Articles

NMR-Based Modification of Matrix Metalloproteinase Inhibitors with Improved Bioavailability

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The NMR-based discovery of biaryl hydroxamate inhibitors of the matrix metalloproteinase stromelysin (MMP-3) has been previously described (Hajduk et al*. J. Am. Chem. Soc.* **1997***, 119,* 5818−5827). While potent in vitro, these inhibitors exhibited no in vivo activity due, at least in part, to the poor pharmacokinetic properties of the alkylhydroxamate moiety. To circumvent this liability, NMR-based screening was implemented to identify alternative zinc-chelating groups. Using this technique, 1-naphthyl hydroxamate was found to bind tightly to the protein ($K_D = 50$ μM) and was identified as a candidate for incorporation into the lead series. On the basis of NMR-derived structural information, the naphthyl hydroxamate and biaryl fragments were linked together to yield inhibitors of this enzyme that exhibited improved bioavailability. These studies demonstrate that the NMR-based screening of fragments can be effectively applied to improve the physicochemical or pharmacokinetic profile of lead compounds.

Introduction

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endoproteinases that are important in tissue remodeling. When overexpressed or dysregulated, these enzymes are associated with pathologies such as arthritis and tumor metastases[1,2] and have thus served as drug targets to treat these diseases. Hydroxamic acid-containing compounds potently inhibit MMPs and have the potential to be useful drugs.[3] In fact, several hydroxamate-containing MMP inhibitors have been clinically investigated, including marimistat,[4] prinomastat,[5] and CGS-27023A.[6] However, many hydroxamate-containing compounds exhibit rapid biliary excretion[7] or are susceptible to hydrolysis to the corresponding carboxylic acid in vivo,[8,9] which may limit their usefulness as clinical agents.

Strategies have been developed to eliminate the metabolic liability of hydroxamate-containing inhibitors. One approach is to utilize replacements for the hydroxamic acid which still bind to the enzyme but that will potentially exhibit improved pharmacokinetic properties. However, many of the known replacements (such as thiol or phosphonate groups) have pharmacokinetic (PK) liabilities of their own, while others (such as carboxylic acids) typically result in compounds with significantly reduced binding affinity for the enzyme.

Another approach is to synthetically incorporate modifications at or near the hydroxamate moiety in an attempt to decrease the rate of hydrolysis or biliary excretion in vivo. Both of these methods require extensive synthetic efforts to produce the fully elaborated compounds before it is known whether the modified inhibitors will still bind to the enzyme or have the desired properties.

We have previously reported on a fragment-based approach for the optimization of lead compounds that can be used to reduce the number of compounds that need to be synthesized.[10] Using this method, only those fragments that bind to the protein are incorporated into the lead series, reducing the synthetic effort and increasing the chances that active compounds will be produced. In addition, structural information on how the fragments bind to the protein can help determine how to incorporate these fragments into the final compound. Here we describe the application of NMR-based fragment optimization to biaryl-hydroxamate inhibitors of stromelysin (MMP-3) that were previously discovered using SAR by NMR.[11] The initial inhibitors exhibited potent ($IC_{50} < 100$ nM) in vitro activity,[11] but lacked oral bioavailability due to rapid hydrolysis of the hydroxamate group.[12] On the basis of this series, potent and orally bioavailable MMP inhibitors have been successfully produced by modification of the hydroxamate moiety.[12,13] Here, we present an alternative approach wherein replacements for the acetohydroxamate fragment of the biaryl-hydroxamate inhibitors were identified using NMR-based screening. Incorporation of an alternative fragment into the lead molecule produced MMP inhibitors that exhibited significantly increased bioavailability. These compounds represent novel MMP

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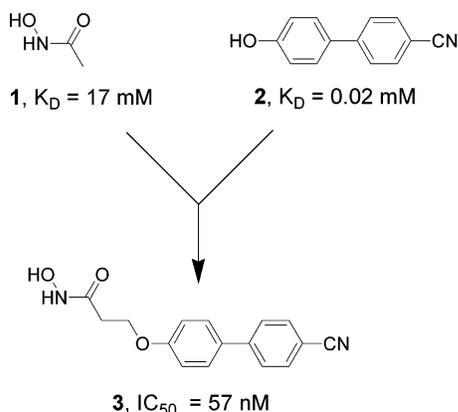
Figure 1. Summary of the SAR by NMR method as applied to the design of biaryl-hydroxamate inhibitors of stromelysin.[11]
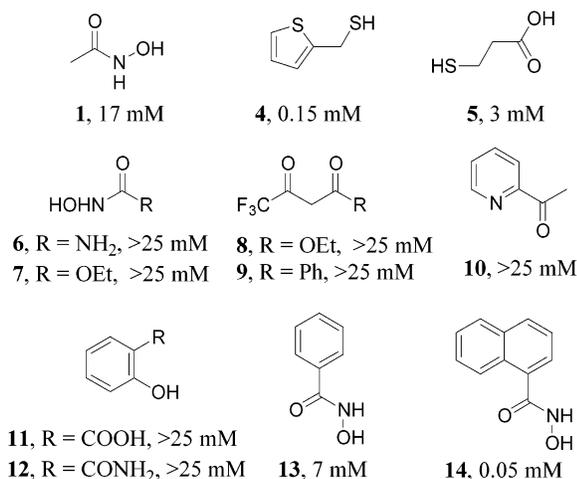
Figure 2. Compounds tested for their ability to chelate the active site zinc in stromelysin and serve as replacement for acetohydroxamic acid (**1**). NMR-derived K_D values are given after the compound number.

inhibitors that may be potentially useful for the treatment of cancer.

Results and Discussion

Identification of Replacements for the Acetohydroxamic Acid Fragment. In our initial NMR work on stromelysin,[11] acetohydroxamic acid (**1**) was linked to biphenyl-containing compounds (e.g., **2**) to produce MMP inhibitors with nanomolar potency (e.g, **3**, see Figure 1). However, all of the initial compounds lacked oral bioavailability due to hydrolysis of the hydroxamic acid.[12] This is not unexpected for alkylhydroxamate-containing compounds such as **3**, where hydrolysis[7,8] and rapid biliary excretion[7] present major hurdles to development. To identify alternative fragments to acetohydroxamate that might have an improved pharmacokinetic profile, compounds were tested for their ability to bind to stromelysin in an NMR-based screen, in which chemical shift changes were monitored in the ^{1}H/^{15}N HSQC spectrum of stromelysin upon addition of test compound. A diverse set of compounds was tested (see Figure 2), which included thiols (e.g., **4** and **5**), hydroxyureas (e.g., **6**), trifluoromethyl ketones (e.g., **8** and **9**), carboxylates (e.g., **11**), and a variety of substituted aromatic compounds. Of the tested compounds, only thiol- (**4** and **5**) and hydroxamate-containing compounds

Table 1. NMR Binding Data for Biaryl Compounds in the Presence of Acetohydroxamate (**1**) and 1-Naphthylhydroxamate (**14**)

No.	Structure	K_D (μM) in presence of **1** (500 mM)	K_D (μM) in presence of **14** (1 mM)
15	HO—⟨⟩—⟨⟩—CN	<50	<50
16	HO—⟨⟩—⟨⟩—OH	160	150
17	N⟨⟩—⟨⟩	170	900

(**1**, **13**, and **14**) exhibited any appreciable binding to stromelysin. On the basis of the pattern of chemical shift changes, all of the active compounds bound to the same site on stromelysin as acetohydroxamate, indicating that these compounds were indeed interacting with the active site zinc (data not shown). 2-Thienylmercaptan (**4**) and 1-naphthylhydroxamate (**14**) bound 100-fold more tightly to stromelysin than acetohydroxamic acid (**1**). This suggests that inhibitors containing these moieties have the potential for even greater binding affinity than those containing a simple alkyl hydroxamic acid.

Since the incorporation of thiol groups (as in **4** and **5**) may introduce another liability in the form of dimer formation and covalent binding to plasma proteins,[14] 1-naphthylhydroxamate (**14**) was chosen as a replacement fragment for acetohydroxamate. In addition to the higher intrinsic affinity of 1-naphthylhydroxamate (K_D = 50 μM) vs acetohydroxamate (K_D = 17,000 μM), the large naphthyl group could significantly change the pharmacokinetic properties of the linked inhibitors (e.g., potentially hindering hydrolysis of the hydroxamate group or potentiating biliary excretion), thereby increasing the bioavailability of the series. Furthermore, on the basis of binding experiments using NMR spectroscopy, biaryls were able to bind with comparable affinity to stromelysin in the presence of either acetohydroxamate or 1-naphthylhydroxamate (see Table 1), indicating that compounds which linked a biaryl to the naphthylhydroxamate could yield potent inhibitors of this enzyme.

