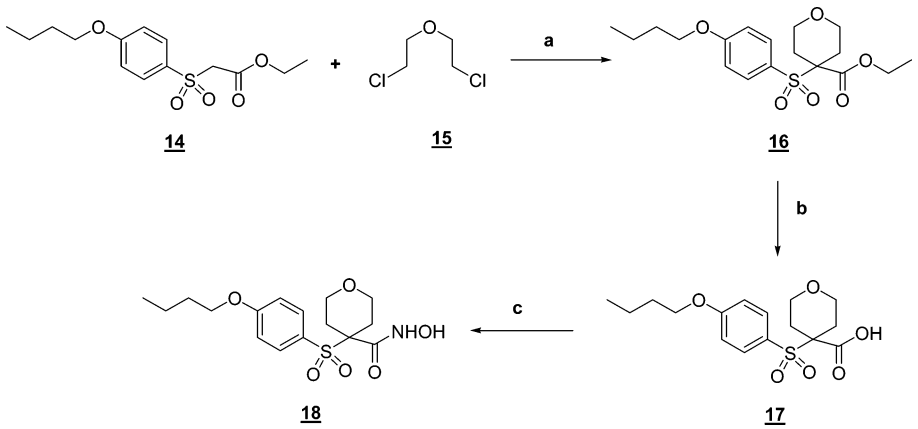
It is evident from the analogues compiled in Table 1 that the N-substituted benzyl and *N*-alkyl derivates are potent inhibitors of both MMP-9 and MMP-13. In particular, these compounds are more potent or equipotent inhibitors of MMP-13 than MMP-9. As TACE inhibitors, all these compounds are moderate to poor. Substitution on the aromatic ring of the *N*-benzyl group did not alter the MMP-13 activity dramatically, but the selectivity of MMP-1 and MMP-9 over MMP-13 is altered slightly, depending on the substituent present on the *N*-benzyl group. The first example illustrated in Table 1, namely, the *N*-benzyl derivative **19** (R_1 = OMe), showed good potency against MMP-13. The selectivity

Scheme 2. Method B: Preparation of Compound **56**



[a] (a) LDA, THF, -78 °C; (b) 10 N NaOH, THF, MeOH, room temp; (c) $(COCl)_2$, DMF, CH_2Cl_2, $NH_2OH{\cdot}HCl$, Et_2N; (d) THF, CH_2Cl_2, room temp.

Scheme 3. Preparation of Compound **18**



[a] (a) K_2CO_3, 18-crown-6, acetone, reflux; (b) 10 N NaOH, THF, MeOH, room temp; (c) $(COCl)_2$, DMF, $NH_2OH.HCl$, Et_2N.

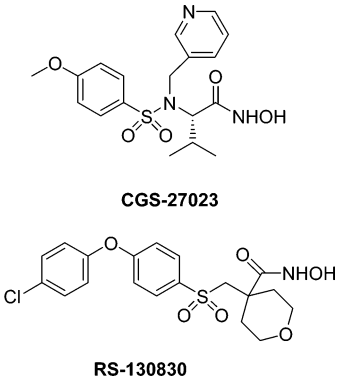
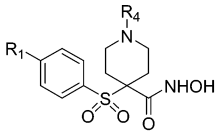


Figure 3.

of MMP-13 over MMP-1 is about 250-fold. Introduction of substituents on the benzyl moiety, such as 3-methoxy (example **20**), 3,4-dichloro (example **21**), 4-methyl (example **22**), and 4-phenyl (example **24**), moderately increased the selectivity of MMP-13 over MMP-1 although the potency against MMP-13 remained unaffected. Even the presence of a bulky substituent such as $-CH_2-$2-naphthyl (example **23**) on the nitrogen of the piperidine was well tolerated. When R_1 = OMe, replacement of the benzyl on the nitrogen with simple alkyl (examples **28**, **29**, **31**−**33**), cycloalkyl (example **30**), and isoprenyl substituents (example **25**) reduced the MMP-1, MMP-9, and MMP-13 potency. Thus, a comparison of examples **19** and **33** reveals that the *N*-methyl compound is 20 times less potent as an MMP-13 inhibitor and 48 times less potent as an MMP-9 inhibitor than the corresponding *N*-benzyl derivative **19**. However, when the R_1 substituent was changed from −OMe to O−*n*-butyl (examples **33**−**48**), there was an impressive increase in the selectivity and potency. Thus,

Table 1. In Vitro[d] (IC_{50}) and in Vivo[d] (Dialysis Implant Data)



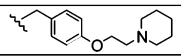
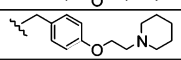
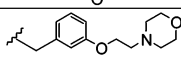
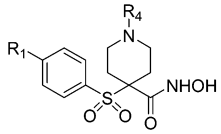
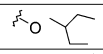
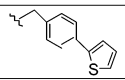
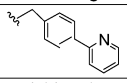
Cpd.#	R_1	R_4	MMP-1 IC_{50} (nM)	MMP-9 IC_{50} (nM)	MMP-13 IC_{50} (nM)	TACE IC_{50} (nM)	% of Enzyme Inhibition @ 25 mg/kg.po
19	-O-Me	Benzyl	492(+/-)8	10(+/-)2	2(+/-)1	229(+/-)6	NT
20	-O-Me	3-Methoxy benzyl	519(+/-)12	9(+/-)2	2(+/-)1	213(+/-)8	70+/-3 vs 60[a]+/-2 (1.1)[c]
21	-O-Me	3,4-Dichloro benzyl	450(+/-)9	6(+/-)2	2(+/-)1	115(+/-)9	47+/-2 vs 51[a]+/-3 (0.9)[c]
22	-O-Me	4-Methyl benzyl	494(+/-)13	17(+/-)3	2(+/-)1	222(+/-)12	89+/-4 vs76[a]+/-2 (1.2)[c]
23	-O-Me	2-CH_2-naphthyl	368(+/-)9	5(+/-)2	2(+/-)1	170(+/-)8	62+/-3 vs 51[a] +/-3 (1.2)[c]
24	-O-Me	4-CH_2-biphenyl	1330(+/-)12	13(+/-)2	3(+/-)1	610(+/-)6	29+/-3 vs 68[a] +/-5 (0.4)[c]
25	-O-Me	Isoprene	1390(+/-)24	39(+/-)4	7(+/-)2	49%[b]	57+/-4 vs 68[a] +/-5 (0.8)[c]
26	-O-Me	4-Bromo benzyl	598(+/-)8	10(+/-)2	2(+/-)1	71%[b]	51+/-2 vs 51[a] +/-3 (1)[c]
27	-O-Me	3-Phenyl propyl	1930(+/-)18	13(+/-)3	11(+/-)3	503(+/-)13	9+/-4 vs 53[a] +/-3 (0.2)[c]
28	-O-Me	Tert-Butyl	59%[b]	649(+/-)9	148(+/-)10	9%[b]	NT
29	-O-Me	n-Butyl	56%[b]	452(+/-)10	38(+/-)5	15%[b]	56+/-2 vs 76[a] +/-3 (0.7)[c]
30	-O-Me	Cyclo octyl	2640(+/-)17	138(+/-)6	29(+/-)4	22%[b]	71+/-3 vs 74[a] +/-2 (0.9)[c]
31	-O-Me	Ethyl	3680(+/-)15	364(+/-)8	33(+/-)5	25%[b]	17+/-4 vs 38[a] +/-3 (0.4)[c]
32	-O-Me	Isopropyl	4440(+/-)28	374(+/-)12	34(+/-)8	18%[b]	49+/-4 vs 68[a] +/-5 (0.7)[c]
33	-O-Me	Methyl	5110(+/-)22	484(+/-)8	44(+/-)5	20%[b]	36+/-3 vs 58[a] +/-2 (0.6)[c]
34	-O-n-Butyl	Benzyl	2380(+/-)19	4(+/-)1	1(+/-)0.5	154(+/-)12	80+/-2 vs 51[a] +/-2 (1.6)[c]
35	-O-Me	4-Fluoro benzyl	656(+/-)12	16(+/-)3	2(+/-)1	250(+/-)8	83+/-3 vs 76[a] +/-3 (1.1)[c]
36	-O-n-Butyl	4-Fluoro benzyl	4730(+/-)10	19(+/-)3	5(+/-)1	39%[b]	48+/-4 vs 35[a] +/-3 (1.3)[c]
37	-O-Me	4-Methoxy benzyl	642(+/-)12	12(+/-)2	2(+/-)1	197(+/-)14	75+/-3 vs 69[a] +/-2 (1.1)[c]
38	-O-Me	4-Methoxy phenyl ethyl	662(+/-)13	34(+/-)3	2(+/-)1	53%[b]	48+/-4 vs 62[a] +/-5 (0.8)[c]
39	-O-Me	2-Phenyl ethyl	1310(+/-)11	45(+/-)4	9(+/-)2	470(+/-)9	68+/-4 vs 68[a] +/-5 (1)[c]
40	-O-n-Butyl	4-Methoxy benzyl	2610(+/-)13	3(+/-)1	1(+/-)0.5	208(+/-)10	69+/-3 vs 54[a] +/-2 (1.3)[c]
41	-O-Me	3-Phenoxy propyl	1210(+/-)11	44(+/-)3	4(+/-)1	50%[b]	28+/-4 vs 60[a] +/-3 (0.5)[c]
42	-O-n-Butyl	3-phenoxy propyl	3790(+/-)18	5(+/-)1	1(+/-)0.5	631(+/-)13	67+/-3 vs 69[a] +/-2 (0.9)[c]
43	-O-Me	2-Phenoxy ethyl	629(+/-)12	26(+/-)3	3(+/-)1	293(+/-)10	6+/-4 vs 54[a] +/-2 (0.1)[c]
44	-O-n-Butyl	2-Phenoxy ethyl	2900(+/-)16	5(+/-)1	2(+/-)1	270(+/-)9	29+/-3 vs 54[a] +/-2 (0.5)[c]
45	-O-Me		393(+/-)12	3(+/-)1	3(+/-)1	386(+/-)11	53+/-3 vs 42[a] +/-2 (1.2)[c]
46	-O-n-Butyl		1950(+/-)28	2(+/-)1	1(+/-)0.5	581(+/-)12	98+/-1 vs 75[a] +/-2 (1.3)[c]
47	-O-n-Butyl		2180(+/-)20	2(+/-)1	2(+/-)1	506(+/-)14	27+/-3 vs 65[a] +/-4 (0.4)[c]
48	-O-n-Butyl	Methyl	3420(+/-)23	10(+/-)2	2(+/-)1	594(+/-)18	64+/-2 vs 43[a] +/-2 (1.5)[c]
49	-O-n-Butyl	Ethyl	7060(+/-)20	43(+/-)4	2(+/-)1	51%[b]	64+/-3 vs 64[a] +/-2 (1)[c]
50	-O-n-Butyl	n-Butyl	50%[b]	28(+/-)5	2(+/-)1	880(+/-)20	86+/-2 vs 74[a] +/-2 (1.2)[c]
51	-O-Benzyl	Benzyl	48%[b]	3(+/-)1	16(+/-)4	277(+/-)18	17+/-3 vs 35[a] +/-4 (0.5)[c]
52	-O-4-chloro phenyl	Methyl	1410(+/-)16	2(+/-)1	2(+/-)1	270(+/-)9	91+/-3 vs 65[a] +/-2 (1.4)[c]
53	-O-4-chloro phenyl	Ethyl	1720(+/-)15	1(+/-)0.5	1(+/-)0.5	413(+/-)12	90+/-4 vs 61[a] +/-3 (1.5)[c]
54	-O-4-chloro phenyl	n-Butyl	1070(+/-)21	1(+/-)0.5	1(+/-)0.5	301(+/-)22	93+/-2 vs 73[a] +/-3 (1.3)[c]

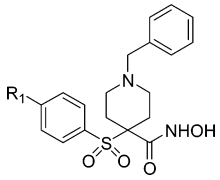
Table 1 (Continued)



Cpd.#	R_1	R_4	MMP-1 IC_{50} (nM)	MMP-9 IC_{50} (nM)	MMP-13 IC_{50} (nM)	TACE IC_{50} (nM)	% of Enzyme Inhibition @ 25 mg/kg.po
55	-O-4-chloro phenyl	Benzyl	801(+/-)23	1(+/-)0.5	1(+/-)0.5	301(+/-)13	53+/-3 vs 48[a] +/-3 (1.1)[c]
56	-O-4-chloro phenyl	H	1260(+/-)27	2(+/-)1	2(+/-)1	848(+/-)18	NT
57		Benzyl	2560(+/-)31	4(+/-)1	2(+/-)1	565(+/-19)	80+/-4 vs 64[a] +/-3 (1.3)[c]
58		Benzyl	3160(+/-)28	14(+/-)3	5(+/-)2	39%[b]	68+/-3 vs 64[a] +/-3 (1.1)[c]
59	-O-n-Butyl	3-Methoxy benzyl	1500(+/-)15	3(+/-)1	1(+/-)0.5	272(+/-)8	82+/-4 vs 67[a] +/-3 (1.2)[c]
60	O-Me		531(+/-)15	11(+/-)2	3(+/-)1	273(+/-)17	12+/-3 vs 41[a] +/-4 (0.3)[c]
61	-O-Me		422(+/-)18	6(+/-)2	2(+/-)1	298(+/-)18	78+/-2 vs 64[a] +/-3 (1.2)[c]
62	-O-n-Butyl	3,4-Dichloro benzyl	3670(+/-)19	20(+/-)3	5(+/-)2	57%[b]	14+/-3 vs 64[a] +/-3 (0.2)[c]
63	-O-benzyl	Benzyl	40(+/-)5	3(+/-)1	1(+/-)0.5	416(+/-)9	NT
64	-O-4-Chloro benzyl	4-Methyl benzyl	4750(+/-)23	6(+/-)2	6(+/-)2	421(+/-)11	NT
65	-2-Furanyl	Benzyl	40(+/-)4	3(+/-)1	1(+/-)0.5	416(+/-)17	95+/-2 vs 71[a] +/-2 (1.3)[c]
66	-O-4-chloro phenyl	4-Methoxy benzyl	490(+/-)18	1(+/-)0.5	1(+/-)0.5	492(+/-)22	93+/-3 vs 73[a] +/-4 (1.3)[c]
		CGS-27023	15(+/-)2	9(+/-)2	8(+/-)2	231(+/-)8	
		RS-130,830	233(+/-)8	3(+/-)1	2(+/-)1	176(+/-)10	

[a] % inhibition for CGS-27023 at 25 mg/kg, po. [b] % inhibition at 10 μM concentration and 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.

Table 2. Comparison of in Vitro Data (IC_{50} [a] Values) of Different R_1 Substituents



example	R_1	MMP-1 IC_{50} (nM)	MMP-9 IC_{50} (nM)	MMP-13 IC_{50} (nM)	TACE IC_{50} (nM)
19	−OMe	492 ± 8	10 ± 2	2 ± 1	229 ± 6
34	−O−*n*butyl	2380 ± 19	4 ± 1	1 ± 0.5	154 ± 12
51	−O−benzyl	48%[b]	3 ± 1	16 ± 4	277 ± 18
55	4-chlorophenoxy	801 ± 23	1 ± 0.5	1 ± 0.5	301 ± 13
57	3-methyl−*n*-butyl−O−	2560 ± 31	4 ± 1	2 ± 1	565 ± 19
58	2-ethyl−*n*-butyl−O−	3160 ± 28	14 ± 3	5 ± 2	39%[b]
65	2-furanyl	40 ± 4	3 ± 1	1 ± 0.5	416 ± 17

[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 at 10 μM concentration and dose−response curves were not generated for compounds at <60% incubation at 10 μM concentration.

comparison of potencies of MMP-13 between examples **29** vs **50** indicates that compound **50** is 19 times more potent than compound **29**. A similar trend is observed between examples **31** vs **49**. However, to achieve potency, it is not necessary to have any substituent on the piperidine nitrogen, as evidenced by example **56**, which exhibits good MMP-9 and MMP-13 potency and good selectivity vs MMP-1 (840 times). Even the pyran derivative **18** shows excellent potency and good selectivity over MMP-1: (MMP-1) 1380 nM, (MMP-9) 9.2 nM, (MMP-13) 1.4 nM, and (TACE) 177 nM.