Structure of Stromelysin/1-Naphthylhydroxamate (14) Complex. To aid in the design of MMP inhibitors containing a naphthylhydroxamate, an NOE-based structure of the stromelysin/**14** complex was determined (Figure 3A). A total of 20 intermolecular contacts between 1-naphthylhydroxamate and stromelysin were derived from ^{13}C-edited/^{12}C-filtered NOESY data sets. Hydrophobic contacts were observed between the naphthyl moiety of **14** and Tyr155, Tyr168, Phe86, His205, and Val163 of stromelysin. These data place the naphthyl group in a hydrophobic pocket located in the *nonprime* region of the active site (near the S$_1$ subsite). The experimentally determined orientation leaves the S$_1$′ subsite exposed and explains why the biaryl compounds are able to bind in the presence of **14**.

Design and Synthesis of Linked Compounds. On the basis of the NMR-derived structural information of the stromelysin/naphthylhydroxamate complex, compounds in which the naphthylhydroxamate is linked to the biaryl ligands were designed. A comparison of the structures of stromelysin complexed to 1-naphthylhy-
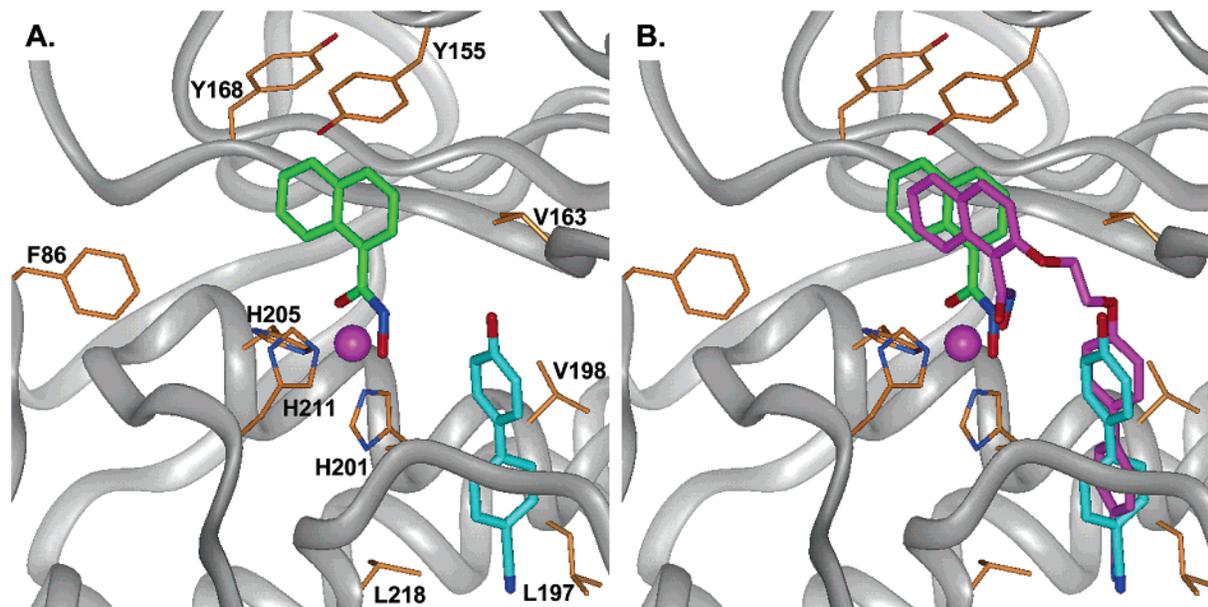
Figure 3. NOE-based structures of (A) 1-naphthylhydroxamate (**14**, green carbon atoms) and (B) 2-[2-[(4′-cyano[1,1′-biphenyl]-4-yl)oxy]ethoxy]-*N*-hydroxy-1-naphthalenecarboxamide (**20**, purple carbon atoms) bound to stromelysin. Residues of stromelysin that make contact with the ligands are shown in orange. Also shown is the biaryl portion of **3** (cyan carbon atoms). Linkers were designed to attach the 2-position of **14** (adjacent to the hydroxamate) to the phenolic hydroxyl of the biaryl.

Scheme 1[a]
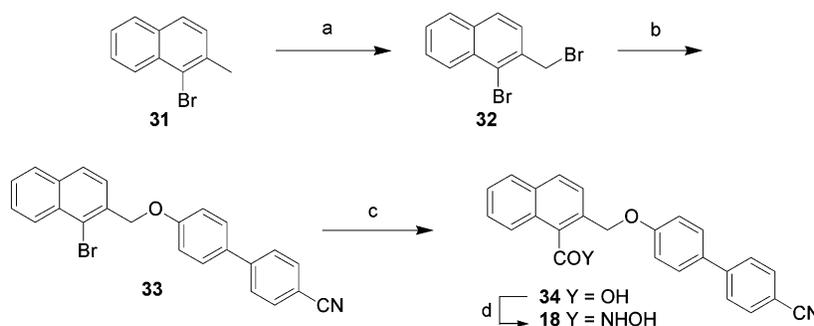
[a] Reagents: (a) NBS, benzoyl peroxide, CCl$_4$, △; (b) Cs$_2$CO$_3$, 4-OHPhPhCN, DMF; (c) 1. PhLi, −78 °C, THF; 2. CO$_2$; (d) 1. (COCl)$_2$, DMF; 2. NH$_2$OH·HCl, Et$_3$N.

Scheme 2[a]
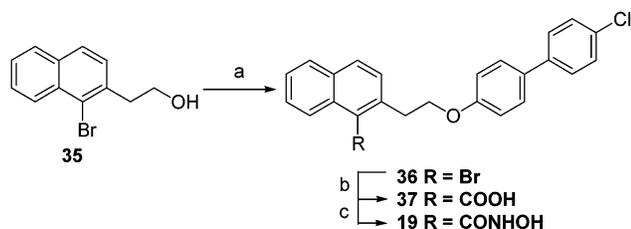
[a] Reagents: (a) 4-ClPhPhOH, Ph$_3$P, DIAD; (b) 1. n-BuLi, −78 °C, THF; 2. CO$_2$; (c) 1. (COCl)$_2$, DMF; 2. NH$_2$OH·HCl, Et$_3$N.

droxamate (**14**) and the biarylhydroxamate **3** suggested that the 2-position of **14** was well situated for incorporating linkers to access the S$_1$′ subsite (see Figure 3). Based on the distance between the 2-position of **14** and the phenolic ether of **3** (∼5 Å), simple methylene/ether linkers of 3−5 heteroatoms were proposed.

Compounds in which the biaryloxy and 1-naphthyl-hydroxamate fragments are linked with two and three atoms were readily synthesized by the routes shown in Schemes 1 and 2 to produce compounds **18** and **19**, respectively. Compounds **20** and **21** (containing four-

and five-atom linkers, respectively) were synthesized according to Schemes 3 and 4.

Biological Activity and Oral Bioavailability of Linked Compounds. Table 2 depicts the structures of the initial series of linked compounds that were synthesized along with their corresponding in vitro IC$_{50}$ values as measured in a stromelysin inhibition assay. The best compound in this series (**20**) exhibited an IC$_{50}$ of 340 nM, 6-fold weaker than the lead biarylhydrox-amate **3** (IC$_{50}$ = 57 nM). There is a marked dependence of the inhibitory potency on the linker length in this series. Compounds with linkers shorter than three atoms (e.g., **18**) show a more than 10-fold loss in enzyme inhibition compared to **20** (see Table 2). Compounds with longer linkers (e.g., **21**) also show a more than 10-fold loss in potency.

To determine whether the naphthylhydroxamate-containing inhibitors of stromelysin had improved pharmacokinetic profiles relative to the original biaryl-hydroxamate inhibitor **3**, the compounds were tested for oral bioavailability in rats. The naphthyl-biaryl-hydrox-amate **20** exhibits a superior pharmacokinetic profile than the biaryl hydroxamate **3**, as shown in Figure 4.

Scheme 3[a]
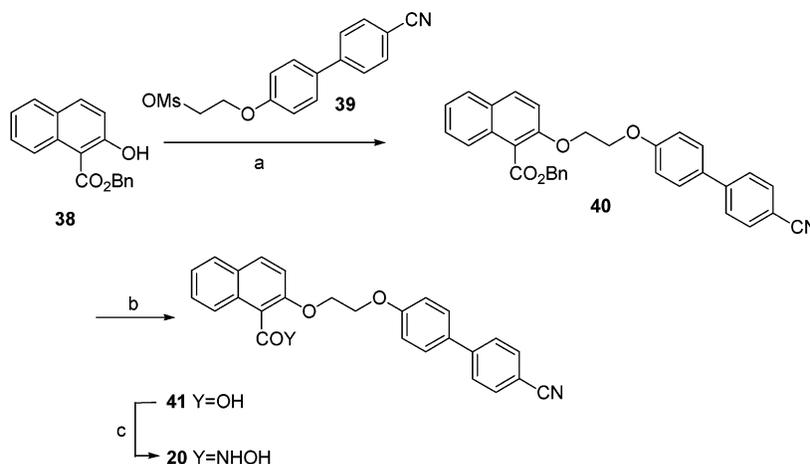
[a] Reagents: (a) K$_2$CO$_3$, DMF; (b) H$_2$, 10% Pd/C, AcOH−THF; (c) 1. (COCl)$_2$, DMF; 2. BnNHOH·HCl, Et$_3$N, 3. H$_2$, 10% Pd/C, THF.

Scheme 4[a]
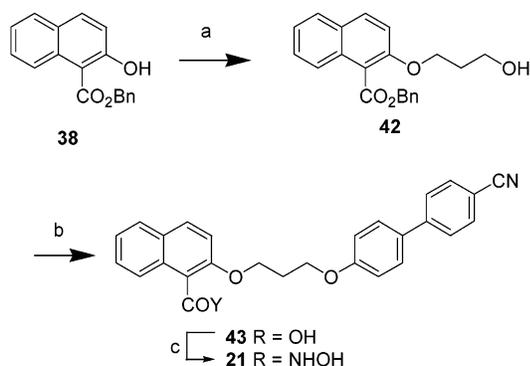
[a] Reagents: (a) 1. Br(CH$_2$)$_3$OAc, DMF, K$_2$CO$_3$; 2. Ba(OH)$_2$. (b) 1. MsCl, Et$_3$N; 2. 4-CNPhPhOH, K$_2$CO$_3$; 3. H$_2$, 10% Pd/C. (c) 1. (COCl)$_2$, DMF; 2. BnONH$_2$·HCl 3. H$_2$, 10% Pd/carbon, THF.

Table 2. Stromelysin Inhibition for Linked Biphenyl-naphthyl-hydroxamate Compounds

No.	X	R	IC$_{50}$ (μM)
14	H	-	50
18			>10
19			0.64
20			0.34
21			10.0

The oral bioavailability for **3** is virtually nonexistent, while the linked naphthylhydroxamate **20** exhibits a C_{max} of 28 uM and a half-life of nearly 2 h.[15] These data indicate that the naphthyl-biaryl-hydroxamate series of compounds represent lead MMP inhibitors with markedly improved bioavailability.

Validation of Binding Mode. NMR binding studies indicated that, on the NMR time scale, **20** was in slow-exchange with stromelysin, consistent with its biochemi-
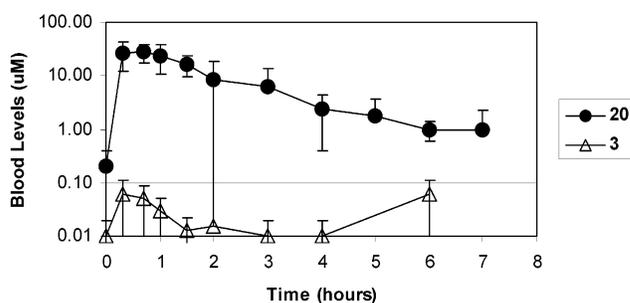

Figure 4. Blood levels of **3** (open triangles) and **20** (filled circles) after oral administration (30 mg/kg) in rats.

cal potency. To verify that the linked compounds were binding to stromelysin as designed, an NOE-based model of the stromelysin/**20** complex was determined (Figure 3B). The biaryl moiety of **20** exhibits NOE contacts to Val163, Leu197, Val198, and Leu218. These contacts are essentially identical to those observed between stromelysin and the biaryl moiety of **3**, indicating that the biaryl groups in these two compounds are binding in very similar orientations. The ethylene linker and the 3-position of the naphthyl ring shows NOEs to Val163, consistent with a binding orientation very similar to that observed for the untethered 1-naphthylhydroxamate (**14**). In addition, upon the binding of **20** to stromleysin, significant chemical shift changes were observed for Tyr155, Val163, Ala165, Ala167, Tyr168, and Ala169 as compared to the stromelysin/**3** complex. These residues are located at or near the proposed naphthyl binding site (see Figure 3). Thus, the linked compound **20** binds to stromelysin as designed, with the biaryl moiety binding to the S1′ subsite and the naphthyl moiety occupying the hydrophobic pocket located in the nonprime region of the active site.

Design and SAR of Second-Generation Naphthyl-biaryl-hydroxamates. Although the naphthyl-hydroxmate inhibitor **20** was bioavailable, the potency of this compound was weaker than the initial lead series. This was contrary to what was expected, since 1-naphthylhydroxamate (**14**) exhibited a higher intrinsic affinity for stromelysin than acetohydroxamate (**1**). The weaker inhibitory potency of the linked compounds is likely due, at least in part, to suboptimal positioning of the naphthyl and/or biaryl fragments for interaction

Scheme 5[a]
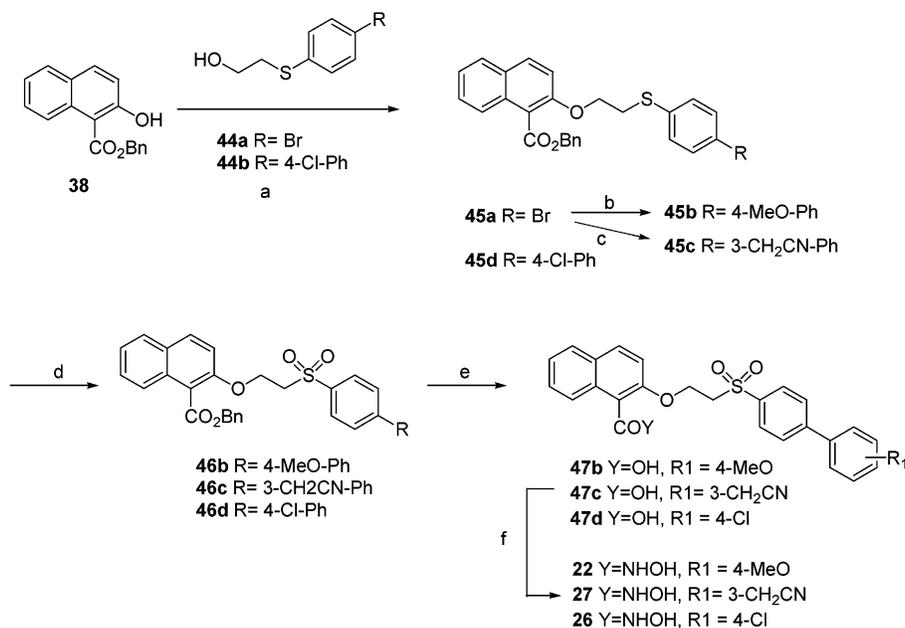
[a] Reagents: (a) **44a**: [n]Bu3P, ADDP; for **44b**; 1.MsCl, Et3N, 2. K2CO3, DMF; (b) 4-MeOPhB(OH)2, Pd(PPh3)4, CsF, DME; (c) 3-(CH2CN)-PhB(OH)2, Pd(PPh3)4, CsF, DME; (d) mCPBA, CH2Cl2; (e) H2, 10% Pd/C, AcOH−THF; (f) 1. (COCl)2, DMF, 2. NH2OH·HCl, Et3N.

Scheme 6[a]
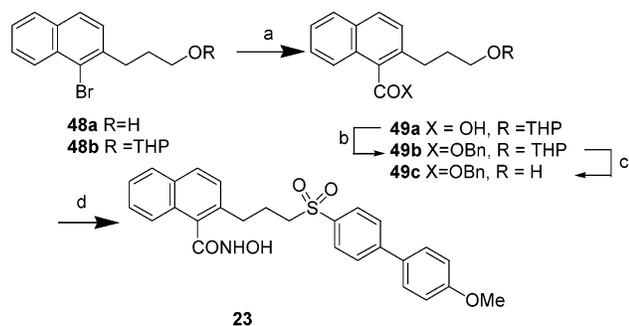
[a] Reagents: (a) 1. n-BuLi, −78 °C, THF; 2. CO2; (b) Cs2CO3, BnBr, DMF, 60 °C; (c) pTsOH·H2O, MeOH; (d) 1. 4-BrPhSH, n-Bu3P, ADDP; 2. 4-MeOPhB(OH)2, (Ph3P)4Pd, CsF, DME; 3. H2, 10% Pd/C; 4. (COCl)2, DMF; 5. NH2OH·HCl, Et3N.

with the enzyme. As linker lengths of three or four atoms gave rise to the most potent compounds in the initial series of naphthyl-biaryl-hydroxmate inhibitors (see Table 2), a variety of three- and four-atom linkers were explored that might be more suitable for the relative positioning of the naphthyl and biaryl groups. In addition, linkers were chosen that had the potential to form a hydrogen bond with the backbone amide of Ala199, as previously observed between this residue and the phenolic oxygen of the biarylhydroxamate **3**.[11] Thus, ethers, ketones, sulfones, and sulfonamides were all proposed as linker elements that possess slightly different geometries and contain at least one hydrogen bond acceptor atom. Compounds containing these linkers were synthesized by the routes shown in Schemes 5−9.

Table 3 depicts second-generation linked compounds that were synthesized along with their corresponding in vitro IC50 values. As can be seen from these data, the inhibitory activity of the linked compounds is significantly modulated not only by the length of the linker, but also by the chemical nature of the linker.