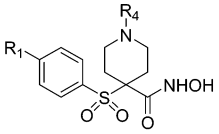
The selectivity of these compounds (MMP-13 over MMP-1) can be improved by replacing the methoxy group (R_1 substituent) with longer alkoxy substituents; as mentioned before, this part of the molecule occupies the S1′ pocket of these enzymes. Hence, we decided to vary the R_1 substituent with −O−*n*-butyl, −O−benzyl, −O−4-chlorophenyl, −O−3-methylbutyl, −O−2-ethylbutyl, and 2-furanyl moieties. Comparison of different examples cited in Table 2 (when R_4 = benzyl and R_1 = different substituents) illustrates that selectivity of MMP-13 over MMP-1 can be achieved by varying the

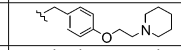
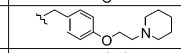
R_1 substituent. Replacement of the methoxy group in compound **19** with the *n*-butoxy group (compound **34**) changes the selectivity dramatically for MMP-13. Compound **34** is 1985 times more selective for MMP-13 over MMP-1. When R_1 substitution in compound **34** is changed from −O−*n*-butyl to −O−benzyl (example **51**), the MMP-13 potency decreases but the selectivity over MMP-1 is increased 625-fold. But in all three examples (examples **19**, **34**, and **51**), the TACE activity remained almost unaffected. Thus, the O−benzyl compound **51** is the most MMP-13 selective compound in this series but is 8-fold less potent against MMP-13 when compared to derivative **19**. When we replace the −O−benzyl group in compound **51** with 4-chlorophenyl (example **55**), the MMP-13 potency increases by 17-fold, but the selectivity of MMP-13 over MMP-1 decreases. The introduction of branching in the −O−*n*-butyl group of example **34** increases the selectivity of MMP-13 over TACE. Comparison of potencies of compounds **34** vs **57** reveals that introduction of branching near the terminal carbon atom of the *n*-butyl group decreases the TACE activity. Further branching at the *n*-butyl group (example **58**) diminishes TACE activity significantly, while there is only a slight decrease in the potency of MMP-13 and MMP-9. Replacement of the ether linkage (R_1 substituent) with a carbon−carbon bond (example **65**) increased the potency of all three classes of MMPs and they became nonselective.

All the compounds listed in Table 1, irrespective of their selectivity data, are potent MMP inhibitors in vitro. Hence, we focused our attention on their in vivo ability to inhibit these enzymes in the dialysis implant model. Their respective percentage inhibition data are tabulated in Table 1. In all the experiments, these compounds were concurrently compared with CGS-27023 (Figure 3) at 25 mg/kg, po. Most of the compounds listed in Table 1 are either more active or as active as CGS-27023 under the same dosage regimen. Comparison of example **19** (R_1 = −OMe; R_4 = benzyl) and example **24** (R_1 = −OMe; R_4 = CH_2−4-bipheny) reveals that even though these compounds show very similar MMP-13 in vitro inhibitory activity, compound **24** is less active than compound **19** in the dialysis implant model. This may be attributed to their difference in lipophillic character. Hence, we prepared compounds with a more basic nitrogen that will enable the molecule to have better water solubility. In this regard, to improve the physicochemical properties, examples **45**−**47** and **61** were prepared. Comparison of the percent inhibition data from the dialysis implant study of examples **45** and **46** reveals that these compounds are more potent in vivo than CGS-27023. However, when a morpholino group (example **47**) replaced the piperidino group, the in vivo activity decreased dramatically. However, in vitro, compound **47** is as active as other examples such as **45** and **46**. Next, the most active compounds in this model were taken to the in vivo model known as the sponge-wrapped cartilage model.

Compounds in this model were tested along with CGS-27023 or Roche Bio-Science molecule (RS-130830) (Figure 3). The results are tabulated in Table 3. Many derivatives that were very active in the dialysis implant model did not work well in the sponge-wrapped cartilage model. Example **23**, the 2-CH_2−naphthyl derivative that was active in the dialysis implant model, did not do well in the sponge-wrapped cartilage model. It was only less than half as active as CGS-27023 (14% inhibition of degradation of cartilage for compound **23** and 33% for CGS-27023). It is evident from Table 3 that all R_1 = 4-chlorophenyloxy derivatives (examples **52**−**55**) are very active in protecting the degradation of the articular cartilage, even at 10 mg/kg, po, bid. In particular, example **53** (when R_1 = 4-chlorophenoxy and R_4 = ethyl) was found to be 3 times more potent than RS-130830. However, when the R_4 = ethyl substituent was replaced with *n*-butyl or benzyl, the activity in the sponge-wrapped cartilage model dropped by 2-fold. The other attractive derivative without the presence of the 4-chlorophenyl ether fragment was found to be compound **46**. This compound exhibited good in vivo activity in the sponge-wrapped cartilage model (2-fold more potent than RS-130830). Compound **46** had excellent solubility in water (24.2 mg/mL) as its HCl salt. On the basis of several other criteria, examples **55** and **46** were chosen for further evaluation. These two derivatives, when tested in the sponge-wrapped cartilage model, along with RS-130830 at 5 mg/kg, po, bid, protected the cartilage by 53% and 56%, respectively, whereas RS-130830 protected the cartilage by 20% in our experiments. These data are tabulated in Table 4.

Table 3. In Vivo Data[e] (Sponge-Wrapped Cartilage Assay)



Cpd #	R_1	R_4	% Inhibition of degradation of cartilage @ 25 mg/ kg. po. bid Compound vs a or b
37	-O-Me	4-Methoxy benzyl	45+/-4 vs 37[a] +/-5 (1.2)[d]
42	-O-n-Butyl	3-Phenoxy propyl	17+/-3 vs 27[a] +/-2 (0.6)[d]
23	-O-Methyl	2-CH_2-naphthyl	14+/-5 vs 33[a] +/-2 (0.4)[d]
34	-O-n-Butyl	Benzyl	53+/-2 vs 39[a] +/-3 (1.4)[d]
40	-O-n-Butyl	4-methoxy benzyl	17+/-2 vs 25[a]+/-4 (0.7)[d]
55	-O-4-Chloro phenyl	Benzyl	43 [c]+/-2 vs 23 [b] +/-2 (1.9)[d]
54	-O-4-Chloro phenyl	n-Butyl	69[c] +/-2vs 39 [b, c] +/-2 (1.8)[d]
52	-O-4-Chloro phenyl	Methyl	73[c] +/-3vs 39[b,c] +/-2 (1.9)[d]
53	-O-4-Chloro phenyl	Ethyl	75[c] +/-2vs 23[b,c] +/-3 (3.2)[d]
50	-O-n-Butyl	n-Butyl	46+/-3 vs 43[b] +/-3 (1)[d]
45	-O-Me		56+/-4 vs 39[a] +/-3 (1.4)[d]
46	-O-n-Butyl		67[c] +/-2 vs 40 [b,c] +/-3 (1.7)[d]
48	-O-n-Butyl	Methyl	12[c] +/-5 vs 40 [b,c] +/-2 (0.3)[d]
49	-O-n-Butyl	Ethyl	34 [c] +/-3 vs 27[b,c] +/-3 (1.3)[d]
57		Benzyl	34[c] +/-2 vs 27[b,c] +/-3 (1.3)[d]
58		Benzyl	27[c] +/-3vs 27[b,c] +/-3 (1)[d]

[a] Compared with CGS 27023. [b] Compared with RS-130830. [c] 10 mg/kg, po, bid. [d] Compounds were dosed either with CGS-27023 or RS-130830, and the data were expressed relative to the activity of these compounds (such that CGS-27023 or RS-130830 = 1).[e] The final % inhibition values given here are the mean of the triplicate values of three experiments.

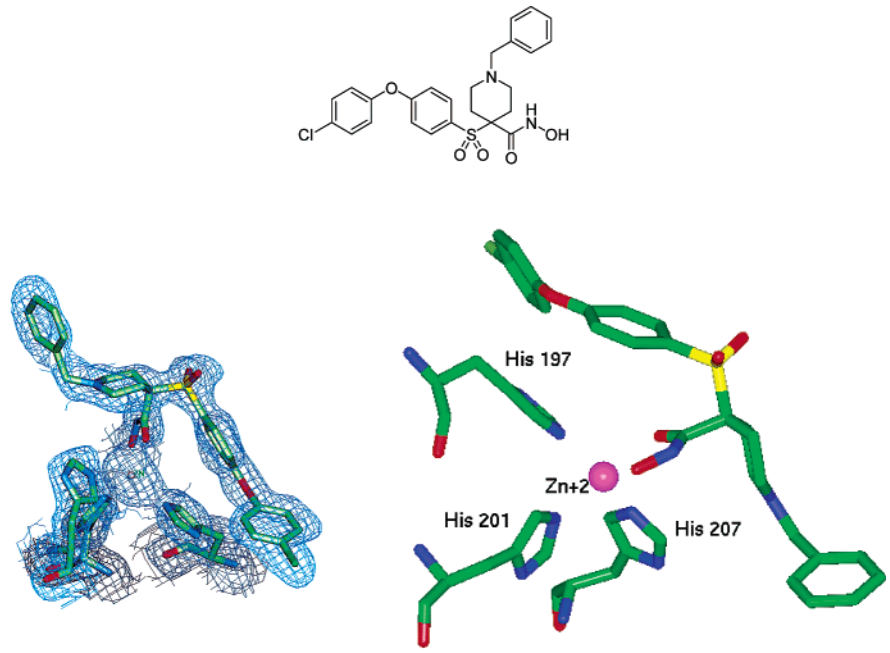


Figure 4. Crystal structure of the MMP-13: compound **55** complex. The active site electron density is at 2.0 Å resolution.

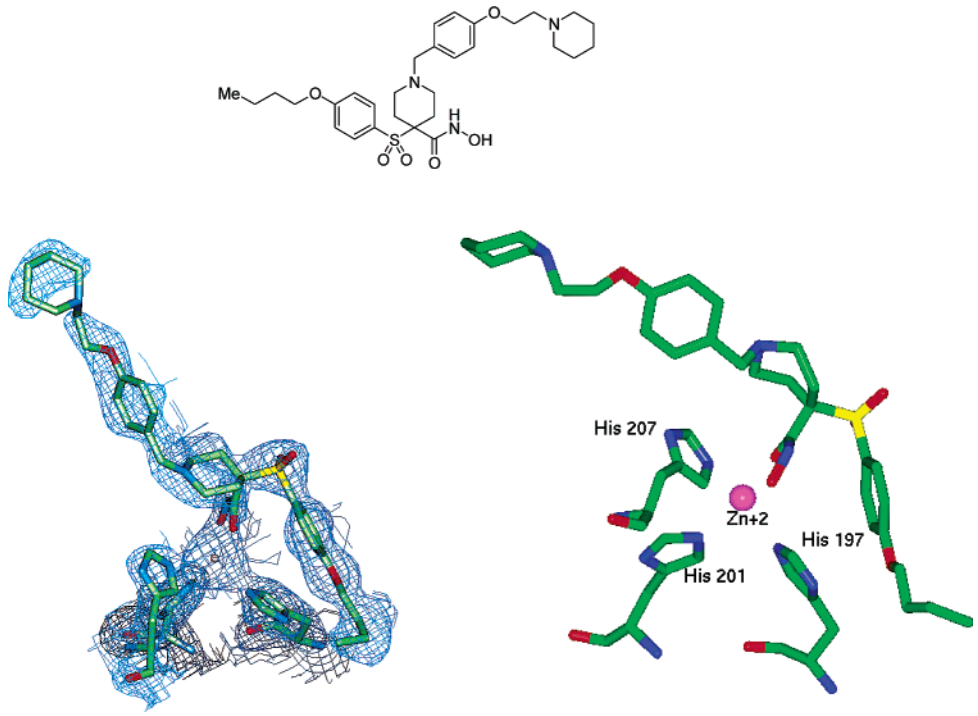


Figure 5. Crystal structure of the MMP-13: compound **46** complex. The active site electron density is at 2.0 Å resolution.

Table 4. In Vivo[a] Data for Compounds **55** and **46** (Sponge-Wrapped Cartilage Assay Compared with RS-130810)

example	% inhibition of collagen degradation @ 5 mg/kg, po, bid	% inhibition of collagen degradation @ 5 mg/kg, po, qd
RS-130830	20 ± 2	inactive
55	53 ± 3	24 ± 4
46	56 ± 2	33 ± 3

*The in vivo data are the mean values of three experiments.

Since these two compounds, **55** and **46**, exhibited very promising in vivo activities, they were cocrystallized with MMP-13 enzymes. Their X-ray crystal structures bound to the active site are shown in Figures 4 and 5. As anticipated, the hydroxamates chelate with the zinc atom, which is present at the active site and is surrounded by four histidine residues.

In the case of example **46**, the benzyl group containing piperidine is projecting into the solvent media. The biaryl ether moiety occupies the S1′ pocket as in the previous Wyeth inhibitors.[17] Among these two compounds, example **55** was selected for various pharmacokinetics (PK) studies and for testing in the clinically relevant surgically induced osteoarthritis model in rabbits. This compound was also tested in vitro in various selected MMPs, and these values are given in Table 5.

These data indicate that example **55** is significantly more potent against MMP-13 than MMP-1. For the most

Table 5. In Vitro Data for Example **55**: Various MMPs (IC_{50} [a] Values in nM)

MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-13	MMP-14
801 ± 6	1 ± 1	55 ± 3	925 ± 6	1 ± 1	1 ± 1	1 ± 1	7 ± 1

[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.

Table 6. Mean Pharmacokinetics of Compound **55** after a Single Oral (25 mg/kg) Administration in Sprague−Dawley Rats, New Zealand Rabbits, Beagle Dogs, and Cynomologus Monkeys

species	T_{max} [a] (h)	C_{max} [a] (μg/mL)	$T_{1/2}$ [a] (h)	AUC [a] (μg·h/mL)	oral bioavailability (%)
rat (po)	1.5	75.2	10.7	899	55
rabbit (po)	10	22.7	7.14	363	11
dog (po)	3.5	96.3	17.6	1810	47
monkey (po)	5.7	50.3	20.0	1410	37

species[b]	C_o [b] (μg/mL)	$T_{1/2}$ [a] (h)	AUC_o [a] (μg·h/mL)	Vd_{ss} [b] (L/kg)	CL_T [b] (mL/(min·kg))
rat (iv)	329	4.4	327	0.1	0.3
rabbit (iv)	126	11.8	640	0.1	0.1
dog (iv)	82	13.5	786	0.1	0.1
monkey (iv)	162	20.7	1510	0.2	0.1

[a] T_{max} = time of peak concentration. C_{max} = maximum plasma concentration. $T_{1/2}$ = apparent elimination half-life. AUC = area under the concentration−time curve. [b] Mean pharmacokinetics of compound **55** after a single iv (5 mg/kg) administration in Sprague−Dawley rats, New Zealand rabbits, Beagle dogs, and Cynomologus monkeys. C_0 = concentration at $T = 0$. Vd_{ss} = volume of distribution at steady state. CL_T = total clearance.

part, the other MMPs tested in the panel are inducibly expressed by selected cell types involved in pathological rather than physiological processes. Activity against these other enzymes, therefore, is not believed to be an issue in terms of side effects and may actually render this compound useful for other therapeutic indications.

Drug Metabolism and Pharmacokinetic Data of Example 55. The pharmacokinetics and metabolism of example **55** have been studied in rats, rabbits, dogs, and monkeys. Following intravenous administration in these species, a low volume of distribution and low plasma clearance generally characterized the PK of example **55**. This compound was highly protein-bound (99%) in rats, rabbit, dog, and human plasma. The compound was well absorbed in all species at relatively low dosages (10−25 mg/kg, po). The oral bioavailability of example **55** in rats was found to be 55%, and in dogs it was found to be 47%. In dogs, systemic exposure did not increase appreciably after oral administration of greater than 75 mg/kg. Select PK parameters of this compound in rats, rabbits, dogs, and monkeys at 25 mg/kg, po, are given in Table 6.

The in vitro metabolic stability of compound **55** (10 μM) was assessed by monitoring the rate of disappearance of the parent compound following incubation with liver microsomes (1 mg of microsomal protein/ml) from various species at 37 °C with or without uridine diphosphate glucuronic acid (UDPGA). In the absence of UDPGA, compound **55** was metabolized at rates of 0.238 and 0.336 nmol/(min·mg of protein) in rat and rabbit microsomes, respectively.

Under these conditions, compound **55** was metabolically stable for up to 30 min of incubation with hepatic microsomes from dog, monkey, and human. When incubated in mixtures containing 10 μM UDPGA, the compound was rapidly metabolized by hepatic microsomes from rat, rabbit, dog, monkey, and human. The rank order of compound **55** stability when incubated in microsomes containing UDPGA was rabbit < monkey < dog < rat < human. Preliminary studies of mixtures of microsomes from dog, monkey, and human after incubation with compound **55** identified mainly a glucuronide conjugate **67** in all the above-mentioned species and a N-debenzylated product **56** in the monkey (Figure 6). The N-debenzylated product **56** is an active metabolite. In vivo, two major metabolites of compound **55** have been identified in plasma samples from rat, rabbit, dog and monkey, amide **68**, and the glucuronide conjugate. The glucuronide conjugate was identified by mass spectrometric determination. The amide derivative was independently synthesized and found to be an inactive metabolite. The reduction of hydroxamic acid to the amide may be due to the activity of gut microflora in addition to hepatic microsomal activity. In rat plasma, three additional metabolites were identified as N-debenzylated carboxylate **69**, *N*-debenzylamide **70**, and carboxylic acid derivative **71** (Figure 6).