For example, with a linker length of four atoms, replacement of the biphenol oxygen of **20** with a sulfone (**22**) resulted in no change in potency. The naphthol oxygen in the linker was also not important, as replacement of the naphthol oxygen of **22** with a methylene (**23**) resulted in compounds with similar IC50 values. However, replacement of the sulfone of **23** with a sulfonamide (**24**) resulted in more than a 20-fold loss in inhibitory activity. Only a modest loss in potency (4-fold) was observed when the sulfone of **23** was replaced by a ketone (**25**). Substituions at the 3′- and 4′-positions of the biaryl also significantly affected potency. For example, 4′-methoxy (**22**) and 4′-chloro (**26**) substituents yielded compounds with similar potency, while the 3′-cyanomethyl substituent (**27**) yielded a nearly 10-fold gain in potency. Interestingly, this SAR matches that previously observed for the unlinked biaryl fragments, in which the potency rank order was 3′-cyanomethyl > 4′-methoxy ∼ 4′-chloro substitutions. This suggests that the sulfone-containing linkers (e.g., compounds **22**, **26**, and **27**) are positioning the biaryl moiety in a comparable position to that of the unlinked fragment. For linker lengths of three atoms, the sulfonamide (**28**) was superior in potency to both the sulfone (**29**) and the ketone (**30**), in direct contrast to the SAR observed for the four-atom linkers. Thus, by modifying the linker and biaryl substitution pattern, a 10-fold gain in potency was achieved, yielding a naphthyl-hydroxamate inhibitor (**27**, IC50 = 62 nM) that is equipotent to the parent biaryl hydroxamate (**3**, IC50 = 57 nM).

Conclusions

The NMR-based screening of fragments has proven to be a valuable tool in the drug discovery process. NMR can be used to identify fragments that bind to protein targets to produce potent leads,[11,16] or to guide the modification of lead compounds through fragment optimization.[10,17] The power of these fragment-based approaches lies in the fact that, out of the hundreds or
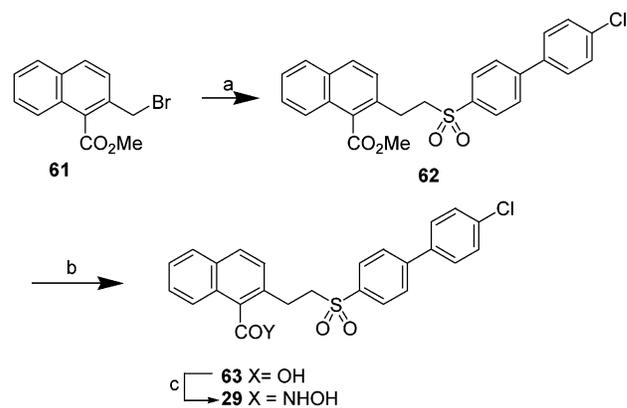
Scheme 7[a]
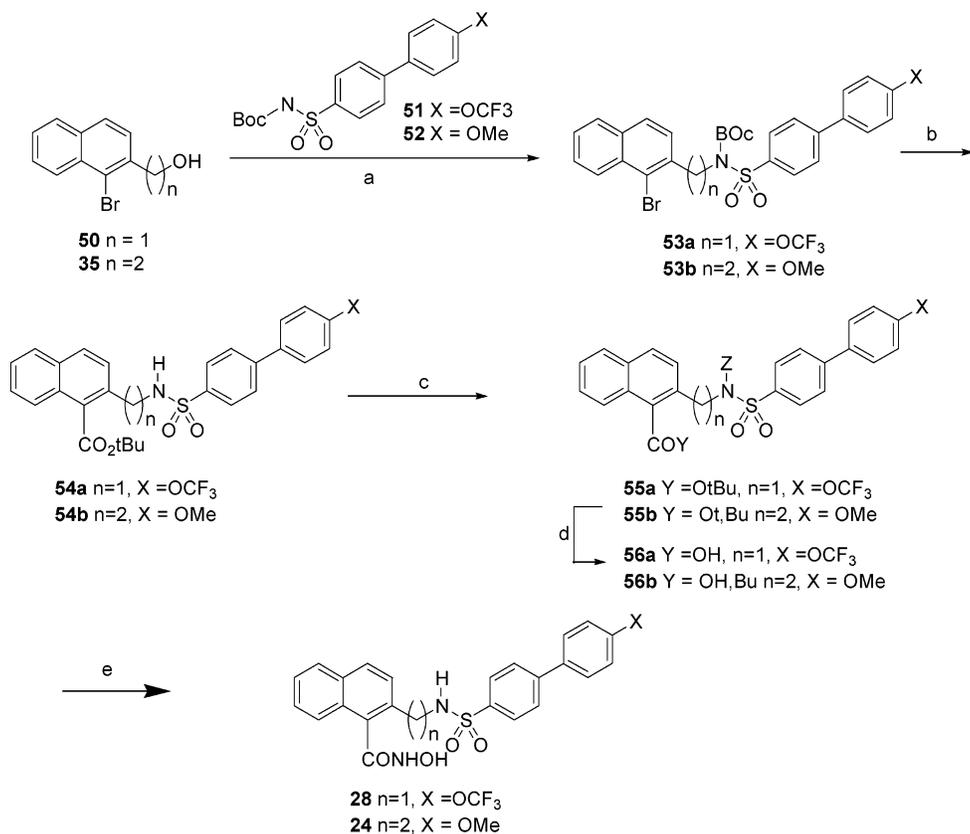
[a] Reagents: (a) Ph3P, DEAD, THF; (b) t-BuLl, −78 °C, THF; (c) NaH, DMF, BnOCOCl; (d) TFA; (e) 1. (COCl)2, DMF; 2. NH2OH.HCl, Et3N; 3, H2, 5% Pd/C, MeOH.

Scheme 8[a]
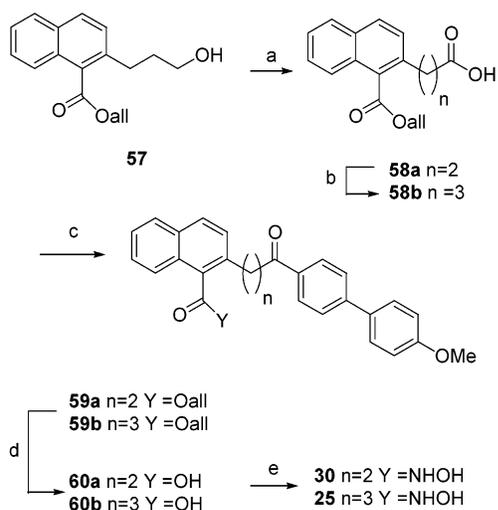
[a] Reagents: (a) Jones reagent, acetone; (b) 1. SOCl2, benzene; 2. CH2N2, Et2O; 3. PhCO2Ag; 4. LiOH, 2-propanol; (c) 1. SOCl2, benzene; 2. 4-MeOPh-Ph, AlCl3; (d) (Ph3P)4Pd, Ph3P, piperidine; (e) 1. (COCl)2, DMF; 2. NH2OH.HCl, Et3N.

Scheme 9[a]

[a] Reagents: (a) 4-(4-Cl-Ph)-PhSO2Me, n-BuLi, THF, −78 °C; (b) LiOH·H2O, 80 °C, 16 h; (c) 1. (COCl)2, DMF; 2. NH2OH·HCl, Et3N.

even thousands of synthetic possibilities that confront any given problem, the NMR-based screen can direct the chemistry to include only those fragments that have demonstrated affinity for the target. In the present example, the chemistry efforts were directed away from proposed zinc chelators that did not exhibit any observable affinity for stromelsyin and that would have most likely resulted in compounds with significantly reduced activity. Instead, efforts were directed at linking the naphthyl hydroxamates, which were shown to bind to the protein. Only four compounds (**18**−**21**) were prepared in order to examine the effects of the naphthyl-hydroxamate on potency and PK, and a sub-micromolar inhibitor that possessed improved oral bioavailability was identified. The SAR developed around this series of inhibitors indicates that the exact positioning of the biaryl and naphthyl moieties is critical for optimizing compound potency. Thus, further modification of the linker is one potential route for improving the potency of this series of MMP inhibitors.