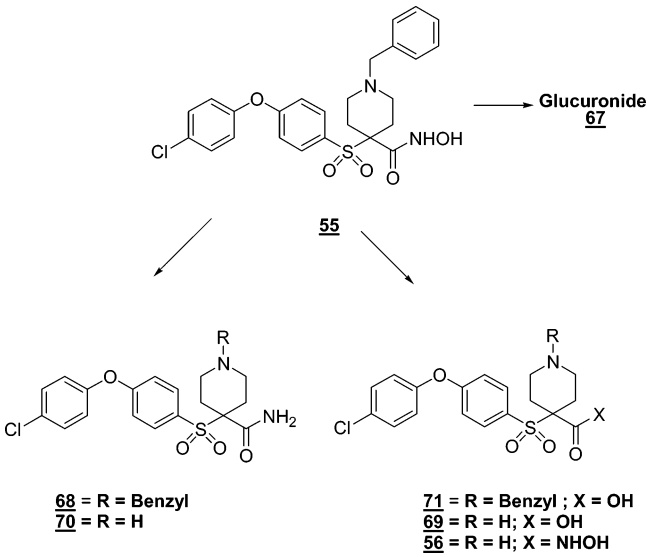


Figure 6. Metabolic pathway for compound **55**.

Surgically Induced Osteoarthritis (OA) Model in Rabbits. An aggressive OA model was established in rabbits by transecting the anterior cruciate ligament (ACL) and removing 50−90% of the medial meniscus in one hind knee (stifle) joint of mature (6-months old) male New Zealand white rabbits. Sham surgery was performed on the contralateral knee. Ten days after the surgery, twelve animals per group were dosed once daily by oral gavage with either vehicle, compound **55** at 25 mg/kg or the Roche reference standared (RS-130380) at 25 mg/kg. After 4 weeks of dosing, the rabbits were sacrificed and the knee joints were collected and scored for gross pathological changes by blinded investigators. The scoring system was based on damage to the articular cartilage. Each parameter is scored: 0, normal or no damage; 1, mild damage; 2, moderate damage; 3, severe damage. The three parameters were weighted as follows: pitting of the cartilage surface multiplied by 1, fissuring of the score multiplied by 2, and the erosion score multiplied by 3.

Table 7. Comparison of Efficacies of Compound **55** vs RS-130830 in the Rabbit OA

compd	average gross pathology scores ± SE
vehicle	23.4 ± 2.2[a]
compound **55** @ 25 mpk	6.8 ± 1.6[a]
RS-130830 @ 25 mpk	7.9 ± 1.5[a]
compound **55** @15 mpk	9.7 ± 1.[a]
sham (all groups)	6.3 ± 0.7[b]

[a] n = 12, right knee with ACL transection and menisectomy. [b] n= 48, left knee with sham surgery, average of all groups.

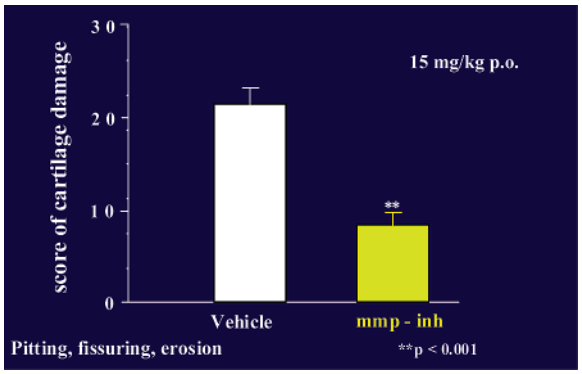


Figure 7. Effect of compound **55** on cartilage in rabbit on model.

The articular cartilage on the thibial plateau and femoral condyles were scored separately, and then the scores were added together. The maximum score per knee is 36. In this experiment, a highly statistically significant protective effect compared to vehicle was observed in the knees with ACL transection and menisectomy for compound **55** (Table 7, Figure 7). These results indicate that compound **55** is as efficacious as RS-130380 at 25 mg/kg, po. The compound is also active at 15 mg/kg, po. These results indicate that compound **55** is a selective, orally active MMP inhibitor.

Conclusion

In this paper, we have presented the design and synthesis of novel, non-peptidal MMP inhibitors with superior pharmacological properties. On the basis of the extensive exploration of analogue SAR and design considerations, a novel non-peptide hydroxamic acid MMP inhibitor was identified that shows potent activity in in vitro and in vivo assays. The desired enzyme selectivity profile (over MMP-1) was attained by structural modification of the P1′ position, taking advantage of distinctions in the depth of and the composition of the S1′ pocket of the MMPs. The enzyme binding interactions were confirmed by X-ray analysis. Among the various derivatives prepared in this series, compound **55** is a highly potent, selective, and orally active MMP-13 inhibitor. This compound showed significant activity in the short-term aggressive rabbit OA model. Compound **55** may or may not have a direct effect on inflammation but could be given concomitantly with agents that provide symptomatic relief in the short term (NSAIDS, Synvisc) with the promise of slowing or halting the destruction of articular cartilage, thus preserving the joints and their functions. Compound **55** exhibited very favorable pK parameters. In this series of compounds, selectivity can be achieved by substituting a proper substituent at the P1′ position. This compound was cocrystallized with the MMP-13 enzyme, and as anticipated, the 4-chlorophenoxy group occupies the S1′ position and the hydroxamic acid is chelated to the zinc atom, which is present at the active site of these enzymes. Although we have synthesized a very selective and potent orally active MMP inhibitor, it is only long-term studies that will tell us about the musculoskeletal side effects that are associated with this MMP inhibitor.

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. The combustion analyses were 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 melting points for the final compounds mentioned in the text were determined for their respective hydrochloride salts. The C, H, and N were determined for the free base of the hydroxamide derivatives.

1-Benzyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (19). Step 1. 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, and 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 water and 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 a pale-yellow oil. Yield: 4.4 g (100%). MS, m/z: 227 $(M + H)^+$.

Step 2. 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. The mixture was stirred for at least 3 h before the mixture was extracted with $CHCl_3$ and washed with water. 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 $(M + H)^+$.

Step 3. To a stirred solution of diethanol amine (10.5 g, 100 mmol) and anhydrous K_2CO_3 (30 g, excess) in dry acetone (250 mL), benzyl bromide (17.2 g, 100 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 cooled, the potassium salts were filtered off, and the reaction mixture was concentrated. The residue was extracted with chloroform and washed with water. The organic layer was further washed well with water, dried over $MgSO_4$, filtered, and concentrated. Colorless oil. Yield: 19.0 g, 97%. MS, m/z: 196 $(M + H)$.

Step 4. *N*-Benzyldiethanolamine (9.75 g, 50 mmol) was dissolved in saturated methanolic hydrochloric acid and concentrated to dryness. The hydrochloride thus formed was dissolved in methylene chloride (300 mL), thionyl chloride (20 g, excess) was added dropwise, and the mixture was stirred at room temperature for 1 h. At the end, the reaction mixture was concentrated to dryness and the product bis(2-chloroethyl)benzylamine hydrochloride was used for further transformation with out any purification. Yield: 13.0 g, 97%. MS, *m*/*z*: 232 $(M + H)^+$.

Step 5. To a stirred solution of bis(2-chloroethyl)benzylamine hydrochloride (6.6 g, 24.7 mmol), 18-crown-6 (500 mg), and anhydrous K_2CO_3 (30 g, excess) in dry acetone (250 mL), (4-methoxyphenylsulfonyl)acetic acid ethyl ester (6.12 g, 24 mmol) was added in a round-bottom flask, and the reaction mixture was heated at reflux for 16 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 water. The organic layer was further washed well with water, dried over $MgSO_4$, filtered, and concentrated. The dark-brown reaction mixture was purified by silica gel column chromatography by eluting it with 30% ethyl acetate/hexane, and the product 4-(4-methoxybenzenesulfonyl)-1-benzylpiperidine-4-carboxylic acid ethyl ester was isolated as a brown oil. Yield: 6.0 g, 60%. MS, *m*/*z*: 418 $(M + H)^+$.

Step 6. 4-(4-Methoxybenzenesulfonyl)-1-benzylpiperidine-4-carboxylic acid ethyl ester (5.0 g, 11.9 mmol) was dissolved in MeOH/THF (1:1, 200 mL), and the mixture was stirred at room temperature for 72 h in the presence of 10 N NaOH (10 mL). At the end, the reaction mixture was concentrated and the product was neutralized with concentrated HCl by dissolving it in water (200 mL). After the neutralization, the reaction mixture was concentrated to dryness. Ice-cold water (100 mL) was added to the solid and filtered. The product 4-(4-methoxybenzenesulfonyl)-1-benzylpiperidine-4-carboxylic acid was dried at 50 °C and taken to the next step without any purification. The product was a colorless solid. Yield: 3.2 g, 69%. MS, *m*/*z*: 390 $(M + H)^+$.

Step 7. To a stirred solution of 4-(4-methoxybenzenesulfonyl)-1-benzylpiperidine-4-carboxylic acid (2.0 g, 5.1 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. After 1 h, the oxalyl chloride reaction mixture was concentrated, the pale-yellow residue was dissolved in 10 mL of CH_2Cl_2, and 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 chloroform. The product 4-(4-methoxybenzenesulfonyl)-1-benzylpiperidine-4-carboxylic acid hydroxyamide was isolated as a colorless solid. Mp 90−95 °C. Yield: 1.2 g, 48%. MS, *m*/*z*: 405 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29 (m, 3H), 2.76−2.79 (m, 2H), 3.43 (m, 4H), 4.30 (s, 2H), 7.14−7.17 (d, 2H), 7.50−7.73 (m, 5H), 9.37 (s, 1H), 10.53 (s, 1H), 11.18 (s, 1H). Anal. ($C_{20}H_{24}N_2O_5S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-(3-methoxybenzyl)piperidine-4-carboxylic Acid Hydroxyamide (20). 2-[(2-Hydroxyethyl)(3-methoxybenzyl)amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (3.1 g, 29.5 mmol) and 3-methoxybenzyl chloride (5 g, 31.9 mmol). Yield: 9.28 g (99%). Yellow oil. MS, *m*/*z*: 226 $(M + H)^+$.

3-Methoxybenzyl-bis(2-chloroethyl)amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from 3-methoxybenzyl diethanolamine (4.4 g, 20 mmol). Yield: 4.5 g, 93%. Yellow solid. Mp 86−88 °C. MS, *m*/*z*: 263. $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(3-methoxybenzyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (5.0 g, 22 mmol) and bis(2-chloroethyl)(3-methoxybenzyl)amine hydrochloride (8.0 g, 23.5 mmol). Yield: 2.4 g, 24%. Low-melting solid. MS, *m*/*z*: 447.9 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(3-methoxybenzyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-(3-methoxybenzyl)piperidine-4-carboxylic acid ethyl ester (2.4 g, 5.36 mmol) dissolved in methanol (30 mL), 10 N sodium hydroxide (10 mL), and tetrahydrohydrofuran (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 710 mg, 32%). White solid. Mp 199 °C. MS, *m*/*z*: 419.9 $(M + H)^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-(3-methoxybenzyl)piperidine-4-carboxylic acid (830 mg, 1.98 mmol) and following the procedure as outlined in example **19** (step 7), 190 mg of 4-(4-methoxybenzenesulfonyl)-1-(3-methoxybenzyl)-piperidine-4-carboxylic acid hydroxamide was isolated as a white solid. Mp 130 °C. Yield: 20.4%. MS, *m*/*z*: 435.0 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24−2.32 (m, 2H), 2.51-(d, 2H), 2.73−2.83 (m, 2H), 3.37 (d, 2H), 3.76 (s, 3H), 3.88 (s, 3H), 4.32 (s, 2H), 7.01−7.77 (m, 8H), 9.38 (s, 1H), 10.1 (s, 1H). Anal. ($C_{21}H_{26}N_2O_6S$) C, H, N.

1-(3,4-Dichlorobenzyl)-4-(4-methoxybenzenesulfonyl)-piperidine-4-carboxylic Acid Hydroxamide (21). 2-[(2-Hydroxyethyl)(3,4-dichlorobenzyl)amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (4.84 g, 46 mmol) and 3,4-dichlorobenzyl chloride (9.0 g, 46 mmol). Yield: 13.8 g, 99%. Colorless oil. MS, *m*/*z*: 264.3 $(M + H)^+$.

3,4-Dichlorobenzyl-bis(2-chloroethyl)amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from 3,4-dichlorobenzyldiethanolamine (10.7 g, 41 mmol). Yield: 99%. Yellow solid. Mp 218−220 °C. MS, *m*/*z*: 301.8 $(M + H)^+$.

1-(3,4-Dichlorobenzyl)-4-(methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (2.9 g, 11 mmol) and 3,4-dichlorobenzyl-bis(2-chloroethyl)amine hydrochloride (3.4 g, 11 mmol). Yield: 5.9 g, 60%. Brown oil. MS, *m*/*z*: 494.5 $(M + H)^+$.

1-(3,4-Dichlorobenzyl)-4-(4-methoxybenzenesulfulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-(3,4-dichlorobenzyl)-4-(methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (5.0 g, 10 mmol) dissolved in methanol (50 mL), 10 N sodium hydroxide (15 mL), and tetrahydrofuran (75 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 2.94 g, 62%). MS, *m*/*z*: 458.3 $(M + H)^+$.

Starting from 1-(3,4-dichlorobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid (2.67 g, 5.8 mmol) and following the procedure as outlined in example **19** (step 7), 0.2 g of 1-(3,4-dichlorobenzyl)-4-(4-methoxybenzenesulfonyl)-piperidine-4-carboxylic acid hydroxamide was isolated as a white solid. Mp 192−195 °C. Yield: 10%. MS, *m*/*z*: 472.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.20−2.28 (m, 2H), 2.76−2.79 (m, 2H), 3.43−3.44 (m, 4H), 4.30 (s, 2H), 7.14−7.17 (d, 2H), 7.50−7.73 (d, 1H), 7.65−7.68 (d, 2H), 7.72−7.75 (d, 2H), 7.87 (s, 1H), 9.37 (s, 1H), 10.53 (s, 1H), 11.18 (s, 1H). Anal. ($C_{20}H_{22}Cl_2N_2O_5S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-(4-methylbenzyl)piperidine-4-carboxylic Acid Hydroxamide (22). 2-[(2-Hydroxyethyl)(4-methylbenzyl)amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (4.8 g, 46 mmol) and 4-methylbenzyl chloride (8.5 g, 46 mmol). Yield: 9.8 g, 99%). MS, *m*/*z*: 209.9 $(M + H)^+$.

4-Methylbenzyl-bis(2-chloroethyl)amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from 4-methylbenzyldiethanol-

amine (6 g, 20 mmol). Yield: 5.2 g, 84%. Yellow solid. Mp 145−147 °C. MS, *m/z*: 245.9 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(4-methylbenzyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (7.0 g, 27 mmol) and 4-methylbenzyl-bis(2-chloroethyl)amine hydrochloride (5.0 g, 17 mmol). Yield: 4.64 g, 63%. Low-melting solid. MS, *m/z*: 431.9 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)1-(4-methylbenzyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (4.3 g, 9.9 mmol) dissolved in methanol (30 mL), 10 N sodium hydroxide (10 mL), and tetrahydrohydrofuran (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 1.6 g, 40%). White solid. Mp 207−208 °C. MS, *m/z*: 404.3 $(M + H)^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-(4-methylbenzyl)piperidine-4-carboxylic acid (1.59 g, 3.9 mmol) and following the procedure as outlined in example **19** (step 7), 0.505 g of 4-(4-methoxybenzenesulfonyl)-1-(4-methylbenzyl)-piperidine-4-carboxylic acid hydroxamide was isolated as a white solid. Mp 176−177 °C. Yield: 32%. MS, *m/z*: 419.0 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24−2.32 (m, 2H), 2.51 (t, 3H), 2.73−2.80 (m, 2H), 3.35−3.50 (m, 4H), 3.87 (s, 3H), 4.24 (s, 2H), 7.13−7.17 (d, 2H), 7.23−7.60 (d, 2H), 7.38−7.41 (d, 2H), 7.65−7.68 (d, 2H). Anal. ($C_{21}H_{26}N_2O_5S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-naphthalene-2-ylmethylpiperidine-4-carboxylic Acid Hydroxamide (23). 2-[(2-Hydroxyethyl)(2-naphthyl-2-ylmethyl)amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (6.18 g, 59 mmol) and 2-(bromomethyl)naphthalene (10 g, 45 mmol). Yield: 12.7 g, 96%. Yellow solid. Mp 162−164 °C. MS, *m/z*: 246.0 $(M + H)^+$.