Table 3. Stromelysin Inhibition for Second-Generation Linked Biphenyl-naphthyl-hydroxamate Compounds

No.	X	R	IC$_{50}$ (μM)
14	H	-	50
22	(sulfonyl linker)	(biphenyl-O)	0.46
23	(sulfonyl linker)	(biphenyl-O)	0.40
24	(sulfonamide linker)	(biphenyl-O)	10.0
25	(ketone linker)	(biphenyl-O)	1.50
26	(sulfonyl linker)	(biphenyl-Cl)	0.67
27	(sulfonyl linker)	(phenyl-CN)	0.062
28	(sulfonamide linker)	(biphenyl-OCF$_3$)	0.69
29	(sulfonyl linker)	(biphenyl-Cl)	3.7
30	(ketone linker)	(biphenyl-O)	0.45

Experimental Methods

Detection of Ligand Binding. The catalytic domain of stromelysin (residues 81−256) was generated as previously described.[11] The NMR samples were composed of uniformly ^{15}N-labeled stromelysin in an H$_2$O/D$_2$O (9/1) Tris-buffered solution (50 mM, pH = 7.0) containing CaCl$_2$ (20 mM) and sodium azide (0.05%). Ligand binding was detected by acquiring sensitivity-enhanced ^{15}N HSQC spectra[11] on 400 μL of 0.3 mM protein in the presence and absence of added compound. Compounds were added as solutions in perdeuterated DMSO. A Bruker sample changer was used on a Bruker AMX500 spectrometer. Compounds were initially tested at 25.0 mM each, and binding was determined by monitoring changes in the ^{15}N HSQC spectrum. Dissociation constants were obtained for selected compounds by monitoring the chemical shift changes of the amide resonances as a function of ligand concentration. Data were fit using a single binding site model. A least squares grid search was performed by varying the values of K_D and the chemical shift of the fully saturated protein.

Structural Studies. The NMR samples were composed of uniformly [15]N- or ^{15}N/^{13}C-labeled stromelysin (0.6 mM) and 1.0 mM **14** or 0.6 mM **20** in a D$_2$O or H$_2$O/D$_2$O (9/1) Tris-buffered solution (50 mM, pH = 7.0) containing CaCl$_2$ (20 mM) and sodium azide (0.05%). All NMR spectra were recorded at 25 and 32 °C on Bruker AMX500, AMX600, or DMX500 NMR spectrometers. In all NMR experiments, pulsed field gradients were applied to afford the suppression of solvent signal and spectral artifacts. Quadrature detection in the indirectly detected dimensions was accomplished by using the States-TPPI method. The data were processed and analyzed on Silicon Graphics computers using in-house written software.

Chemical shift assignments for the stromelysin/**14** and stromelysin/**20** complexes were obtained by comparison of multidimensional ^{1}H/^{13}C double-resonance NMR experiments with those obtained on the stromelysin/**3** complex, for which

the assignments were known.[11] The ^{1}H and ^{13}C chemical shifts of the side chain resonances were assigned from 3D HCCH-TOCSY and ^{1}H/^{13}C NOESY spectra. NOEs between the ligand and the protein were obtained from 2D and 3D ^{12}C-filtered, ^{13}C-edited NOESY spectra using mixing times ranging from 80 to 150 ms.

Intermolecular distance restraints between stromelysin and **14** were derived from the 3D ^{12}C-filtered, ^{13}C-edited NOESY spectra and were given a lower bound of 1.8 Å and an upper bound of 5.0 Å. Distance restraints between the catalytic zinc and the hydroxamate were employed as previously described.[11] Structures were calculated using a genetic algorithm-based protocol (EGADS).[18] The coordinates of the protein and the catalytic zinc were taken from the structure of stromelysin complexed to **3**[11] and were held constant. Repulsive van der Waals and NOE energies were employed as described[18] using force constants of 50 kcal mol^{-1} Å^{-2}. A total of 45 structures were generated with E_{total} < 25 kcal mol^{-1} (E_{NOE} < 10 and E_{VDW} < 20 kcal mol^{-1} for all structures), with a calculated rmsd of 0.77 Å to the average structure. The lowest energy structure (E_{total} = 20.7, E_{NOE} = 4.9, and E_{VDW} = 15.6 kcal mol^{-1}) was used for the linker design and is shown in Figure 3.

Intermolecular distance restraints between stromelysin and **20** were also derived from 3D ^{12}C-filtered, ^{13}C-edited NOESY spectra. All of the proton resonances for the biaryl and ethylene linker moieties of **20** could be assigned. However, when complexed to stromelysin, only the H3 position of the naphthyl moiety of **20** could be observed. All of the other proton resonances of the naphthyl moiety (H4 and H5−8) were broadened due to chemical exchange phenomena and could not be analyzed. Intermolecular distance restraints between stromelysin and **20** were given a lower bound of 1.8 Å and an upper bound of 5.0 Å. As with **14**, distance restraints between the catalytic zinc and the hydroxamate were employed as previously described, and the coordinates of the protein and the catalytic zinc were taken from the structure of stromelysin complexed to **3**[11] and held constant. **20** was initially docked to stromelysin and then energy minimized using the program XPLOR.[19] The X-PLOR F_{repel} function was used to simulate van der Waals interactions with a force constant of 4.0 kcal mol^{-1} and with atomic radii set to 0.8 times their CHARMM values. Distance restraints were employed with a square well potential (F_{NOE} = 50 kcal mol^{-1} Å^{-2}). The resulting energy-minimized structure exhibited no significant steric or NOE violations.

Determination of Stromelysin Inhibition. IC$_{50}$ values were obtained for recombinant, truncated stromelysin as previously described.[11]

Bioavailability Measurements. 3 and **20** were administered po (30 mg/kg) in hydroxypropyl methyl cellulose vehicle to a total of 4 rats each over two studies. Blood samples were collected via tail vein at various intervals for 7 h after dosing and deproteinated with 2 volumes of methanol containing 0.1% acetic acid. Concentration of the compound in the methanol extract was determined by bioassay using recombinant stromelysin.

Chemical Synthesis. General. ^{1}H NMR spectra were recorded on a GE QE300 spectrometer and chemical shifts are reported in parts per million (δ, ppm) relative to tetramethylsilane as an internal standard. Melting points were determined using an Electrothermal digital melting point apparatus and are uncorrected. Mass spectra were obtained on a Kratos MS-50 instrument. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., of Madison, NJ. Unless otherwise noted, all chemicals and reagents were obtained commercially and used without purification. Reported chemical yields are unoptimized and generally represent the result of a single experiment.

General Conditions for Procedure A (Suzuki couplings). A solution of the aryl bromide, 1.1 equiv of the arylboronic acid, 3 equiv of cesium fluoride, and 0.05 equiv of tetrakis(triphenylphosphine)palladium(0) in DME (75 mL) was heated to reflux for 16 h, concentrated, and purified on silica

gel with 30% ethyl acetate/hexanes to provide the biaryl intermediate.

General Conditions for Procedure B (preparation of *N*-hydroxy-1-naphthalenecarboxamides). To a cooled (0 °C) solution of the 1-naphthalenecarboxylic acid intermediate in dichloromethane (20 mL) was added 1.2 equiv of oxalyl chloride and DMF (2 drops). The mixture was stirred cold for 20 min and then allowed to come to ambient temperature over 1 h. The solution was then added dropwise to a rapidly stirred solution of 5 equiv of both hydroxylamine hydrochloride and triethylamine in a mixture of THF:water (110 mL, 10:1). The mixture was stirred for 2 h, reduced in volume under reduced pressure, poured into aqueous H_3PO_4, and extracted with ethyl acetate (3 × 35 mL). The combined organic layers were washed with water (2 × 25 mL), brine (1 × 25 mL), dried (MgSO$_4$), and filtered, and the solvents were removed under reduced pressure. The residue was crystallized from hot ethyl acetate to provide the final *N*-hydroxy-1-naphthalenecarboxamide product.

Synthesis of 2-[2-[(4′-Cyano[1,1′-biphenyl]-4-yl)oxy]methyl]-*N*-hydroxy-1-naphthalenecarboxamide (18, Scheme 1). A solution of 1-bromo-2-methylnaphthalene (**31**) (22.11 g, 0.10 mol), *N*-bromosuccinimide (19.57 g, 0.11 mol), and benzoyl peroxide (2.42 g, 10 mmol) in carbon tetrachloride (85 mL) was heated to reflux for 16 h, cooled to ambient temperature, and filtered. The liquid was reduced in volume and filtered. The solvents were removed under reduced pressure, and the resulting oil was crystallized from hot diethyl ether/hexane. The resulting solid was recrystallized from hot benzene/hexane to provide 1-bromo-2-bromomethyl)naphthalene (**32**) (13.4 g, 45%). ^{1}H NMR (DMSO-d_6) δ 4.99 (s, 2H), 7.68 (m, 3H), 8.01 (m, 2H), 8.25 (d, J = 9.8 Hz, 1H), MS (ESI) m/z 300 [M + H]$^+$.

A mixture of **32** (2.0 g, 6.71 mmol), 4′-hydroxy[1,1′-biphenyl]-4-carbonitrile (1.44 g, 7.38 mmol) and cesium carbonate (3.28 g, 10 mmol) in DMF (10 mL) was stirred under an atmosphere of nitrogen for 16 h. The mixture was poured into cold aqueous ammonium chloride, stirred for 0.5 h, and filtered. The residue was crystallized from hot ethyl acetate to provide 4′-[(1-bromo-2-naphthyl)methoxy][1,1′-biphenyl]-4-carbonitrile (**33**) (2.19 g, 79%). ^{1}H NMR (DMSO-d_6) δ, 5.46 (s, 2H), 7.20 (d, J = 8.82 Hz, 2H), 7.67 (m, 1H), 7.75 (m, 4H), 7.86 (m, 4H), 8.03 (dd, J = 3.68, 7.72 Hz, 2H), 8.28 (d, J = 8.46, 1H), MS (ESI) m/z 415 [M + H]$^+$.