2-Naphthyl-2-ylmethyl-bis(2-chloroethyl)amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from 2-naphthylylmethyldiethanolamine (10 g, 36 mmol). Yield: 9.1 g, 79%. Brown solid. Mp 124−126 °C. MS, *m/z*: 281.9 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-naphthalene-2-ylmethylpiperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (8.4 g, 32 mmol) and 1-naphthaleneylmethyl-bis(2-chloroethyl)amine hydrochloride ((8.6 g, 27 mmol). Yield: 6.5 g, 52%. Low-melting solid. MS, *m/z*: 440.0 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-naphthalene-2-ylmethylpiperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-naphthalene-2-ylmethylpiperidine-4-carboxylic acid ethyl ester (6.3 g, 13 mmol) dissolved in methanol (30 mL), 10 N sodium hydroxide (30 mL), and tetrahydrofuran (30 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 2.3 g, 36%). Yellow solid. Mp 226−228 °C. MS, *m/z*: 440.0 $(M + H)^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-naphthalene-2-yl-methylpiperidine-4-carboxylic acid (2.18 g, 5.0 mmol) and following the procedure as outlined in example **19** (step 7), 0.753 g of 4-(4-methoxybenzenesulfonyl)-1-naphthalene-2-ylmethylpiperidine-4-carboxylic acid hydroxamide was isolated as a off-white solid. Mp 168−170 °C. Yield: 31%. MS, *m/z*: 455.0 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.29−2.33 (m, 2H), 2.86−2.89 (m, 2H), 3.42−3.46 (m, 4H), 3.85 (s, 3H), 4.46 (s, 2H), 7.13−7.16 (d, 2H), 7.56−7.64 (m, 3H), 7.65−7.68 (d, 2H), 7.98−8.00 (m, 3H), 8.21 (s, 1H), 10.70 (s, 1H), 11.20 (s, 1H). Anal. ($C_{24}H_{26}N_2O_5S$) C, H, N.

1-Biphenyl-4-ylmethyl-4-(4-methoxybenzenesulfonyl)-piperidine-4-carboxylic Acid Hydroxamide (24). 2-[(2-Hydroxyethyl)(1-biphenyl-4-ylmethyl))amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (5.2 g, 49 mmol) and 4-(chloromethyl)biphenyl (10 g, 49 mmol). Yield: 9.98 g, 66%. White solid. Mp 160−162 °C. MS, *m/z*: 271.9 $(M + H)^+$. This was converted to the 1-biphenyl-4-ylmethyl-bis(2-chloroethyl)-amine hydrochloride as outlined in example **19**, step 4.

1-Biphenyl-4-ylmethyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (2.85 g, 11 mmol) and 1-biphenyl-4-ylmethyl-bis(2-chloroethyl)amine hydrochloride (3.4 g, 11 mmol). Yield: 2.1 g, 39%. White solid, Mp 176−178 °C. MS, *m/z*: 494.1 $(M + H)^+$.

1-Biphenyl-4-ylmethyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-biphenyl-4-ylmethyl(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (5.7 g, 12 mmol) dissolved in ethanol (20 mL), tetrahydrofuran (20 mL), and 10 N sodium hydroxide (10 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 2.1 g, 39%. MS, *m/z*: 465.8 $(M + H)^+$.

Starting from 1-biphenyl-4-ylmethyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid (1.0 g, 2.2 mmol) and following the procedure as outlined in example **19** (step 7), 0.132 g of 1-biphenyl-4-ylmethyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxamide was isolated as a tan solid. Mp 168 °C. Yield: 20%. MS, *m/z*: 440.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30−2.35 (m, 2H), 2.83−2.87 (m, 2H), 3.35−3.5 (m, 4H), 3.87 (s, 3H), 7.15−7.721 (d, 2H), 7.49−7.65 (m, 5H), 7.68−7.74 (d, 2H), 9.3 (s, 1H), 10.3 (s, 1H), 11.15 (s, 1H). Anal. ($C_{26}H_{28}N_2O_5S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-(3-methylbut-2-enyl)-piperidine-4-carboxylic Acid Hydroxamide (25). 2-[(2-Hydroxyethyl)-1-(3-methylbut-2-enyl)amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (4.1 g, 39 mmol) and 4-bromo-2-methylbutene (6.0 g, 40 mmol). Yield: 98%. Brown oil. MS, *m/z*: 173.8 $(M + H)^+$.

1-(3-Methylbut-2-enyl)]-bis(2-chloroethyl)amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from 2-[(2-hydroxyethyl)-1-(3-methylbut-2-enyl)amino]ethanol (10.4 g, 50 mmol). Yield: 10.5 g, 99%. Brown solid. MS, *m/z*: 210.3 $(M + H)$.

4-(4-Methoxybenzenesulfonyl)-1-(3-methylbut-2-enyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (11.32 g, 44 mmol) and 3-methylbut-2-enyl)bis(2-chloroethyl)amine (10.4 g, 50 mmol). Yield: 6.2 g, 36%. Brown oil. MS, *m/z*: 395.6 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(3-methylbut-2-enyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-(3-methylbut-2-enyl)piperidine-4-carboxylic acid ethyl ester (6.2 g, 16 mmol) dissolved in ethanol (15 mL), 10 N sodium hydroxide (10 mL), and tetrahydrofuran (75 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 1.2 g, 21%. Brown solid. Mp 196−197 °C. MS, *m/z*: 367.9 $(M + H)^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-(3-methylbut-2-enyl)piperidine-4-carboxylic acid (1.0 g. 3.0 mmol) and following the procedure as outlined in example **19** (step 7), 110 mg of 4-(4-methoxybenzenesulfonyl)-1-(3-methylbut-2-enyl)piperidine-4-carboxylic acid hydroxamide was isolated as a pale-yellow solid. Mp 142−145 °C. Yield: 12%. MS, *m/z*: 383.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.67 (s, 3H), 1.79 (s, 3H), 2.18−2.23 (m, 2H), 2.66−2.73 (m, 2 H), 3.37−3.46 (m, 2H), 3.67−3.69 (m, 2H), 5.19−5.24 (m, 1H), 7.15−7.18 (d, 2H), 7.67−7.70 (d, 2H), 9.34 (s, 1H), 9.88 (s, 1H), 11.15 (s, 1H). Anal. ($C_{18}H_{26}N_2O_5S$) C, H, N.

1-(4-Bromobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (26). 2-[(4-Bromobenzyl)(2-hydroxyethyl)amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (22.5 g, 150 mmol) and 4-bromobenzyl bromide (25 g, 100 mmol). Yield: 33.66 g, 99%. Yellow oil. MS, *m/z*: 273.8 $(M + H)^+$.

(4-Bromobenzyl)bis(2-chloroethyl)amine was prepared according to the general method as outlined in example **19** (step

4), starting from 2-[(4-bromobenzyl)(2-hydroxyethyl)amino]-ethanol (33.28 g, 122 mmol). Yield: 47 g, 99%. Brown solid. Mp 125 °C. MS, *m/z*: 309.8 $(M + H)^+$.

1-(4-Bromobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (8.6 g, 33.5 mmol) and (4-bromobenzyl)bis(2-chloroethyl)amine (13.3 g, 38.6 mmol). Yield: 17 g, 44%. Brown oil. MS, *m/z*: 497.8 $(M + H)^+$.

1-(4-Bromobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-(4-bromobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (16.5 g, 33.3 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 6.18 g, 40%. Tan solid. Mp 215 °C. MS, *m/z*: 469.7 $(M + H)^+$.

Starting from 1-(4-bromobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid (1.95 g, 4.2 mmol) and following the procedure as outlined in example **19** (step 7), 1.29 g of 1-(4-bromobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as an off-white solid. Yield: 60%. Mp 180 °C. MS, *m/z*: 484.7 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.18−2.29 (m, 2H), 2.46 (d, 2H), 2.74−2.89 (m, 2H), 3.39 (d, 2H), 3.87 (s, 3H), 4.28 (s, 2H), 7.18 (d, 2H), 7.49 (d, 2H), 7.65−7.68 (m, 4H), 9.37 (s, 1H), 10.5 (s, 1H). Anal. ($C_{20}H_{23}BrN_2O_5S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-(3-phenylpropyl)piperidine-4-carboxylic Acid Hydroxyamide (27). 2-[(2-Hydroxyethyl)(3-phenylpropyl)amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (15.8 g, 151 mmol) and 1-bromo-3-phenylpropane (20 g, 101 mmol). Yield: 21.31 g, 95%. Yellow oil. MS, *m/z*: 223.9 $(M + H)^+$.

Bis(2-chloroethyl)(3-phenylpropyl)amine was prepared according to the general method as outlined in example **19** (step 4), starting from 2-[(2-hydroxyethyl)(3-phenylpropyl)amino]-ethanol (20.32 g, 90.7 mmol). Yield: 24.9 g, 92%. Brown oil. MS, *m/z*: 259.8 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(3-phenylpropyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (12 g, 46.5 mmol) and bis(2-chloroethyl)(3-phenylpropyl)amine (24.8 g, 93.8 mmol). Yield: 11.24 g, 54%. Brown oil. MS, *m/z*: 446 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(3-phenylpropyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-(3-phenylpropyl)piperidine-4-carboxylic acid ethyl ester (10.74 g, 24.13 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (40 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 4.67 g, 47%. Off-white powder. Mp 203 °C. MS, *m/z*: 418.2 $(M + H)^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-(3-phenylpropyl)piperidine-4-carboxylic acid (4.37 g, 10.4 mmol) and following the procedure as outlined in example **19** (step 7), 1.64 g of 4-(4-methoxybenzenesulfonyl)-1-(3-phenylpropyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as an off-white solid. Yield: 37%. Mp 143 °C. MS, *m/z*: 432.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.92−1.97 (m, 2H), 2.18−2.29 (m, 2H), 2.47 (d, 2H), 2.58 (t, J = 7.7 Hz, 2H), 2.6−2.73 (m, 2H), 3.0−3.06 (m, 2H), 3.60 (d, J = 12.3 Hz, 2H), 3.87 (s, 2H), 7.15−7.30 (m, 7H), 7.68, (d, J = 9 Hz, 2H), 9.3 (s, 1H), 10.1 (s, 1H). Anal. ($C_{22}H_{28}N_2O_5S$) C, H, N.

1-*tert*-Butyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (28). *tert*-Butyl-bis(2-chloroethyl)amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from 1-*tert*-butyldiethanolamine (6 g, 37.2 mmol). Yield: 11.15 g, 99%. White solid. MS, *m/z*: 197.8 $(M + H)^+$.

1-*tert*-Butyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (10 g, 38.76 mmol) and *tert*-butyl-bis(2-chloroethyl)amine (5.25 g, 22.43 mmol). Yield: 5.37 g, 62%. Brown oil. MS, *m/z*: 384 $(M + H)^+$.

1-*tert*-Butyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-*tert*-butyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (5.37 g, 14 mmol) dissolved in methanol (300 mL) and 10 N NaOH (23 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 1.52 g, 30.6%. White powder. Mp 204 °C. MS, *m/z*: 356 $(M + H)^+$.

Starting from 1-*tert*-butyl-4-(4-methoxybenzenesulfonyl)-piperidine-4-carboxylic acid (320 mg, 0.9 mmol) and following the procedure as outlined in example **19** (step 7), 190 mg of 1-*tert*-butyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as a green solid. Yield: 52%. Mp 40°C. MS, *m/z*: 371.1 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (s, 9H), 1.54 (m, 2H), 1.66 (m, 2H), 2.39 (m, 2H), 2.98 (m, 2H), 3.88 (s, 3H), 7.18 (d, 2H), 7.67 (d, 2H). Anal. ($C_{17}H_{26}N_2O_5S$) C, H, N.

1-Butyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (29). Butyl-bis(2-chloroethyl)amine was prepared according to the general method as outlined in example **19** (step 4), starting from *N*-butyldiethanolamine (6 g, 37.2 mmol). Yield: 11.3 g, 99%. White powder. Mp 165 °C. MS, *m/z*: 197.9 $(M + H)^+$.

1-Butyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (5 g, 19.38 mmol) and butyl-bis(2-chloroethyl)amine hydrochloride (4.52 g, 19.38 mmol). Yield: 6.86 g, 93%. Brown oil. MS, *m/z*: 384 $(M + H)^+$.

1-Butyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-butyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (6.42 g, 16.8 mmol) dissolved in methanol (200 mL) and 10 N NaOH (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 1.6 g, 27%. White powder. Mp 206°C. MS, *m/z*: 356.4 $(M + H)^+$.

Starting from 1-butyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid (1.51 g, 4.3 mmol) and following the procedure as outlined in example **19** (step 7), 200 mg of 1-butyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as an off-white solid. Yield: 9.3%. Mp 75 °C. MS, *m/z*: 371.1 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, J = 7.2 Hz, 3H), 1.27 (m, 2H), 1.59 (m, 2H), 2.27 (m, 2H), 2.45 (m, 2H), 2.50 (m, 2H), 2.65 (m, 2H), 2.97 (m, 2H), 3.88 (s, 3H), 7.18 (d, 2H), 7.69 (d, 2H). Anal. ($C_{17}H_{26}N_2O_5S$) C, H, N.

1-Cyclooctyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (30). Cyclooctyl-bis(2-chloroethyl)amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from *N*-cyclooctyldiethanolamine (6 g, 28 mmol). Yield: 10 g, 99%. Off-white solid. Mp 158 °C. MS, *m/z*: 251.9 $(M + H)^+$.

1-Cyclooctyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (5 g, 19.4 mmol) and cyclooctyl-bis(2-chloroethyl)amine hydrochloride (5.57 g, 19.4 mmol). Yield: 8.2 g, 96%. Brown oil. MS, *m/z*: 438 $(M + H)^+$.

1-Cyclooctyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-cyclooctyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (8 g, 18.3 mmol) dissolved in methanol (200 mL) and 10 N NaOH (25 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 2.36 g, 32%. White powder. Mp 180 °C. MS, *m/z*: 410 $(M + H)^+$.

Starting from 1-cyclooctyl-4-(4-methoxybenzenesulfonyl)-piperidine-4-carboxylic acid (2.26 g, 5.53 mmol) and following the procedure as outlined in example **19** (step 7), 570 mg of 1-cyclooctyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as a white powder. Yield:

22%. Mp >200 °C. MS, *m/z*: 425 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.42−1.66 (m, 14H), 1.83 (m, 2H), 2.33 (m, 2H), 2.67 (m, 2H), 3.30−3.51 (m, 3H) 3.88 (s, 3H) 7.17 (d, 2H), 7.66 (d, 2H). Anal. ($C_{21}H_{32}N_2O_5S$) C, H, N.

1-Ethyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (31). 1-Ethyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)-acetic acid ethyl ester (3 g, 11.6 mmol) and ethyl-bis(2-chloroethyl)amine hydrochloride (2.39 g, 11.6 mmol). Yield: 3.09 g, 75%. Low-melting brown solid. MS, *m/z*: 356 $(M + H)^+$.

1-Ethyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-ethyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (2.42 g, 6.8 mmol) dissolved in methanol (100 mL) and 10 N NaOH (15 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 1.29 g, 58%. White solid. Mp 209 °C. MS, *m/z*: 328 $(M + H)^+$.

Starting from 1-ethyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid (1.23 g, 3.76 mmol) and following the procedure as outlined in example **19** (step 7), 1.02 g of 1-ethyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as an off-white powder. Yield: 80%. Mp 85 °C. MS, *m/z*: 343 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.926 (t, J = 7.1 Hz, 3H), 1.68−1.89 (m, 4H), 2.05−2.24 (m, 4H), 2.73 (q, 2H), 3.85 (s, 3H), 7.07 (d, 2H), 7.64 (d, 2H). Anal. ($C_{15}H_{22}N_2O_5S$) C, H, N.

1-Isopropyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (32). 1-Isopropyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (5.7 g, 22.2 mmol) and isopropyl-bis(2-chloroethyl)amine hydrochloride (4.9 g, 22.2 mmol). Yield: 5.64 g, 68%. Low-melting brown solid. MS, *m/z*: 370 $(M + H)^+$.

1-Isopropyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-isopropyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (5.6 g, 15.2 mmol) dissolved in methanol (75 mL) and 10 N NaOH (25 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 2.18 g, 42%. White powder. Mp 204 °C. MS, *m/z*: 341.9 $(M + H)^+$.

Starting from 1-isopropyl-4-(4-methoxybenzenesulfonyl)-piperidine-4-carboxylic acid (2.13 g, 6.25 mmol) and following the procedure as outlined in example **19** (step 7), 590 mg of 1-isopropyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as a white powder. Yield: 2.4%. Mp 75 °C. MS, *m/z*: 357 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.21 (d, J = 6.6 Hz, 6H), 2.33−3.53 (m, 9H), 3.88 (s, 3H), 7.16 (d, 2H), 7.66 (d, 2H). Anal. ($C_{16}H_{24}N_2O_5S$) C, H, N.

1-Methyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (33). 1-Methyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)-acetic acid ethyl ester (3 g, 11.6 mmol) and methyl-bis(2-chloroethyl)amine hydrochloride (2.2 g, 11.6 mmol). Yield: 3.09 g, 75%. Low-melting brown solid. MS, *m/z*: 342 $(M + H)^+$.

1-Methyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-methyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (8.7 g, 25.6 mmol) dissolved in methanol (300 mL) and 10 N NaOH (35 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 3.23 g, 41%. White solid. Mp 204 °C. MS, *m/z*: 313.9 $(M + H)^+$.

Starting from 1-methyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid (2.0 g, 6.38 mmol) and following the procedure as outlined in example **19** (step 7), 1.10 g of 1-methyl-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as a yellow powder. Yield: 53%. Mp 89 °C. MS, *m/z*: 329 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.67−1.76 (m, 2H), 1.85−1.96 (m, 2H), 2.05 (s, 3H), 2.17 (d, J = 11.4 Hz, 2H), 2.57 (d, J = 10.4 Hz, 2H), 3.83 (s, 3H), 7.02 (d, 2H), 7.62 (d, 2H). Anal. ($C_{14}H_{20}N_2O_5S$) C, H, N.

1-Benzyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (34). 1-Benzyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(butoxybenzenesulfonyl)acetic acid ethyl ester (6 g, 20 mmol) and bis(2-chloroethyl)benzylamine hydrochloride (10 g, 30 mmol). Yield: 5.15 g, 56%. Yellow oil. MS, *m/z*: 460 $(M + H)^+$.

1-Benzyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-benzyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (5.1 g, 11.1 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (10 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 2.66 g, 56%. Off-white solid. Mp 210 °C. MS, *m/z*: 432 $(M + H)^+$.

Starting from 1-benzyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid (2.61 g, 6.06 mmol) and following the procedure as outlined in example **19** (step 7), 860 mg of 1-benzyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as an off-white powder. Yield: 32%. Mp 144 °C. MS, *m/z*: 446.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.94 (t, J = 7.3 Hz, 3H), 1.44 (q, J = 7.5 Hz, 2H), 1.70 (q, 2H), 2.28−2.32 (m, 2H), 2.50 (d, 2H), 2.74−2.83 (m, 2H), 3.35 (d, 2H), 4.08 (t, J = 6.3 Hz, 2H), 4.34 (s, 2H), 7.13 (d, J = 8.7, 2H), 7.45 (s, 3H), 7.54 (s, 2H), 7.74 (d, J = 8.7, 2H), 9.35 (s, 1H), 10.7 (s, 1H). Anal. ($C_{23}H_{30}N_2O_5S$) C, H, N.

1-(4-Fluorobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (35). 1-(4-Fluorobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (18.8 g, 72.8 mmol) and (4-fluorobenzyl)bis(2-chloroethyl)amine hydrochloride (20.8 g, 73 mmol). Yield: 25 g, 79%. Brown oil. MS, *m/z*: 436.9 $(M + H)^+$.

1-(4-Fluorobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-(4-fluorobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (17.4 g, 40 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (40 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 10.8 g, 66%. White solid. Mp 154°C. MS, *m/z*: 408 $(M + H)^+$.

Starting from 1-(4-fluorobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid (8.14 g, 20 mmol) and following the procedure as outlined in example **19** (step 7), 4.3 g of 1-(4-fluorobenzyl)-4-(4-methoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as an off-white solid. Yield: 51%. Mp 176−178°C. MS, *m/z*: 484.7 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.12−2.20 (m, 2H), 2.64−2.79 (m, 2H), 3.32−3.45 (m, 4H), 3.87 (s, 3H), 4.31 (s, 2H), 7.14−7.19 (d, J = 17 Hz, 2H), 7.27−7.33 (d, J = 8.1 Hz, 2H), 7.50−7.54 (d, 2H), 7.65−7.68 (d, 2H), 9.38 (s, 1H), 9.75 (s, 1H). Anal. ($C_{20}H_{23}FN_2O_5S$) C, H, N.

1-(4-Fluorobenzyl)-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (36). 1-(4-Fluorobenzyl)-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from from 4-(butoxybenzenesulfonyl)acetic acid ethyl ester (6 g, 20 mmol) and (4-fluorobenzyl)bis(2-chloroethyl)amine hydrochloride (5.73 g, 20 mmol). Yield: 8.2 g, 86%. Yellow oil. MS, *m/z*: 478 $(M + H)^+$.

1-(4-Fluorobenzyl)-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-(4-fluorobenzyl)-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (4.77 g, 10 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (10 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 3.5 g, 79%. White solid. Mp 114 °C. MS, *m/z*: 450 $(M + H)^+$.

Starting from 1-(4-fluorobenzyl)-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid (2.24 g, 5.0 mmol) and following the procedure as outlined in example **19** (step 7), 200 mg of 1-(4-fluorobenzyl)-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as an off-white powder. Yield: 9%. Mp 112 °C. MS, *m*/*z*: 465.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.94 (t, $J = 7.3$ Hz, 3H), 1.35−1.50 (m, 2H), 1.68−1.77 (m, 2H), 2.20−2.28 (m, 2H), 2.66−2.77 (m, 2H), 3.77−3.78 (m, 4H), 4.06−4.10 (m, 2H), 4.19 (s, 2H), 7.14−7.19 (d, $J = 8.7$, 2H), 7.27−7.33 (d, 2H), 7.50−7.54 (d, 2H), 7.65−7.68 (d, 2H), 9.34 (s, 1H), 10.55 (s, 1H). Anal. ($C_{23}H_{29}FN_2O_5S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-(4-methoxybenzyl)piperidine-4-carboxylic Acid Hydroxyamide (37). 2-[(2-Hydroxyethyl)(4-methoxybenzyl)amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (12.0 g, 114 mmol) and 4-methoxybenzyl chloride (14.2 g, 100 mmol). Yield: 17.5 g, 77%. Yellow oil. MS, *m*/*z*: 226 (M + H).

4-Methoxybenzyl-bis(2-chloroethyl)amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from 4-methoxybenzyldiethanolamine (10 g, 44 mmol). Yield: 10 g, 75%. Yellow solid. Mp 55 °C. MS, *m*/*z*: 263.1 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(4-methoxybenzyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (5.0 g, 20 mmol) and bis(2-chloroethyl)(4-methoxybenzyl)amine hydrochloride (7.0 g, 22 mmol). Yield: 5.0 g, 56%. Low-melting solid. MS, *m*/*z*: 448.5 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(4-methoxybenzyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-(4-methoxybenzyl)piperidine-4-carboxylic acid ethyl ester (4.2 g, 10 mmol) dissolved in methanol (30 mL), 10 N sodium hydroxide (10 mL), and tetrahydrohydrofuran (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 3.0 g, 71%. White solid. Mp 190 °C. MS, *m*/*z*: 420.4 $(M + H)^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-(4-methoxybenzyl)piperidine-4-carboxylic acid (2.0 g, 4.7 mmol) and following the procedure as outlined in example **19** (step 7), 1.2 g of 4-(4-methoxybenzenesulfonyl)-1-(4-methoxybenzyl)-piperidine-4-carboxylic acid hydroxamide was isolated as a white solid. Mp 175 °C. Yield: 1.2 g, 59%. MS, *m*/*z*: 435.0 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.8 (m, 4H), 2.3 (m, 2H), 2.73 (m, 2H), 3.37 (d, 2H), 3.76 (s, 3H), 3.88 (s, 3H), 6.87 (d, 2H), 7.11 (d, 2H), 7.21 (d, 2H), 7.65 (d, 2H), 9.2 (brs, 1H), 10.9 (brs, 1H). Anal. ($C_{21}H_{26}N_2O_6S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-[2-(4-methoxyphenyl)ethyl]piperidine-4-carboxylic Acid Hydroxyamide (38). 2-{(2-Hydroxyethyl)[2-(4-methoxyphenyl)ethyl]amino}-ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (10.0 g, excess) and 1-(2-chloroethyl)-4-methoxybenzene (8.5 g, 50 mmol). Yield: 11 g, 92%. Yellow oil. MS, *m*/*z*: 240 $(M + H)^+$.

The corresponding dichloride, bis(2-chloroethyl)(4-methoxyphenyl-2-ethyl)amine hydrochloride, was prepared according to the general method as outlined in example **19** (step 4), starting from 2-{(2-hydroxyethyl)[2-(4-methoxyphenyl)ethyl]-amino}ethanol (10 g, 41.8 mmol). Yield: 11 g, 95%. Brown oil. MS, *m*/*z*: 277.2 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-[2-(4-methoxyphenyl)ethyl]-piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (5.0 g, 20 mmol) and bis(2-chloroethyl)(4-methoxyphenyl-2-ethyl)amine hydrochloride (6.4 g, 20 mmol). Yield: 6.0 g, 65%. Brown oil. MS, *m*/*z*: 462.5 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-[2-(4-methoxyphenyl)ethyl]-piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-[2-(4-methoxyphenyl)ethyl]piperidine-4-carboxylic acid ethyl ester (5.0 g, 10.8 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (40 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 4.0 g, 85%. White powder. Mp 205 °C. MS, *m*/*z*: 434.5 $(M + H)^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-[2-(4-methoxyphenyl)ethyl]piperidine-4-carboxylic acid (1.5 g, 3.46 mmol) and following the procedure as outlined in example **19** (step 7), 900 mg of 4-(4-methoxybenzenesulfonyl)-1-[2-(4-methoxyphenyl)ethyl]piperidine-4-carboxylic acid hydroxyamide was isolated as an off-white solid. Yield: 58%. Mp 206 °C. MS, *m*/*z*: 449.5 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.3 (m, 2H), 2.5 (m, 3H), 2.8 (m, 2H), 2.95 (m, 2H), 3.25 (m, 2H), 3.4 (m,4H), 3.60 (d, $J = 12.3$ Hz, 2H), 3.77 (s, 3H), 3.99 (s, 3H), 6.9 (d, 2 H), 7.1−7.25, (q, 4H), 7.7 (d, 2H), 9.3 (s, 1H), 10.6 (s, 1H). Anal. ($C_{22}H_{28}N_2O_6S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-(2-phenylethyl)piperidine-4-carboxylic Acid Hydroxyamide (39). 2-[(2-Hydroxyethyl)(2-phenylethyl)amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (6.0 g, 57). and 2-bromoethylbenzene (9.0 g, 48.3 mmol). Yield: 9 g, 90%. Yellow oil. MS, *m*/*z*: 210 $(M + H)^+$.

Bis-(2-chloroethyl)(2-phenylethyl)amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from 2-[(2-hydroxyethyl)(2-phenylethyl)amino]ethanol (8.5 g, 40.6 mmol). Yield: 11 g, 95%. Brown oil. MS, *m*/*z*: 247.1 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(2-phenylethyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (5.0 g, 20 mmol) and bis(2-chloroethyl)(2-phenylethyl)amine hydrochloride (5.6 g, 20 mmol). Yield: 5.5 g, 63%. Brown oil. MS, *m*/*z*: 432.5 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(2-phenylethyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-(2-phenylethyl)piperidine-4-carboxylic acid ethyl ester (3.0 g, 6.9 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (40 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 2.0 g, 72%. White powder. Mp 208° C. MS, *m*/*z*: 404.5 $(M + H)^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-(2-phenylethyl)piperidine-4-carboxylic acid (1.5 g, 3.7 mmol) and following the procedure as outlined in example **19** (step 7), 900 mg of 4-(4-methoxybenzenesulfonyl)-1-(2-phenylethyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as a white solid. Yield: 58%. Mp 205°C. MS, *m*/*z*: 419.4 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.3 (m, 2H), 2.5 (m, 3H), 2.8 (m, 2H), 2.95 (m, 2H), 3.25 (m, 2H), 3.4 (m, 4H), 3.9 (s, 3H), 7.22−7.8 (m, 9H), 10.6 (s, 1H), 11.2 (brs, 1H). Anal. ($C_{21}H_{26}N_2O_5S$) C, H, N.

4-(4-*n*-Butoxybenzenesulfonyl)-1-(4-methoxybenzyl)-piperidine-4-carboxylic Acid Hydroxyamide (40). 4-(4-*n*-Butoxybenzenesulfonyl)-1-(4-methoxybenzyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(*n*-butoxybenzenesulfonyl)acetic acid ethyl ester (2.5 g, 10 mmol) and bis(2-chloroethyl)(4-methoxybenzyl)amine hydrochloride (3.0 g, 10 mmol). Yield: 3.5 g, 71%. Low-melting solid. MS, *m*/*z*: 490.5 $(M + H)^+$.

4-(4-*n*-Butoxybenzenesulfonyl)-1-(4-methoxybenzyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-butoxybenzenesulfonyl)-1-(4-methoxybenzyl)piperidine-4-carboxylic acid ethyl ester (3.0 g, 6.1 mmol) dissolved in methanol (30 mL), 10 N sodium hydroxide (10 mL), and tetrahydrohydrofuran (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 1.5 g, 53%. White solid. Mp 207 °C. MS, *m*/*z*: 462.5 $(M + H)^+$.

Starting from 4-(4-*n*-butoxybenzenesulfonyl)-1-(4-methoxybenzyl)piperidine-4-carboxylic acid (1.0 g, 2.1 mmol) and following the procedure as outlined in example **19** (step 7), 1.2 g of 4-(4-butoxybenzenesulfonyl)-1-(4-methoxybenzyl)piperidine-4-carboxylic acid hydroxamide was isolated as a white solid. Mp 173 °C. Yield: 800 mg, 77%. MS, *m*/*z*: 477.5 (M +

H)$^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.9 (t, 3H), 1.4 (m, 2H), 1.7 (m, 2H), 2.3 (m, 2H), 2.5 (m, 2H), 2.7 (m, 2H), 3.3 (m, 2H), 3.5 (m, 2H), 4.1 (t, 2H), 4.3 (m, 2H), 6.97 (d, 2H), 7.14 (d, 2H), 7.48 (d, 2H), 7.7 (d, 2H), 9.4 (brs, 1H), 10.9 (brs, 1H). Anal. ($C_{24}H_{32}N_2O_6S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-(3-phenoxypropyl)piperidine-4-carboxylic Acid Hydroxyamide (41). 2-[(2-Hydroxyethyl)(3-phenoxypropyl)amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (15.8 g, 151 mmol) and 3-phenoxypropyl bromide (21.5 g, 100 mmol). Yield: 21.31 g, 95%. Yellow oil. MS, *m/z*: 238.1 (M + H)$^+$.

Bis(2-chloroethyl)(3-phenoxypropyl)amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from 2-[(2-hydroxyethyl)(3-phenoxypropyl)amino]ethanol (20.0 g, 84 mmol). Yield: 24.0 g, 91%. Brown oil. MS, *m/z*: 277.8 (M + H)$^+$.

4-(4-Methoxybenzenesulfonyl)-1-(3-phenoxypropyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (5.2 g, 20 mmol) and bis(2-chloroethyl)(3-phenoxypropyl)amine hydrochloride (7.0 g, 22 mmol). Yield: 6.5 g, 70%. Brown oil. MS, *m/z*: 462.5 (M + H)$^+$.

4-(4-Methoxybenzenesulfonyl)-1-(3-phenoxypropyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-(3-phenoxypropyl)piperidine-4-carboxylic acid ethyl ester (4.2 g, 9.1 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (40 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 3.0 g, 75%. Off-white powder. Mp 195 °C. MS, *m/z*: 434.5 (M + H)$^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-(3-phenoxypropyl)piperidine-4-carboxylic acid (2.5 g, 5.77 mmol) and following the procedure as outlined in example **19** (step 7), 1.2 g of 4-(4-methoxybenzenesulfonyl)-1-(3-phenoxypropyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as an off-white solid. Yield: 46%. Mp 101 °C. MS, *m/z*: 448.5 (M + H)$^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.18 (m, 2H), 2.3 (m, 2H), 2.58 (m, 2H), 2.6−2.73 (m, 2H), 3.0−3.06 (m, 2H), 3.60 (m, 2H), 3.87 (s, 3H), 4.01 (t, 2H), 6.9−7.7 (m, 9H), 9.33 (brs, 1H), 10.28 (brs, 1H). Anal. ($C_{22}H_{28}N_2O_6S$) C, H, N.

4-(4-*n*-Butoxybenzenesulfonyl)-1-(3-phenoxypropyl)-piperidine-4-carboxylic Acid Hydroxyamide (42). 4-(4-*n*-Butoxybenzenesulfonyl)-1-(3-phenoxypropyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from from 4-(butoxybenzenesulfonyl)acetic acid ethyl ester (3.0 g, 10 mmol) and bis(2-chloroethyl)(3-phenoxypropyl)amine hydrochloride (3.0 g, 11 mmol). Yield: 4.5 g, 89%. Brown oil. MS, *m/z*: 504.6 (M + H)$^+$.

4-(4-*n*-Butoxybenzenesulfonyl)-1-(3-phenoxypropyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-*n*-butoxybenzenesulfonyl)-1-(3-phenoxypropyl)piperidine-4-carboxylic acid ethyl ester (4.0 g, 7.9 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (40 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 3.0 g, 79%. Off-white powder. Mp 191 °C. MS, *m/z*: 476.5 (M + H)$^+$.

Starting from 4-(4-*n*-butoxybenzenesulfonyl)-1-(3-phenoxypropyl)piperidine-4-carboxylic acid (700 mg, 1.4 mmol) and following the procedure as outlined in example **19** (step 7), 300 mg of 4-(4-*n*-butoxybenzenesulfonyl)-1-(3-phenoxypropyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as an off-white solid. Yield: 43%. Mp 84 °C. MS, *m/z*: 491.5 (M + H)$^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.9 (t, 3H), 1.5 (m, 2H), 1.8 (m, 2H), 2.18 (m, 2H), 2.3 (m, 2H), 2.58 (m, 2H), 2.6−2.73 (m, 2H), 3.2 (m, 2H), 3.40 (m 6H), 3.97 (t, 2H), 4.1 (t, 2H), 6.9−7.7 (m, 9H), 10.7 (brs, 1H), 11.28 (brs, 1H). Anal. ($C_{25}H_{34}N_2O_6S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-(2-phenoxyethyl)piperidine-4-carboxylic Acid Hydroxyamide (43). 2-[(2-Hydroxyethyl)(2-phenoxyethyl)amino]ethanol was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (15.0 g, 150) and 2-chlorophenetol (15.6 g, 100 mmol). Yield: 18 g, 80%. Colorless oil. MS, *m/z*: 226 (M + H)$^+$.