To a solution of **33** (1.43 g, 3.47 mmol) in THF (30 mL) cooled to −78 °C was slowly added phenyllithium (2.22 mL, 3.99 mmol). The mixture was stirred cold for 45 min, CO_2 gas was bubbled through for 5 min, and the mixture was allowed to warm to 0 °C. The mixture was then quenched with 1 M aqueous H_3PO_4 and extracted with ethyl acetate (3 × 35 mL). The combined organic layers were washed with water (2 × 20 mL) and aquoues brine (1 × 20 mL), dried MgSO$_4$, and filtered and the sovents removed under reduced pressure. The residue was precipitated from diethyl ether to provide 2-{[(4′-cyano-[1,1′-biphenyl]-4-yl)oxy]methyl}-1-naphthoic acid (**34**) (0.99 g, 76%). ^{1}H NMR (300 MHz, DMSO-d_6) δ, 5.37 (s, 2H), 7.15 (d, J = 8.82 Hz, 2H), 7.62 (m, 2H), 7.72 (m, 4H), 7.86 (m, 4H), 8.01 (m, 3H), MS (ESI) m/z 378 [M + H]$^-$.

The carboxylate intermediate **34** (0.98 g, 2.6 mmol) was converted to the titled compound **18** (0.45 g) using procedure B. ^{1}H NMR (DMSO-d_6) δ, 5.29 (s, 2H), 7.17 (d, J = 9.16 Hz, 2H), 7.61 (m, 2H), 7.70 (m, 4H), 7.85 (m, 4H), 8.01 (m, 2H), 9.37 (s, 1H), 11.14 (s, 1H), MS (ESI) m/z 393 [M + H]$^-$. Anal. Calcd for $C_{25}H_{18}N_2O_3 \cdot 0.25H_2O$: C, 75.27; H, 4.67,:N, 7.02. Found: C, 75.68; H, 4.68,:N, 6.62.

Synthesis of 2-[2-[(4′-Chloro[1,1′-biphenyl]-4-yl)oxy]ethyl]-*N*-hydroxy-1-naphthalenecarboxamide (19, Scheme 2). A solution of (methoxymethyl)triphenyl phosphonium chloride (32.0 g, 93.3 mmol) in THF (100 mL) at −78 °C was treated with potasium *tert*-butoxide (9.90 g, 88.1 mmol), stirred cold for 1 h, treated with a solution of 1-bromo-2-naphthaldehyde (12.1 g, 51.7 mmol) in THF (75 mL) over 15 min, stirred for 16 h at room temperature, treated with aqueous ammonium chloride (200 mL), and extracted with ethyl acetate. The ethyl acetate was washed with brine, dried (MgSO$_4$),

filtered, and concentrated to an oil. The oil was purified on silica gel with a gradient of 2% to 5% ethyl acetate/hexanes to provide 11.8 g (87%) of 1-bromo-2-(2-methoxyethenyl)naphthalene. MS (DCI/NH$_3$) m/e 263 (M + H)$^+$.

A solution of 1-bromo-2-(2-methoxyethenyl)naphthalene (11.8 g, 45.0 mmol) in 20% aqueous dioxane (150 mL) was treated with *p*-toluenesulfonic acid (1.71 g, 9.00 mmol), heated to reflux for 2 h, cooled to room temperature, and concentrated. The residue was dissolved in diethyl ether, washed with aqueous NaHCO$_3$ and brine, dried (MgSO$_4$), filtered, and concentrated to an oil. The oil was purified on silica gel with a gradient of 2% to 5% ethyl acetate/hexanes to provide 2.07 g (18%) 1-bromo-2-naphthaleneacetaldehyde MS (DCI/NH$_3$) m/e 249 (M + H)$^+$.

A solution of 1-bromo-2-naphthaleneacetaldehyde (2.07 g, 8.35 mmol) in methyl alcohol (15 mL) was treated with sodium borohydride (0.47 g, 12.5 mmol), stirred for 2 h, quenched by addition to 1.0 M H$_3$PO$_4$, and concentrated. The residue was dissolved in ethyl acetate, washed with water and brine, dried (MgSO$_{4)}$, filtered, and concentrated to provide 1.52 g (73%) of 1-bromo-2-naphthalene ethanol (**35**). MS (DCI/NH$_3$) m/e 252 (M + H)$^+$.

A solution of **35** (1.51 g, 6.04 mmol), 4 chloro-4′-hydroxybiphenyl (1.35 g, 6.64 mmol), triphenylphosphine (2.37 g, 9.06 mmol), and diisobutylcarbodiimide (1.78 mL, 9.06 mmol) in THF (10 mL) was stirred for 24 h, concentrated, and purified on silica gel with 10% ethyl acetate/hexanes to provide 0.33 g (28%) of 2-[2-[(4′-chloro[1,1′-biphenyl]-4-yl)oxy]ethyl]-1- bromonaphthalene (**36**). MS (DCI/NH$_3$) m/e 456 (M + NH$_4$)$^+$.

A solution of **36** (0.33 g, 0.82 mmol) in THF (10 mL) at −78 °C was treated with *n*-butyllithium (0.37 mL, 0.92 mmol), stirred cold for 15 min, treated with gaseous carbon dioxide, stirred cold 15 min, quenched into 0.5 M aqueous HCl, and extracted with ethyl acetate. The ethyl acetate was washed with water and brine, dried (MgSO$_4$), filtered, and concentrated to provide 0.33 g (89%) of 2-[2-[(4′-chloro[1,1′-biphenyl]-4-yl)oxy]ethyl]-1-naphthoic acid **37**. MS (DCI/NH$_3$) m/e 420 (M + NH$_4$).

The carboxylate intermediate **37** (0.32 g, 0.80 mmol) was converted to the titled compound **19** (0.15 g, 46%) using procedure B. MS (DCI/NH$_3$) m/e 417 (M + H)$^+$; ^{1}H NMR (DMSO-d_6) δ 3.20 (t, 2H), 4.28 (t, 2H), 7.03 (d, 2H), 7.45 (d, 2H), 7.62 (m, 7H), 7.80 (d, 1H), 7.93 (m, 2H), 9.37 (s, 1H), 11.08 (s, 1H). Anal. Calcd for $C_{25}H_{20}NO_3Cl \cdot 0.5 H_2O$: C, 70.34; H, 4.96; N, 3.28. Found: C, 70.48; H, 4.87; N, 3.29.

Synthesis of 2-[2-[(4′-Cyano[1,1′-biphenyl]-4-yl)oxy]ethoxy]-*N*-hydroxy-1-naphthalenecarboxamide (20, Scheme 3)**.** To a solution of 4′-hydroxy-4-biphenylcarbonitrile (1.014 g, 5.19 mmol) in 10 mL of DMF was added potassium carbonate (2.15 g, 15.6 mmol, 3 equiv) and acetic acid 2-bromoethyl ester (1.0 g). After 2 h at 50 °C, the reaction mixture was cooled to room temperature, diluted with 50 mL of EtOAc, washed with H$_2$O (3 × 10 mL), dried (Na$_2$SO$_4$), filtered, and concentrated to provide a white solid. The solid was dissolved in 20 mL of MeOH, and 5 mL of H$_2$O and potassium carbonate (2.15 g, 15.6 mmol) were added. After 30 min, the MeOH was evaporated and the crude reaction was taken up in EtOAc and washed with H$_2$O (10 mL × 3), dried (Na$_2$SO$_4$), filtered, concentrated, and purified on silica gel to provide 0.967 g (78%) of 2-[(4′-cyano[1,1′-biphenyl]-4-yl)oxy]ethanol. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.79−7.60 (m, 4H), 7.57−7.52 (m, 2H), 7.05−7.01 (m, 2H), 4.15 (2H), 4.08−3.98 (m, 2H), 2.04 (t, 1H).

To a solution of 2-[(4′-cyano[1,1′-biphenyl]-4-yl)oxy]ethanol (150 mg, 0.63 mmol) in 6 mL CH$_2$Cl$_2$ at 0 °C was added triethylamine (127 mg, 1.26 mmol, 2 equiv) followed by methanesulfonyl chloride (108 mg, 0.94 mmol, 1.5 equiv). After stirring at ambient temperature for 4 h, the reaction mixture was concentrated and purified on silica gel with 25% EtOAc/hexanes to provide 185 mg (92%) of 4′-(2-hydroxyethoxy)[1,1′-biphenyl]-4-carbonitrile methanesulfonate (**39**) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.73−7.70 (m, 2H), 7.66−7.62 (m, 2H), 7.58−7.52 (m, 2H), 7.04−6.99 (m, 2H), 4.63−4.60 (m, 2H), 4.33−4.30 (m, 2H), 3.11 (s, 3H).