Bis(2-chloroethyl)(2-phenoxyethyl)amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from 2-[(2-hydroxyethyl)(2-phenoxyethyl)amino]ethanol (20.0 g, 88.8 mmol). Yield: 25 g, 94%. Brown oil. MS, *m/z*: 263.1 (M + H)$^+$.

4-(4-Methoxybenzenesulfonyl)-1-(2-phenoxyethyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (5.0 g, 20 mmol) and bis(2-chloroethyl)(2-phenoxyethyl)amine hydrochloride (6.0 g, 20 mmol). Yield: 5.8 g, 64%. Brown oil. MS, *m/z*: 448.5 (M + H)$^+$.

4-(4-Methoxybenzenesulfonyl)-1-(2-phenoxyethyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-(2-phenylethoxy)piperidine-4-carboxylic acid ethyl ester (5.0 g, 11.1 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (40 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 3.0 g, 63%. Off-white powder. Mp 235 °C. MS, *m/z*: 420.5 (M + H)$^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-(2-phenoxyethyl)piperidine-4-carboxylic acid (2.5 g, 5.9 mmol) and following the procedure as outlined in example **19** (step 7), 1.3 g of 4-(4-methoxybenzenesulfonyl)-1-(2-phenoxyethyl)piperidine-4-carboxylic acid hydroxyamide was isolated as an off-white solid. Yield: 50%. Mp 168−172 °C. MS, *m/z*: 435.4 (M + H)$^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.3 (m, 2H), 2.5 (m, 2H), 2.9 (m, 2H), 3.4 (m, 4H), 3.5 (m, 2H), 3.7 (m, 2H), 3.9 (s, 3H), 4.4 (m, 2H), 6.9−7.8 (m, 9H), 9.3 (s, 1H), 10.2 (brs, 1H), 11.3 (s, 1H). Anal. ($C_{21}H_{26}N_2O_6S$) C, H, N.

4-(4-*n*-Butoxybenzenesulfonyl)-1-(2-phenoxyethyl)piperidine-4-carboxylic Acid Hydroxyamide (44). 4-(4-Butoxybenzenesulfonyl)-1-(2-phenoxyethyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (2.5 g, 10 mmol) and bis(2-chloroethyl)(2-phenoxyethyl)amine hydrochloride (2.98 g, 10 mmol). Yield: 3.0 g, 69%. Brown oil. MS, *m/z*: 490.6 (M + H)$^+$.

4-(4-*n*-Butoxybenzenesulfonyl)-1-(2-phenoxyethyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-*n*-butoxybenzenesulfonyl)-1-(2-phenylethoxy)piperidine-4-carboxylic acid ethyl ester (2.5 g, 5.76 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (40 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 1.5 g, 56%. Off-white powder. Mp 204 °C. MS, *m/z*: 462.5 (M + H)$^+$.

Starting from 4-(4-*n*-butoxybenzenesulfonyl)-1-(2-phenoxyethyl)piperidine-4-carboxylic acid (1.0 g, 2.16 mmol) and following the procedure as outlined in example **19** (step 7), 600 mg of 4-(4-butoxybenzenesulfonyl)-1-(2-phenoxyethyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as an off white solid. Yield: 58%. Mp 112°C. MS, *m/z*: 477.4 (M + H)$^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.942 (t, 3H), 1.4 (m, 2H), 1.7 (m, 2H), 2.3 (m, 2H), 2.5 (m, 4H), 2.8 (m, 2H), 2.9−3.4 (m, 4H), 3.3 (m, 4H), 4.2 (t, 2H), 4.4 (m, 2H), 6.9−7.7 (m, 9H), 9.4 (s, 1H), 10.5 (brs, 1H), 11.3 (s, 1H). Anal. ($C_{24}H_{32}N_2O_6S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)benzyl]piperidine-4-carboxylic Acid Hydroxyamide (45). 2-[(2-Hydroxyethyl)-[4-(2-piperidin-1-ylethoxy)-benzyl]amine was prepared according to the general method as outlined in example **19** (step 3), starting from diethanolamine (15.0 g, 150) and 4-(2-piperidin-1-ylethoxy)benzyl chloride (5.9 g, 20 mmol). Yield: 5.5 g, 85%. Brown semisolid. MS, *m/z*: 323 (M + H)$^+$.

Bis(2-chloroethyl)[4-(2-piperidin-1-ylethoxy)benzyl]amine hydrochloride was prepared according to the general method as outlined in example **19** (step 4), starting from 2-[(2-hydroxyethyl)-[4-(2-piperidin-1-ylethoxy)benzyl]amine (3.22 g, 10 mmol). Yield: 4.0 g, 92%. Brown semisolid. MS, *m/z*: 361.1 (M + H)$^+$.

4-(4-Methoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)-benzyl]piperidine-4-carboxylic acid ethyl ester was prepared

according to the general method as outlined in example **19** (step 5), starting from 4-(methoxybenzenesulfonyl)acetic acid ethyl ester (5.0 g, 20 mmol) and bis(2-chloroethyl)[4-(2-piperidin-1-ylethoxy)benzyl]amine hydrochloride (8.6 g, 20 mmol). Yield: 6.0 g, 55%. Brown oil. MS, *m/z*: 545.7 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)-benzyl]piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)benzyl]piperidine-4-carboxylic acid ethyl ester (5.4 g, 10 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (40 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 4.0 g, 77%. Off-white powder. Mp 174 °C. MS, *m/z*: 517.6 $(M + H)^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)benzyl]piperidine-4-carboxylic acid (3.5 g, 6.78 mmol) and following the procedure as outlined in example **19** (step 7), 1.8 g of 4-(4-methoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)benzyl]piperidine-4-carboxylic acid hydroxy amide was isolated as a pale-yellow solid. Yield: 49%. Mp 114 °C. MS, *m/z*: 532 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.4−1.6 (m, 4H), 1.9 (m, 2H), 2.3 (m, 2H), 2.8 (m, 2H), 3.4 (m, 4H), 3.9 (s, 3H), 4.2 (m, 1H), 6.9−7.8 (m, 8H), 9.1 (s, 1H), 10.8 (brs, 1H). Anal. ($C_{27}H_{37}N_3O_6S$) C, H, N.

4-(4-Butoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)benzyl]piperidine-4-carboxylic Acid Hydroxyamide (46). 4-(4-Butoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)benzyl]piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from 4-(butoxybenzenesulfonyl)acetic acid ethyl ester (6.0 g, 20 mmol) and bis(2-chloroethyl)[4-(2-piperidin-1-ylethoxy)benzyl]amine hydrochloride (8.6 g, 20 mmol). Yield: 8.0 g, 68%. Brown oil. MS, *m/z*: 587.7 $(M + H)^+$.

4-(4-Butoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)-benzyl]piperidine-4-carboxylic acid was prepared starting from 4-(4-butoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)benzyl]piperidine-4-carboxylic acid ethyl ester (5.8 g, 10 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (40 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 4.8 g, 86%. Spongy brown solid. Mp 98 °C. MS, *m/z*: 559.6 $(M + H)^+$.

Starting from 4-(4-butoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)benzyl]piperidine-4-carboxylic acid (5.5 g, 10 mmol) and following the procedure outlined in example **19** (step 7), 2.4 g of 4-(4-butoxybenzenesulfonyl)-1-[4-(2-piperidin-1-ylethoxy)benzyl]piperidine-4-carboxylic acid hydroxyamide was isolated as a pale-yellow solid. Yield: 41%. Mp 155 °C. MS, *m/z*: 574 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.9 (t, 3H), 1.1−1.8 (m, 6H), 1.9 (m, 4H), 2.3 (m, 4H), 2.8 (m, 6H), 3.2−3.6 (m, 8H), 4.2 (m, 2H), 6.9−7.8 (m, 8H), 9.1 (s, 1H), 10.8 (brs, 1H). Anal. ($C_{30}H_{43}N_3O_6S$) C, H, N.

4-(4-Butoxybenzenesulfonyl)-1-[3-(2-morpholinyl-1-ylethoxy)benzyl]piperidine-4-carboxylic Acid Hydroxyamide (47). Bis(2-hydroxyethyl)[3-(2-morpholin-1-ylethoxy)-benzyl]amine was prepared according to the general method outlined in example **19** (step 3) starting from diethanolamine (15.0 g, 150) and 3-(2-morpholin-1-ylethoxy)benzyl chloride (5.9 g, 20 mmol). Yield: 6.2 g, 95%. Brown semisolid. MS, *m/z*: 325 $(M + H)^+$.

Bis(2-chloroethyl)[3-(2-morpholin-1-ylethoxy)benzyl]amine hydrochloride was prepared according to the general method outlined in example **19** (step 4) starting from bis(2-hydroxyethyl)[3-(2-morpholin-1-ylethoxy)benzyl]amine (3.24 g, 10 mmol). Yield: 4.0 g, 92%. Brown semisolid. MS, *m/z*: 363.1 $(M + H)^+$.

4-(4-Butoxybenzenesulfonyl)-1-[3-(2-morpholin-1-ylethoxy)-benzyl]piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from 4-(butoxybenzenesulfonyl)acetic acid ethyl ester (6.0 g, 20 mmol) and bis(2-chloroethyl)[3-(2-morpholin-1-ylethoxy)benzyl]amine hydrochloride (8.6 g, 20 mmol). Yield: 8.5 g, 72%. Brown oil. MS, *m/z*: 589.7 $(M + H)^+$.

4-(4-Butoxybenzenesulfonyl)-1-[3-(2-morpholin-1-ylethoxy)-benzyl]piperidine-4-carboxylic acid was prepared starting from 4-(4-butoxybenzenesulfonyl)-1-[3-(2-morpholin-1-ylethoxy)benzyl]piperidine-4-carboxylic acid ethyl ester (5.8 g, 10 mmol) dissolved in THF/methanol, 3:1, and 10 N NaOH (40 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 4.8 g, 85%. Spongy brown solid. MS, *m/z*: 561.6 $(M + H)^+$.

Starting from 4-(4-butoxybenzenesulfonyl)-1-[3-(2-morpholin-1-ylethoxy)benzyl]piperidine-4-carboxylic acid (5.6 g, 10 mmol) and following the procedure outlined in example **19** (step 7), 4.02 g of 4-(4-butoxybenzenesulfonyl)-1-[3-(2-morpholin-1-ylethoxy)benzyl]piperidine-4-carboxylic acid hydroxyamide was isolated as a pale-yellow solid. Yield: 62%. Mp 123°C. MS, *m/z*: 576 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.9 (t, 3H), 1.4 (m, 2H), 1.8 (t, 2H), 2.3−4.7 (m, 24H), 7.0−7.8 (m, 8H), 9.1 (s, 1H), 10.8 (brs, 1H). Anal. ($C_{29}H_{41}N_3O_7S$) C, H, N.

1-Methyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (48). 1-Methyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from 4-(butoxybenzenesulfonyl)acetic acid ethyl ester (3 g, 10 mmol) and methyl-bis(2-chloroethyl)amine hydrochloride (2.2 g, 11.6 mmol). Yield: 4.0 g, 98%. Low-melting brown solid. MS, *m/z*: 384 $(M + H)^+$.

1-Methyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-methyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (7.6 g, 20 mmol) dissolved in methanol (300 mL) and 10 N NaOH (35 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 6.0 g, 84%. White solid. Mp 195 °C. MS, *m/z*: 356.4 $(M + H)^+$.

Starting from 1-methyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid (4.0 g, 11.2 mmol) and following the procedure outlined in example **19** (step 7), 3.9 g of 1-methyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as a yellow powder. Yield: 85%. Mp 118 °C. MS, *m/z*: 371 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.9 (t, 3H), 1.45 (q, 2H), 1.8 (q, 2H), 2.1 (s, 3H), 2.3 (d, J = 11.4 Hz, 2H), 2.5−3.7 (m, 8H), 4.1 (t, 2H), 7.16 (d, 2H), 7.67 (d, 2H). Anal. ($C_{17}H_{26}N_2O_5S$) C, H, N.

1-Ethyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (49). 1-Ethyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from 4-(butoxybenzenesulfonyl)acetic acid ethyl ester (3 g, 10 mmol) and ethyl-bis(2-chloroethyl)amine hydrochloride (2.2 g, 10.6 mmol). Yield: 3.5 g, 88%. Low-melting brown solid. MS, *m/z*: 398 $(M + H)^+$.

1-Ethyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-ethyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (7.94 g, 20 mmol) dissolved in methanol (300 mL) and 10 N NaOH (35 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 6.5 g, 88%. White solid. Mp 162 °C. MS, *m/z*: 370 $(M + H)^+$.

Starting from 1-ethyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid (3.7 g, 10 mmol) and following the procedure outlined in example **19** (step 7), 3.2 g of 1-ethyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as a yellow powder. Yield: 76%. Mp 98 °C. MS, *m/z*: 385 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.9 (t, 3H), 1.2 (t, 3H), 1.46 (q, 2H), 1.9 (q, 2H), 2.3 (d, J = 11.4 Hz, 2H), 2.5−3.6 (m, 10H), 4.1 (t, 2H), 7.16 (d, 2H), 7.67 (d, 2H). Anal. ($C_{18}H_{28}N_2O_5S$) C, H, N.

1-*n*-Butyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (50). 1-*n*-Butyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from 4-(butoxybenzenesulfonyl)-acetic acid ethyl ester (3 g, 10 mmol) and *n*-butyl-bis(2-chloroethyl)amine hydrochloride (2.0 g, 10.1 mmol). Yield: 3.8 g, 89%. Low-melting brown solid. MS, *m/z*: 426 $(M + H)^+$.

1-*n*-Butyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 1-*n*-butyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid ethyl ester (8.5 g, 20 mmol) dissolved in methanol (300 mL) and 10 N NaOH (35

mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 7.5 g, 88%. White solid. Mp 182 °C. MS, *m/z*: 398 $(M + H)^+$.

Starting from 1-*n*-butyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid (3.9 g, 10 mmol) and following the procedure outlined in example **19** (step 7), 1.8 g of 1-*n*-butyl-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as a yellow powder. Yield: 40%. Mp 121 °C. MS, *m/z*: 413 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.9−1.0 (m, 6H), 1.2−1.8 (m, 8H), 2.2−2.8 (m, 8H), 3.0−3.6 (m, 4H), 4.2 (t, 2H), 7.16 (d, 2H), 7.67 (d, 2H), 9.3 (brs, 1H), 10.3 (brs, 1H), 11.1 (brs, 1H). Anal. ($C_{20}H_{32}N_2O_5S$) C, H, N.

1-Benzyl-4-(4-benzyloxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (51). To a stirred solution of 4-hydroxybenzenethiol (2.52 g, 20 mmol) in chloroform, a mixture of triethylamine (2.5 g, 25 mmol) and α-bromoethyl acetate (3.3 g, 20 mmol) was added at room temperature. The reaction mixture became exothermic. After the reaction mixture was stirred for 2 h, it was quenched with water and washed well with water. The chloroform layer was separated and dried over anhydrous $MgSO_4$. It was concentrated and taken to the next step without any purification. Yield: 4.2 g, 100%. MS, *m/z*: 213 $(M + H)^+$.

To a stirred solution of (4-hydroxyphenylsulfanyl)acetic acid ethyl ester (4.2 g, 20 mmol) and anhydrous K_2CO_3 (10 g, excess) in dry acetone (100 mL), benzyl bromide (3.5 g, 20 mmol) was added. The mixture was refluxed for 4 h. At the end, reaction mixture was filtered and concentrated and the residue was extracted with chloroform. It was washed well with water, dried, and concentrated. The crude product obtained was converted to (4-benzyloxyphenylsulfonyl)acetic acid ethyl ester by oxidizing with *m*-chloroperbenzoic acid as described in example **19** (step 2). Low-melting solid. Yield: 6.6 g, 97%. MS, *m/z*: 335 $(M + H)^+$.

To a stirred solution of bis(2-chloroethyl)benzylamine hydrochloride (6.6 g, 24.7 mmol), 18-crown-6 (500 mg), and anhydrous K_2CO_3 (30 g, excess) in dry acetone (250 mL), (4-benzyloxyphenylsulfonyl)acetic acid ethyl ester (8.01 g, 24 mmol) was added in a round-bottom flask, and the reaction mixture was heated at reflux for 16 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 water. The organic layer was further washed well with water, dried over $MgSO_4$, filtered, and concentrated. The dark-brown reaction mixture was purified by silica gel column chromatography by eluting it with 30% ethyl acetate/hexane, and the product 4-(4-benzyloxybenzenesulfonyl)-1-benzylpiperidine-4-carboxylic acid ethyl ester was isolated as a brown oil. Yield: 6.5 g, 55%. MS, *m/z*: 494 $(M + H)^+$.

4-(4-Benzyloxybenzenesulfonyl)-1-benzylpiperidine-4-carboxylic acid ethyl ester (5.0 g, 10.1 mmol) was dissolved in MeOH/THF (1:1, 200 mL), and the mixture was stirred at room temperature for 72 h. At the end reaction, mixture was concentrated and the product was neutralized with concentrated HCl by dissolving it in water (200 mL). After the neutralization, the reaction mixture was concentrated to dryness. Ice-cold water (100 mL) was added to the solid and filtered. The product 4-(4-benzyloxybenzenesulfonyl)-1-benzylpiperidine-4-carboxylic acid was dried at 50 °C and taken to the next step with out any purification. White solid. Mp 66−68 °C. Yield: 4.3 g, 91%. MS, *m/z*: 466 $(M + H)^+$.

Starting from 4-(4-benzyloxybenzenesulfonyl)-1-benzylpiperidine-4-carboxylic acid (4.65 g, 10.0 mmol) and following the procedure outlined in example **19** (step 7), 1.1 g of 4-(4-benzyloxybenzenesulfonyl)-1-benzylpiperidine-4-carboxylic acid hydroxyamide was isolated as a white solid. Yield: 21%. Mp 89 °C. MS, *m/z*: 481.1 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (m, 3H), 2.76−2.79 (m, 2H), 3.43 (m, 4H), 4.30 (s, 2H), 7.14−7.17 (d,2H), 7.50−7.73 (m, 5H), 9.37 (s,1H), 10.53 (s,1H), 11.18 (s,1H). Anal. ($C_{26}H_{28}N_2O_5S$) C, H, N.

4-[4-(4-Chlorophenoxy)benzenesulfonyl]-1-methylpiperidine-4-carboxylic Acid Hydroxyamide (52). Step 1. A mixture of 4-bromochlorobenzene (1.92 g, 10 mmol), (4-hydroxyphenylsulfanyl)acetic acid ethyl ester (2.12 g, 10 mmol), sodium hydride (460 mg, 10 mmol), and copper(II) chloride (500 mg) was refluxed in anhydrous pyridine (50 mL) for 12 h. The reaction mixture was carefully quenched with ice-cold water and acidified with concentrated HCl. The product was extracted with chloroform, washed well with water, dried, and concentrated. The product was purified by silica gel column chromatography by eluting with 30% ethyl acetate/hexane. Yield: 2.5 g, 77%. Colorless low-melting solid. MS, *m/z*: 323 $(M + H)^+$.

Step 2. [4-(4-Chlorophenoxy)benzenesulfonyl]acetic acid ethyl ester was prepared according to the general method outlined in example **19** (step 2) starting from [4-(4-chlorophenoxy)phenylsulfanyl]acetic acid ethyl ester (3.23 g, 10 mmol) and Oxone (10 g). Yield: 3.5 g, 99%. oil. EI-MS, *m/z*: 356 $(M + H)^+$.

Step 3. 4-[4-(4-Chlorophenoxy)benzenesulfonyl]-1-methylpiperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from [4-(4-chlorophenoxy)benzenesulfonyl]acetic acid ethyl ester (2.0 g, 5.6 mmol) and bis(2-chloroethyl)methylamine hydrochloride (1.9 g, 10 mmol). Yield: 2 g, 81%. Brown oil. MS, *m/z*: 438 $(M + H)^+$.

Step 4. 4-[4-(4-Chlorophenoxy)benzenesulfonyl]-1-methylpiperidine-4-carboxylic acid was prepared starting from 4-[4-(4-chlorophenoxy)benzenesulfonyl]-1-methylpiperidine-4-carboxylic acid ethyl ester (4.3 g, 10 mmol) dissolved in THF/methanol (3:1, 150 mL) and 10 N NaOH (100 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 3.5 g, 86%. White solid. Mp 185 °C. MS, *m/z*: 410 $(M + H)^+$.

Step 5. Starting from 4-[4-(4-chlorophenoxy)benzenesulfonyl]-1-methylpiperidine-4-carboxylic acid (1.0 g, 2.4 mmol) and following the procedure outlined in example **19** (step 7), 460 mg of 4-[4-(4-chlorophenoxy)benzenesulfonyl]-1-methylpiperidine-4-carboxylic acid hydroxyamide was isolated as a HCl salt, a white powder. Yield: 41%. Mp 52 °C. MS, *m/z*: 426 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.3 (s, 3H), 2.2−2.9 (m, 6H), 3.5 (d, 2H), 7.2−7.9 (m, 8H), 8.1 (s, 1H), 11.0 (brs, 1H). Anal. ($C_{19}H_{21}Cl\ N_2O_5S$) C, H, N.

4-[4-(4-Chlorophenoxy)benzenesulfonyl]-1-ethylpiperidine-4-carboxylic Acid Hydroxyamide (53). 4-[4-(4-Chlorophenoxy)benzenesulfonyl]-1-ethylpiperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from [4-(4-chlorophenoxy)benzenesulfonyl]acetic acid ethyl ester (4 g, 11.3 mmol) and ethyl-bis(2-chloroethyl)amine hydrochloride (2.32 g, 16.9 mmol). Yield: 3.36 g, 66%. Brown oil. MS, *m/z*: 452.0 $(M + H)^+$.

4-[4-(4-Chlorophenoxy)benzenesulfonyl]-1-ethylpiperidine-4-carboxylic acid was prepared starting from 4-[4-(4-chlorophenoxy)benzenesulfonyl]-1-ethylpiperidine-4-carboxylic acid ethyl ester (3.02 g, 6.7 mmol) dissolved in THF/methanol (3:1, 150 mL) and 10 N NaOH (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 1.8 g, 65%. White solid. Mp 184°C. MS, *m/z*: 423.9 $(M + H)^+$.

Starting from 4-[4-(4-chlorophenoxy)benzenesulfonyl]-1-ethylpiperidine-4-carboxylic acid (1.75 g, 4.14 mmol) and following the procedure outlined in example **19** (step 7), 650 mg of 4-[4-(4-chlorophenoxy)benzenesulfonyl]-1-ethylpiperidine-4-carboxylic acid hydroxyamide was isolated as a HCl salt, a white powder. Yield: 33%. Mp 158 °C. MS, *m/z*: 438.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.78 (t, $J = 7.23$ Hz, 3H), 2.23−2.27 (m, 2H), 2.51−2.73 (m, 4H), 3.04 (m, 2H), 3.81 (d, $J = 24$ Hz, 2H), 7.16−7.27 (m, 4H), 7.50−7.57 (m, 2H), 7.76 (d, $J = 7$ Hz, 2H), 9.34 (s, 1H), 9.85 (s, 1H). Anal. ($C_{20}H_{23}Cl\ N_2O_5S$) C, H, N.

1-Butyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]-piperidine-4-carboxylic Acid Hydroxyamide (54). 1-Butyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from [4-(4-chlorophenoxy)benzenesulfonyl]acetic acid ethyl ester (6 g, 18.3

mmol) and butyl-bis(2-chloroethyl)amine hydrochloride (5.2 g, 22 mmol). Yield: 3.3 g, 38%. Yellow oil. MS, *m/z*: 480 $(M + H)^+$.

1-Butyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]piperidine-4-carboxylic acid was prepared starting from 1-butyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]piperidine-4-carboxylic acid ethyl ester (3.3 g, 6.9 mmol) dissolved in THF/methanol (3:1, 150 mL) and 10 N NaOH (25 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 2.08 g, 67%. White solid. Mp 201°C. MS, *m/z*: 451.9 $(M + H)^+$.

Starting from 1-butyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]piperidine-4-carboxylic acid (2 g, 4.43 mmol) and following the procedure outlined in example **19** (step 7), 630 mg of 1-butyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]piperidine-4-carboxylic acid hydroxyamide was isolated as a HCl salt, a white solid. Yield: 31%. Mp 212 °C. MS, *m/z*: 466.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, J = 7.3 Hz, 3H), 1.32 (m, 2H), 1.60 (m, 2H), 2.21 (m, 2H), 2.50 (m, 2H), 2.70 (q, 2H), 3.00 (m, 2H), 3.57 (d, 2H), 7.16−7.26 (m, 4H), 7.49−7.56 (m, 2H), 7.77 (d, J = 9 Hz, 2H), 9.34 (s, 1H), 10.13 (s, 1H). Anal. ($C_{22}H_{27}Cl\ N_2O_5S$) C,H, N.

1-Benzyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]-piperidine-4-carboxylic Acid Hydroxyamide (55). 1-Benzyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from [4-(4-chlorophenoxy)benzenesulfonyl]acetic acid ethyl ester (6 g, 16.9 mmol) and bis(2-chloroethyl)benzylamine hydrochloride (6.44 g, 24 mmol). Yield: 2.21 g, 25%. Yellow oil. MS, *m/z*: 513.9 $(M + H)^+$.

1-Benzyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]piperidine-4-carboxylic acid was prepared starting from 1-benzyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]piperidine-4-carboxylic acid ethyl ester (2.11 g, 4.1 mmol) dissolved in THF/methanol (3:1, 150 mL) and 10 N NaOH (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 1.11 g, 56%. White solid. Mp 201 °C. MS, *m/z*: 485.9 $(M + H)^+$.

Starting from 1-benzyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]piperidine-4-carboxylic acid (1 g, 2.06 mmol) and following the procedure outlined in example **19** (step 7), 430 mg of 1-benzyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]piperidine-4-carboxylic acid hydroxyamide was isolated as a HCl salt, an off-white solid. Yield: 39%. Mp 90.4 °C. MS, *m/z*: 501.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.18−2.30 (m, 2H), 2.73−2.81 (m, 4H), 3.36 (d, 2H), 4.28 (d, J = 4.5 Hz, 2H), 7.15−7.25 (m, 4H), 7.43−7.48 (m, 3H), 7.51−7.56 (m, 4H), 7.74 (d, J = 9 Hz, 2H), 9.53 (s, 1H), 10.47 (s, 1H). Anal. ($C_{25}H_{25}Cl\ N_2O_5S$) C, H, N.

1-Benzyl-4-[4-(3-methylbutoxy)benzenesulfonyl]-piperidine-4-carboxylic Acid Hydroxyamide (57). To a stirred solution of (4-hydroxyphenylsulfanyl)acetic acid ethyl ester (2.12 g, 10 mmol), K_2CO_3 (anhydrous, 10 g), and 1-bromo-3-methylbutane (3 g, excess) was added boiling acetone. The reaction mixture was refluxed for 24 h and cooled to room temperature. The reaction mixture was filtered and concentrated. The residue obtained was extracted with chloroform, washed well with water, and concentrated. The crude product obtained was taken to the next step without purification. Yield: 2.7 g, 94%. MS, *m/z*: 283 $(M + H)^+$.

[4-(3-Methylbutoxy)phenylsulfonyl]acetic acid ethyl ester was prepared according to the general method outlined in example **19** (step 2) starting from [4-(3-methylbutoxy)phenylsulfanyl]acetic acid ethyl ester (2.8 g, 10 mmol) and Oxone (10 g). Yield: 3.0 g, 99%. Oil. EI-MS, *m/z*: 314 $(M + H)^+$.

1-Benzyl-4-[4-(3-methylbutoxy)benzenesulfonyl]piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from [4-(3-methylbutoxy)phenylsulfonyl]acetic acid ethyl ester (6.2 g, 20 mmol) and bis(2-chloroethyl)benzylamine hydrochloride (6.44 g, 24 mmol). Yield: 8 g, 84%. Yellow oil. MS, *m/z*: 474 $(M + H)^+$.

1-Benzyl-4-[4-(3-methylbutoxy)benzenesulfonyl]piperidine-4-carboxylic acid was prepared starting from 1-benzyl-4-[4-(3-methylbutoxy)benzenesulfonyl]piperidine-4-carboxylic ethyl ester (4.7 g, 10 mmol) dissolved in THF/methanol (3:1, 150 mL) and 10 N NaOH (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 3 g, 67%. White solid. Mp 182 °C. MS, *m/z*: 446 $(M + H)^+$.

Starting from 1-benzyl-4-[4-(3-methylbutoxy)benzenesulfonyl]piperidine-4-carboxylic acid (2.2 g, 5 mmol) and following the procedure outlined in example **19** (step 7), 1.82 g of 1-benzyl-4-[4-(3-methylbutoxy)benzenesulfonyl]piperidine-4-carboxylic acid hydroxyamide was isolated as a HCl salt, an off-white solid. Yield: 73%. Mp 106 °C. MS, *m/z*: 461 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.8 (d, 6H), 1.5 (m, 1H), 1.6−2.0 (m, 6H), 2.73−2.81 (m, 4H), 3.5 (d, 2H), 4.28 (d, J = 4.5 Hz, 2H), 7.15−7.25 (m, 4H), 7.43−7.48 (m, 3H), 7.51−7.56 (m, 4H), 7.74 (d, J = 9 Hz, 2H), 9.53 (s, 1H), 10.47 (s, 1H). Anal. ($C_{24}H_{32}\ N_2O_5S$) C, H, N.

1-Benzyl-4-[4-(2-ethylbutoxy)benzenesulfonyl]piperidine-4-carboxylic Acid Hydroxyamide (58). To a stirred solution of (4-hydroxyphenylsulfanyl)acetic acid ethyl ester (2.12 g, 10 mmol), K_2CO_3 (anhydrous, 10 g), and 1-bromo-2-ethylbutane (3 g, excess) was added boiling acetone. The reaction mixture was refluxed for 24 h and cooled to room temperature. The reaction mixture was filtered and concentrated. The residue obtained was extracted with chloroform, washed well with water, and concentrated. The crude product obtained was taken to the next step without purification. Yield: 2.8 g, 94%. MS, *m/z*: 297 $(M + H)^+$.

[4-(2-Ethylbutoxy)phenylsulfonyl]acetic acid ethyl ester was prepared according to the general method outlined in example **19** (step 2) starting from [4-(2-ethylbutoxy)phenylsulfanyl]-acetic acid ethyl ester (2.96 g, 10 mmol) and Oxone (10 g). Yield: 3.1 g, 99%. Oil. EI-MS, *m/z*: 329 $(M + H)^+$.

1-Benzyl-4-[4-(2-ethylbutoxy)benzenesulfonyl]piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from [4-(2-ethylbutoxy)phenylsulfonyl]acetic acid ethyl ester (6.4 g, 20 mmol) and bis(2-chloroethyl)benzylamine hydrochloride (6.44 g, 24 mmol). Yield: 8 g, 82%. Yellow oil. MS, *m/z*: 488 $(M + H)^+$.

1-Benzyl-4-[4-(2-ethylbutoxy)benzenesulfonyl]piperidine-4-carboxylic acid was prepared starting from 1-benzyl-4-[4-(2-ethylbutoxy)benzenesulfonyl]piperidine-4-carboxylic ethyl ester (4.8 g, 10 mmol) dissolved in THF/methanol (3:1, 150 mL) and 10 N NaOH (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 4 g, 87%. Semisolid. MS, *m/z*: 460 $(M + H)^+$.

Starting from 1-benzyl-4-[4-(2-ethylbutoxy)benzenesulfonyl]-piperidine-4-carboxylic acid (2.2 g, 5 mmol) and following the procedure outlined in example **19** (step 7), 1.02 g of 1-benzyl-4-[4-(2-ethylbutoxy)benzenesulfonyl]piperidine-4-carboxylic acid hydroxyamide was isolated as a HCl salt, an off-white solid. Yield: 40%. Mp 114°C. MS, *m/z*: 475 $(M + H)^+$. Anal. ($C_{25}H_{34}\ N_2O_5S$) C, H, N.

4-(4-Butoxybenzenesulfonyl)-1-(3-methoxybenzyl)piperidine-4-carboxylic Acid Hydroxyamide (59). 4-(4-Butoxybenzenesulfonyl)-1-(3-methoxybenzyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from 4-(4-butoxybenzenesulfonyl)acetic acid ethyl ester (20 g, 77.5 mmol) and bis(2-chloroethyl)(3-methoxybenzyl)amine hydrochloride (34 g, 116 mmol). Yield: 9.53 g, 25%. Brown oil. MS, *m/z*: 490.2 $(M + H)^+$.

4-(4-Butoxybenzenesulfonyl)-1-(3-methoxybenzyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-(3-methoxybenzyl)piperidine-4-carboxylic acid ethyl ester (2.61 g, 5.34 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 **19** (step 6). Yield: 1 g, 41%. Brown solid. Mp 175°C. MS, *m/z*: 462.0 $(M + H)^+$.