To a solution of benzyl 2-hydroxy-1-naphthalenecarboxylate (**38**) (459 mg, 1.65 mmol) and mesylate **39** (475 mg, 1.5 mmol) in 20 mL of DMF was added K_2CO_3 (623 mg, 4.5 mmol). The reaction was allowed to stir at 50 °C for 14 h and then partitioned between EtOAc and sat. NH_4Cl, washed with brine, dried ($MgSO_4$), filtered, and concentrated to give benzyl 2-[2-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]ethoxy]-1-naphthoic acid (**40**) which was used as is in the following experiment. In a separate experiment the compound was purified via silica gel chromatography eluting with 25% ethyl acetate/hexanes. ^{1}H NMR (CDCl$_3$) δ 7.91 (d, 1H), 7.82–7.63 (m, 6H), 7.55–7.28 (m, 10H), 7.02–6.97 (m, 2H), 5.45 (s, 2H), 4.49 (dd, 2H), 4.26 (dd, 2H). A solution of crude **40** (theory 1.5 mmol) in THF (30 mL) was treated with 10% Pd on carbon (20 mg), and the gas in the reaction vessel was evacuated twice and replaced with hydrogen. The reaction mixture was stirred overnight at rt and then filtered. The filtrate was concentrated to give 294 mg (48% yield) of **41**, which was used as is in the following experiment. Oxalyl chloride (0.54 mL, 1.08 mmol) was added dropwise over 15 min to a suspension of **41** (150 mg, 0.26 mmol) in CH_2Cl_2 (15 mL) and DMF (0.02 mL) resulting in a clear solution, which was stirred at rt an additional 15 min and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and then treated with *O*-benzylhydroxylamine hydrochloride (117 mg, 0.73 mmol). The reaction mixture was stirred at rt for 15 min, washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated. The solid residue was washed with EtOAc, dissolved in THF (10 mL), and treated with 10%Pd on carbon (10 mg), and the gas in the reaction vessel was evacuated twice and replaced with hydrogen. The reaction mixture was stirred overnight at rt and then filtered. The filtrate was washed with EtOAc and dried to give 44 mg (40% yield) of **20**. mp = 168–171 °C (dec). ^{1}H NMR (DMSO-d_6) δ 9.18 (d, J = 1.7 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.87–7.83 (m, 5H), 7.75–7.70 (m, 3H), 7.55–7.49 (m, 3H), 4.43–7.38 (m, 1H), 7.16–7.13 (m, 2H), 4.54–4.51 (m, 2H), 7.40–7.38 (m, 2H); MS (APCI) m/e 425 (M + H)$^+$. HRMS (FTMS) $C_{26}H_{21}N_2O_4$ [M + Na]$^+$ Calcd 447.1315, found 447.1310.

Synthesis of 2-[2-[(4'-Cyano[1,1'-biphenyl]-4-yl)oxy]-propyloxy]-*N*-hydroxy-1-naphthalenecarboxamide (21, Scheme 4). A solution of **38** (600 mg, 2.16 mmol) and 3-acetyl-oxy-1-propyl bromide (469 mg, 2.59 mmol) in DMF (15 mL) was treated with K_2CO_3 (894 mg, 6.47 mmol), stirred at 55 °C for 3 h, and then cooled to room temperature and partitioned between EtOAc and water. The organic extract was washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was dissolved in MeOH saturated with $Ba(OH)_2$·8H_2O (20 mL), and the resulting suspension was stirred for 15 min at room temperature and then partitioned between saturated aqueous NH_4Cl and EtOAc (2×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified via silica gel chromatography to give 441 mg (61% yield) of 2-(3-hydroxypropoxy)naphthalene-1-carboxylic acid benzyl ester (**42**).

A solution of **42** (441 mg, 1.31 mmol), methylsulfonyl chloride (0.122 mL, 1.57 mmol), and Et$_3$N (0.219 mL, 1.57 mmol) in CH_2Cl_2 (15 mL) was stirred at 40 °C for 18 h and then allowed to cool to room temperature and partitioned between saturated aqueous NH_4Cl and EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was dissolved in DMF (15 mL), treated with 4-(4'-hydroxyphenyl)benzonitrile (307 mg, 1.57 mmol), K_2CO_3 (540 mg, 3.91 mmol), and stirred at 60 C for 3 h. The reaction mixture was then allowed to cool to room temperature and partitioned between water and EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was dissolved in THF (15 mL) treated with catalytic amount of 10% Pd/carbon (30 mg), and the atmosphere in the flask was evacuated and filled with H_2 (via a hydrogen balloon). The reaction was stirred under H_2 overnight, the catalyst was removed via filtration, and the filtrate was concentrated. The residual solid was

washed with EtOAc and dried to give 138 mg (24% yield) of 2-[2-[(4'-cyano[1,1'-biphenyl]-4-yl)oxy]propyloxy]-*N*-hydroxy-1-naphthalenecarboxylic acid (**43**).

The carboxylate intermediate **43** (0.14 g, 0.32 mmol) was converted to the titled compound **21** (0.01 g, 17%) following the procedure described for the conversion of **41** to **20**. ^{1}H NMR (CDCl$_3$), δ 8.2–7.75 (m, 3H), 7.70–7.25 (m, 9H), 7.05–6.95 (m, 2H), 4.45–4.35 (m,2H), 4.3–4.2 (m, 2H), 2.4–2.3 (m, 2H). HRMS (FAB) $C_{27}H_{22}N_2O_4$ MH$^+$ Calcd. 439.1658, found 439.1680.

Synthesis of *N*-Hydroxy-2-[2-[(4'-methoxy[1,1'-biphenyl]-4-yl)thio]ethoxy]-1-naphthalenecarboxamide (22, Scheme 5). A room-temperature solution of 1,1'-(azodicarbonyl)dipiperidine) (ADDP) (0.684 g, 2.7 mmol) in benzene (6 mL) was treated with tributylphosphine (0.695 mL, 2.7 mmol) and a solution of **44a** (0.42 g, 1.80 mmol) in benzene (3 mL) and stirred for 5 min, followed by addition of **38** (0.503 g, 1.81 mmol). The resulting mixture was diluted with 3 mL of benzene, stirred for 45 min, and concentrated in vacuo. The residue was purified on silica gel using 10% ethyl acetate in hexanes to provide 0.62 g (70%) of 2-[2-(4-bromophenylsulfanyl)ethoxy]naphthalene-1-carboxylic acid benzyl ester (**45a**). 2-[2-(4-(4-methoxyphenyl)phenylsulfanyl)ethoxy]naphthalene-1-carboxylic acid benzyl ester (**45b**) was prepared from **45a** using 4-methoxyphenylboronic acid in procedure A.

The title compound (**22**) was converted from **45b** according to the procedure described for the conversion of **45d** to **26**. MS (DCI/NH$_3$) m/e 478 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.87 (m, 2H), 4.46 (m, 2H), 3.80 (s, 3H), 7.41 (m, 2H), 7.56 (m, 4H), 7.78 (m, 3H), 7.98 (m, 5H), 9.20 (s, 1H), 11.02 (s, 1H). Anal. Calcd for $C_{26}H_{23}NO_6S$: C, 65.39; H, 4.85; N, 2.93. Found: C, 65.09; H, 5.02; N, 2.72.

Synthesis of *N*-Hydroxy-2-[3-[(4'-methoxy[1,1'-biphenyl]-4-yl)sulfonyl]propyl]-1-naphthalenecarboxamide (23, Scheme 6). A mixture of **48a** (2.96 g, 11.2 mmol) and 3,4-dihydro-2*H*-pyran (2.04 mL, 22.4 mmol) in CH_2Cl_2 and was stirred at 0 °C for 10 min and at room temperature for 40 min. The reaction mixture was partitioned between CH_2Cl_2 and water, dried (Na_2SO_4), filtered, concentrated, and purified on silica gel with 10% ethyl acetate/hexanes to provide 3.73 g (95%) of **48b**. MS (DCI) m/e 366, 368 (M + NH$_4$)$^+$.

48b was converted to **49a** according to the procedure described for the conversion of **36 to 37**. MS (DCI) m/e 313 (M − H)$^-$, 337 (M + Na)$^+$, 332 (M + NH$_4$)$^+$.

A solution of **49a** (2.05 g, 6.53 mmol) in DMF (25 mL) was treated with cesium carbonate (3.2 g, 9.8 mmol) and benzyl bromide (1.16 mL, 9.75 mmol), stirred at 60 °C for 40 min, partitioned between ethyl acetate and water, dried (Na_2SO_4), filtered, concentrated, and purified on silica gel with 7% ethyl acetate/hexanes to provide 2.0 g (76%) of **49b**. MS (DCI) m/e 422 (M + NH$_4$)$^+$.