Starting from 4-(4-butoxybenzenesulfonyl)-1-(3-methoxybenzyl)piperidine-4-carboxylic acid (900 mg, 1.95 mmol) and following the procedure outlined in example **19** (step 7), 200 mg of 4-(4-butoxybenzenesulfonyl)-1-(3-methoxybenzyl)piperi-

dine-4-carboxylic acid hydroxyamide was isolated as a HCl salt, a brown powder. Yield: 20%. Mp 137 °C. MS, *m/z*: 477.0 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.96 (t, $J = 7.11$ Hz, 3H), 1.48 (m, 2H), 1.73 (m, 2H), 2.27 (m, 2H), 2.47 (m, 2H), 2.78 (m, 2H), 3.35 (m, 2H), 3.77 (s, 2H), 4.08 (t, $J = 6.3$ Hz, 3H), 4.32 (s, 2H), 7.03 (t, 2H), 7.15 (m, 3H), 7.36 (t, $J = 7.8$ Hz, 1H), 7.64 (d, $J = 9$ Hz, 2H), 9.36 (s, 1H), 10.22 (s, 1H). Anal. ($C_{24}H_{32}N_2O_6S$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-(4-thiophen-2-ylbenzyl)piperidine-4-carboxylic Acid Hydroxyamide (60). 4-(4-Methoxybenzenesulfonyl)-1-(4-thiophen-2-ylbenzyl)piperidine-4-carboxylic acid ethyl ester was prepared starting from 1-(4-bromobenzyl)-4-(4-methoxybenzensulfonyl)piperidine-4-carboxylic acid ethyl ester (3 g, 6.05 mmol) and 2-(tributylstannyl)thiophene (6.8 g, 18.14 mmol) in the presence of tetrakispalladium(0) in boiling toluene. Yield: 1.58 g, 52%. Brown solid. Mp 130 °C. MS, *m/z*: 500 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(4-thiophen-2-ylbenzyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-(4-thiophen-2-ylbenzyl)piperidine-4-carboxylic acid ethyl ester (1.3 g, 2.61 mmol) dissolved in THF/methanol (3:1, 150 mL) and 10 N NaOH (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 950 mg, 77%. Brown solid. Mp 235°C. MS, *m/z*: 471.8 $(M + H)^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-(4-thiophen-2-ylbenzyl)piperidine-4-carboxylic acid (920 mg, 1.95 mmol) and following the procedure outlined in example **19** (step 7), 510 mg of 4-(4-methoxybenzenesulfonyl)-1-(4-thiophen-2-ylbenzyl)piperidine-4-carboxylic acid hydroxyamide was isolated as a HCl salt, a brown solid. Yield: 50%. Mp 166 °C. MS, *m/z*: 487 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.12−2.21 (m, 2H), 2.50 (m, 2H), 2.78 (m, 2H), 3.39 (m, 2H), 3.87 (s, 3H), 4.29 (d, 2H), 7.17 (m, 3H), 7.54−7.75 (m, 8H), 9.36 (s, 1H), 10.07 (s, 1H). Anal. ($C_{24}H_{26}N_2O_5S_2$) C, H, N.

4-(4-Methoxybenzenesulfonyl)-1-(4-pyridin-2-ylbenzyl)-piperidine-4-carboxylic Acid Hydroxyamide (61). 4-(4-Methoxybenzenesulfonyl)-1-(4-pyridin-2-ylbenzyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **60**, starting from 1-(4-bromobenzyl)-4-(4-methoxybenzensulfonyl)piperidine-4-carboxylic acid ethyl ester (4.65 g, 9.38 mmol) and 2-(tributylstannyl)pyridine (12.08 g, 32.8 mmol). Yield: 2.79 g, 60%. Brown oil. MS, *m/z*: 495.1 $(M + H)^+$.

4-(4-Methoxybenzenesulfonyl)-1-(4-pyridin-2-ylbenzyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxybenzenesulfonyl)-1-(4-pyridin-2-ylbenzyl)piperidine-4-carboxylic acid ethyl ester (1.83 g, 3.7 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 **19** (step 6). Yield: 1.38 g, 80%. Off-white solid. Mp 217°C. MS, *m/z*: 466.9 $(M + H)^+$.

Starting from 4-(4-methoxybenzenesulfonyl)-1-(4-pyridin-2-ylbenzyl)piperidine-4-carboxylic acid (1.32 g, 2.83 mmol) and following the procedure outlined in example **19** (step 7), 480 mg of 4-(4-methoxybenzenesulfonyl)-1-(4-pyridin-2-ylbenzyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as a HCl salt, a white powder. Yield: 33%. Mp 214 °C. MS, *m/z*: 482.0 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30 (m, 2H), 2.80 (m, 2H), 3.42 (d, $J = 12.5$ Hz, 2H), 3.75 (m, 2H), 3.88 (s, 3H), 4.36 (s, 2H), 7.15 (d, $J = 8.9$ Hz, 2H), 7.59−7.74 (m, 4H), 7.84−7.95 (m, 3H), 8.55 (d, $J = 8.1$ Hz, 1H), 8.79 (s, 1H), 9.14 (s, 1H), 10.68 (s, 1H), 11.17 (s, 1H). Anal. ($C_{25}H_{27}N_3O_5S$) C, H, N.

1-(3,4-Dichlorobenzyl)-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic Acid Hydroxyamide (62). 4-(4-Butoxybenzenesulfonyl)-1-(3,4-dichlorobenzyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5), starting from (4-butoxybenzenesulfonyl)acetic acid ethyl ester (13.2 g, 44 mmol) (3,4-dichlorobenzyl)bis(2-chloroethyl)amine hydrochloride (14.3 g, mmol). Yield: 14.1 g, 60%. White solid. Mp 86 °C. MS, *m/z*: 527.9 $(M + H)^+$.

1-(3,4-Dichlorobenzyl)-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid was prepared starting from 4-(4-butoxybenzenesulfonyl)-1-(3,4-dichlorobenzyl)piperidine-4-carboxylic acid ethyl ester (14.0 g, 26.5 mmol) dissolved in THF/methanol (100:50 mL/mL) and 10 N NaOH (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 7.87 g, 60%. Off-white solid. Mp 239 °C. MS, *m/z*: 501.9 $(M + H)^+$.

Starting from 1-(3,4-dichlorobenzyl)-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid (7.7 g, 15.5 mmol) and following the procedure outlined in example **19** (step 7), 4.05 g of 1-(3,4-dichlorobenzyl)-4-(4-butoxybenzenesulfonyl)piperidine-4-carboxylic acid hydroxyamide was isolated as a HCl salt, a white solid. Yield: 48%. Mp 256.8 °C. MS, *m/z*: 516 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.94 (t, 3H), 1.43 (q, 2H), 1.71 (q, 2H), 2.27 (m, 4H), 2.72 (m, 2H), 4.10 (t, 2H), 4.24 (s, 2H), 7.12−7.15 (d, $J = 8.9$, 2H), 7.51−7.53 (d, $J = 8.1$, 1H), 7.63−7.65 (d, $J = 8.8$, 2H), 7.72−7.75 (d, $J = 9.9$, 2H), 7.87 (s, 1H), 9.36 (s, 1H), 10.5 (s, 1H), 11.2 (s, 1H). Anal. ($C_{23}H_{28}Cl_2N_2O_5S$) C, H, N.

[4-(Benzyloxy)benzenesulfonyl]-1-benzylpiperidine-4-carboxylic Acid Hydroxamide (63). [4-(Benzyloxy)benzenesulfonyl]-1-benzylpiperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from [4-(benzyloxy)benzenesulfonyl]acetic acid ethyl ester (12.35 g, 37 mmol) and bis(2-chloroethyl)benzylamine hydrochloride (9.24 g, 40 mmol). Yield: 12.0 g, 60%. Brown oil. MS, *m/z*: 494 $(M + H)^+$.

[4-(Benzyloxy)benzenesulfonyl]-1-benzylpiperidine-4-carboxylic acid was prepared starting from [4-(benzyloxy)benzenesulfonyl]-1-benzylpiperidine-4-carboxylic acid ethyl ester (11.8 g, 24 mmol) dissolved in THF/methanol (75:75 mL/mL) and 10 N NaOH (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 5.58 g, 50%. White solid. MS, *m/z*: 466.2 $(M + H)^+$.

Starting from [4-(benzyloxy)benzenesulfonyl]-1-benzylpiperidine-4-carboxylic acid (5.59 g, 12 mmol) and following the procedure outlined in example **19** (step 7), 1.2 g of [4-(benzyloxy)benzenesulfonyl]-1-benzylpiperidine-4-carboxylic acid hydroxamide was isolated as a white solid. Yield: 20%. Mp 117.8 °C (HCl salt). MS, *m/z*: 481 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.2 (m, 2H), 2.49 (m, 4H), 2.5 (s, 3 H), 2.6 (m, 2H), 5.2 (s, 2H), 7.25−7.23 (d, 2H), 7.5 (d, 4H), 7.68−7.71 (d, 2H), 9.33 (s, 1H), 10.11 (s, 1H). Anal. ($C_{26}H_{28}N_2O_5S$) C, H, N.

[4-(4-Chlorobenzyloxy)benzenesulfonyl]-1-(4-methylbenzyl)piperidine-4-carboxylic Acid Hydroxamide (64). [4-(4-Chlorobenzyloxy)benzenesulfonyl]-1-(4-methylbenzyl)piperidine-4-carboxylic acid ethyl ester was prepared according to the general method outlined in example **19** (step 5) starting from [1-(4-chlorobenzyloxy)benzenesulfonyl]acetic acid ethyl ester (5.47 g, 15 mmol) and 1-(4-methylbenzyl)bis(2-chloroethyl)amine hydrochloride (5.23 g, 18 mmol). Yield: 8.0 g, 96%. Brown oil. MS, *m/z*: 542.0 $(M + H)$.

[4-(4-Chlorobenzyloxy)benzenesulfonyl]-1-(4-methylbenzyl)-piperidine-4-carboxylic acid was prepared starting from [4-(4-chlorobenzyloxy)benzenesulfonyl]-1-(4-methylbenzyl)piperidine-4-carboxylic acid ethyl ester (7.9 g, 124 mmol) dissolved in THF/methanol (50:50 mL/mL) and 10 N NaOH (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 4.6 g, 61%. Off-white solid. Mp 204 °C. MS, *m/z*: 514.2 $(M + H)^+$.

Starting from [4-(4-chlorobenzyloxy)benzenesulfonyl]-1-(4-methylbenzyl)piperidine-4-carboxylic acid (4.2 g, 8 mmol) and following the procedure outlined in example **19** (step 7), 1.3 g of [4-(4-chlorobenzyloxy)benzenesulfonyl]-1-(4-methylbenzyl)-piperidine-4-carboxylic acid hydroxamide was isolated as a yellow solid. Yield: 29%. Mp 172 °C (HCl salt). MS, *m/z*: 528.9 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ. 2.2−2.4 (m, 5H), 2.5−2.62 (m, 4H), 2.7−2.9 (m, 2H), 4.2−4.45 (m, 2H), 5.25 (s, 2H), 7.2−7.75 (m, 12H), 9.40 (brs, 1H), 10.42 (brs, 1H). Anal. ($C_{27}H_{29}ClN_2O_5S$) C, H, N.

1-(4-Methoxy)benzyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]piperidine-4-carboxylic Acid Hydroxyamide (66). 1-(4-Methoxy)benzyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]-piperidine-4-carboxylic acid ethyl ester was prepared according

to the general method outlined in example **19** (step 5) starting from [4-(4-chlorophenoxy)benzenesulfonyl]acetic acid ethyl ester (6 g, 16.9 mmol) and bis(2-chloroethyl)-4-methoxybenzylamine hydrochloride (7.15 g, 24 mmol). Yield: 6.0 g, 65%. Yellow oil. MS, *m/z*: 544 $(M + H)^+$.

1-(4-Methoxy)benzyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]-piperidine-4-carboxylic acid was prepared starting from 1-(4-methoxy)benzyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]-piperidine-4-carboxylic acid ethyl ester (2.22 g, 4.1 mmol) dissolved in THF/methanol (3:1, 150 mL) and 10 N NaOH (20 mL). The resulting reaction mixture was worked up as outlined in example **19** (step 6). Yield: 1.11 g, 56%. White solid. Mp 176 °C. MS, *m/z*: 516 $(M + H)^+$.

Starting from 1-(4-methoxy)benzyl-4-[4-(4-chlorophenoxy)-benzenesulfonyl]piperidine-4-carboxylic acid (1 g, 1.94 mmol) and following the procedure outlined in example **19** (step 7), 620 mg of 1-benzyl-4-[4-(4-chlorophenoxy)benzenesulfonyl]-piperidine-4-carboxylic acid hydroxyamide was isolated as a HCl salt, an off-white solid. Yield: 60%. Mp 122 °C. MS, *m/z*: 530 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.39−2.2 (m, 2H), 2.4−2.6 (m, 4H), 2.85−2.65 (m, 2H), 3.65−3.59 (m, 2H), 3.75 (s, 3H), 4.2−4.45 (m, 2H), 6.98 (d, 2H), 7.24−7.1 (m, 2H), 7.52−7.4 (m, 4H), 7.75 9 (d, 2H), 10.9 (brs, 1H), 11.2 (brs, 1H). Anal. ($C_{26}H_{27}Cl\ N_2O_6S$) C, H, N.

4-{[4-(4-Chlorophenoxy)phenyl]sulfonyl}-*N*-hydroxy-4-piperidinecarboxamide (56). To a solution of the 4-(4-chlorophenoxy)phenylsulfonyl chloride(770 mg, 2.54 mmol) in acetonitrile was added a fused potassium fluoride/calcium fluoride mixture (1.47 g, 2 equiv). The resulting suspension was stirred for 18 h at 20−25 °C. The suspension was filtered, and the solid was washed with diethyl ether. The mother liquor was concentrated in vacuo, and the resulting oil was seeded to produce the product as a white crystalline solid. Yield: 660 mg, 91%.

To a solution of lithium diisopropylamide (2.31 mmol) (either commercially available or freshly prepared from *n*-butyllithium and diisopropylamine) in tetrahydrofuran cooled to −78°C was added a solution of 1-(*tert*-butyl) 4-methyl-1,4-piperidinecarboxylate (510 mg, 2.1 mmol) in tetrahydrofuran, and the resulting mixture was stirred for 0.5−1 h at that temperature. A solution of the 4-(4-chlorophenoxy)phenylsulfonyl fluoride (510 mg, 2.1 mmol) in tetrahydrofuran was then added to the mixture, and the resulting mixture was stirred for 4−15 h at room temperature, quenched with saturated aqueous ammonium chloride solution, and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The crude product was purified by silica gel chromatography to obtain the desired product. Yield: 520 mg, 49%. MS, *m/z*: 532.1152 $(M + Na)^+$.

A stirred solution of 1-(*tert*-butyl) 4-methyl-4-{[4-(4-chlorophenoxy)phenyl]sulfonyl}-1,4-piperidinedicarboxylate (450 mg, 0.88 mmol) and lithium hydroxide (32 mg, 1.32 mmol) in tetrahydrofuran (3 mL)/methanol (3 mL)/water (2 mL) was heated at 55 °C for 15 h. The mixture was concentrated, acidified to pH 3−5 with 1 N aqueous hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave 1-(*tert*-butoxycarbonyl)-4-{[4-(4-chlorophenoxy)phenyl]sulfonyl}-4-piperidine carboxylic acid. Yield: 375 mg, 86%. MS, *m/z*: 532.1152 $(M + Na)^+$.

To a solution of 1-(*tert*-butoxycarbonyl)-4-{[4-(4-chlorophenoxy)phenyl]sulfonyl}-4-piperidine carboxylic acid ((350 mg, 0.71 mmol)) in dimethylformamide was added hydroxybenzotriazol (114 mg, 0.85 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (190 mg, 0.99 mmol) and *N*-methylmorpholine *N*-methylmorpholine (117 μL, 1.06 mmol). The resulting mixture was stirred for 1 h at room temperature when 50% aqueous hydroxylamine solution (217 μL, 3.55 mmol) was added, and the mixture was stirred for 15 h at room temperature. The solvent was removed in vacuo, and ethyl acetate/water was added to the crude product. The organic layer was separated and washed successively with 1 N aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate, and water. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed in vacuo to obtain the 1-(*tert*-butyl) 4-{[4-(4-chlorophenoxy)-phenyl]sulfonyl}-4-[(hydroxyamino)carbonyl]-1-piperidinecarboxylate. Yield: 150 mg, 41%. MS, *m/z*: 1021.2523. $(2M + H)^+$.

To a solution of 1-(*tert*-butyl) 4-{[4-(4-chlorophenoxy)phenyl]-sulfonyl}-4-[(hydroxyamino)carbonyl]-1-piperidinecarboxylate (105 mg, 0.21 mmol) in methylene chloride (20 mL) was added a 4 M hydrochloric acid solution (258 μL, 1.03 mmol), and the resulting mixture was stirred for 4 h at room temperature. The solvent was removed, and diethyl ether was added. The precipitated solid was filtered and dried to obtain 80 mg (85%) of 4-{[4-(4-chlorophenoxy)phenyl]sulfonyl}-*N*-hydroxy-4-piperidinecarboxamide as a white solid. ^{1}H NMR (300 MHz, DMSO): δ 2.13 (m, 2H), 2.46 (m, 2H), 2.59 (m, 2H), 3.33 (m, 2H), 7.19 (m, 4H), 7.52 (d, 2H, J = 9.0 Hz), 7.72 (d, 2H, J = 9.0 Hz), 9.19 (brs, 1H), 9.56 (brs, 1H). MS, *m/z*: 411.0777 $(M + H)^+$. Anal. ($C_{18}H_{19}Cl\ N_2O_5S$) C, H, N.

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