A solution of **49b** (2.0 g, 4.95 mmol) in methanol was treated with *p*-toluenesulfonic acid hydrate (84 mg, 0.44 mmol), stirred at room temperature for 2 h, partitioned between ethyl acetate and water, dried (Na_2SO_4), filtered, concentrated, and purified on silica gel with 30% ethyl acetate/hexanes to provide 1.5 g (95%) of 2-(3-hydroxypropyl)naphthalene-1-carboxylic acid benzyl ester (**49c**). MS (DCI) m/e 321 (M + H)$^+$, 338 (M + NH$_4$)$^+$.

49c was reacted with 4-bromothiophenol using the standard Mitsunobu conditions described for the preparation of **45a** to give phenylmethyl 2-[3-[(4-bromophenyl)thio]propyl]-1-naphthalenecarboxylate, which was then reacted with 4-methoxybenzene boronic acid under the described conditions in procedure A to give phenylmethyl 2-[3-[(4'-methoxy[1,1'-biphenyl]-4-yl)thio]propyl]-1-naphthalenecarboxylate. This was converted to **23** in the same fashion as the **46d** was converted to **26**. mp 105.4 °C decomposed; MS (APCI) m/e 585 (M + Cl)$^-$, 568 (M + NH$_4$)$^+$; ^{1}H NMR (DMSO-d_6) δ 1.90–2.02 (m, 2H), 2.757–2.806 (t, 2H, J = 6.9 Hz), 3.819 (s, 3H), 7.058 (td, 2H, J = 2.1, 8.7 Hz), 7.372–7.400 (d, 1H, J = 8.4 Hz), 7.540–7.572 (2H), 7.704–7.758 (m, 3H), 7.880–7.908 (m, 6H), 9.226 (s, 1H), 10.968 (s, 1H). Anal. Calcd for $C_{27}H_{25}NO_5S$·0.5H_2O, C, 66.92; H, 5.40; N, 2.89. Found: C, 66.93; H, 5.37; N, 2.67.

Synthesis of *N*-Hydroxy-2-[2-[[(4′-methoxy[1,1′-biphenyl]-4-yl)sulfonyl]amino]ethyl]-1-naphthalenecarboxamide (24, Scheme 7). The title compound was prepared following the procedures for the preparation of **28**, substituting 4-methoxyphenyl boronic acid for 4-trifluomethoxyphenyl boronic acid and **35** for **50**. ¹H NMR (CD₃OD) δ 7.84 (d, 1H), 7.74−7.69 (m, 4H), 7.56−7.51 (m, 5H), 7.48−7.43 (m, 1H), 7.26 (d, 1H), 7.02 (d, 2H), 3.85 (s, 3H), 3.27−3.25 (m, 2H), 2.92 (t, 2H); HRMS (FAB) C₂₆H₂₄N₂O₅S MH⁺ Calcd 477.1484, found 477.1479.

Synthesis of *N*-Hydroxy-2-[4-(4′-methoxy[1,1′-biphenyl]-4-yl)-4-oxobutyl]-1-naphthalenecarboxamide (25, Scheme 8). A solution of **57** (1.4 g, 5.18 mmol) in acetone (20 mL) was treated with Jones reagent (CrO₃/H₂SO₄) until the orange color persisted, quenched with isopropyl alcohol, and partitioned between ethyl acetate and water. The organic layer was washed with water, dried (Na₂SO₄), filtered, concentrated, and purified on silica gel with a gradient of 30% ethyl acetate/hexanes to 10% MeOH/dichloromethane to provide 1.27 g (86%) 2-(2-carboxyethyl)naphthalene-1-carboxylic acid allyl ester (**58a**) as a yellow oil. MS (ESI) *m/e* 283 (M − H)⁻.

A solution of **58a** (600 mg, 2.11 mmol) in benzene (5 mL) was treated with thionyl chloride (0.184 mL, 2.53 mmol) at room temperature and allowed to stir for 1 h. The reaction mixture was concentrated to dryness, redissolved in benzene (5 mL), treated with CH₂N₂/Et₂O at 0 °C, and allowed to stir at room temperature for 2 h. The reaction mixture was concentrated under a stream of nitrogen, and the residue was dissolved in methanol (30 mL), treated with silver benzoate (1.1 g, 4.85 mmol) and triethylamine (11 mL, 79.7 mmol), and allowed to stir at room temperature for 1.5 h. The organic layer was partitioned between saturated sodium bicarbonate and ethyl acetate, dried (Na₂SO₄), filtered, concentrated, and purified on silica gel with 10% ethyl acetate/hexanes to provide 402 mg (61%) of methyl 1-[(2-propenyloxy)carbonyl]-2-naphthalenebutanoate as an yellow oil. MS (DCI) *m/e* 330 (M + NH₄)⁺.

A solution of ester (400 mg, 1.28 mmol) in isopropyl alcohol (5 mL) was treated with lithium hydroxide (1.0 M, 1.28 mL, 1.28 mmol), stirred at room temperature for 1.5 h, and partitioned between ethyl acetate and water. The aqueous layer was then acidified with 1 N HCl, extracted with dichloromethane, dried (Na₂SO₄), filtered, and concentrated to provide 282.8 mg (74%) of 2-(2-carboxypropyl)naphthalene-1-carboxylic acid allyl ester (**58b**) as a yellow oil. MS (ESI) *m/e* 299 (M + H)⁺, 297 (M − H)⁻, 321 (M + Na)⁺.

A solution of **58b** (282 mg, 0.953 mmol) in benzene (5 mL) was treated with thionyl chloride (0.138 mL, 1.89 mmol) and DMF (1 drop), stirred at room temperature for 30 min, concentrated to dryness, and redissolved in dichloromethane (5 mL). The resulting solution was treated with 4-methoxybiphenyl (355 mg, 1.89 mmol) and aluminum chloride (377 mg, 2.84 mmol) at 0 °C, stirred at room temperature for 40 min, quenched with ice−water, extracted with dichloromethane, dried (Na₂SO₄), filtered, concentrated, and purified on silica gel with a gradient of 5% to 20% ethyl acetate/hexanes to provide 200 mg (45%) of 2-[4-(4′-methoxybiphenyl-4-yl)-4-oxobutyl]naphthalene-1-carboxylic acid allyl ester (**59b**) contaminated with 30% of the ortho-substituted isomer. MS (APCI) *m/e* 535 (M + H)⁺, 552 (M + NH₄)⁺.

A solution of **59b** (200 mg, 0.431 mmol) in dichloromethane (5 mL) at room temperature was treated with tetrakis(triphenylphosphine)palladium (43 mg, 0.0375 mmol), triphenylphosphine (19.6 mg, 0.075 mmol), and piperidine (0.0454 mL, 0.452 mmol) and allowed to stir at room temperature for 30 min. The reaction mixture was diluted with 0.5 N HCl and extracted with dichloromethane. The organic layer was dried (Na₂SO₄), filtered, concentrated, and purified on silica gel with 10% methanol/CH₂Cl₂ to provide 197 mg (100%) 2-[4-(4′-methoxybiphenyl-4-yl)-4-oxobutyl]naphthalene-1-carboxylic acid (**60b**) as a white solid. MS (ESI) *m/e* 425 (M + H)⁺, 423 (M − H)⁻, 454 (M + Na)⁺.

The carboxylate intermediate **60b** was converted to the titled compound **25** following procedure B. mp 160−163 °C decomposed; MS (APCI) *m/e* 440 (M + H)⁺, 457 (M + NH₄)⁺;

¹H NMR (DMSO-*d₆*) δ 2.008−2.037 (m, 2H), 2.799−2.830 (t, 2H, *J* = 4.5 Hz), 3.072−3.101 (t, 2H, *J* = 4.2 Hz), 3.813 (s, 3H), 7.049−7.066 (d, 2H, *J* = 5.1 Hz), 7.553−7.558 (3H), 7.694−7.711 (d, 2H, *J* = 5.1 Hz), 7.758−7.784 (3H), 7.906−7.935 (t, 2H, *J* = 3.9 Hz), 7.997−8.014 (d, 2H, *J* = 5.1 Hz), 9.223 (s, 1H), 10.974 (s, 1H); HRMS (FAB) calculated *m/e* for (M + H)⁺: C₂₈H₂₆NO₄, 440.1862. Found 440.1882.

Synthesis of 2-[[2-(4′-Chloro[1,1′-biphenyl]-4-yl)sulfonyl]ethoxy]-*N*-hydroxy-1-naphthalenecarboxamide (26, Scheme 5). A solution of 2-hydroxy-1-carboxynaphthalene (4.70 g, 25.0 mmol) and 20% cesium carbonate (20.3 mL, 12.5 mmol) in methanol (20 mL) was stripped to dryness, dissolved in DMF (10 mL), treated with benzyl bromide (2.67 mL, 22.5 mmoL), stirred for 20 h, diluted with brine, and extracted with ethyl acetate. The ethyl acetate was washed with water, 1 M NaOH, water, and brine, dried (MgSO₄), filtered, and concentrated to provide 3.98 g (57%) of 2-hydroxynaphthalene-1-carboxylic acid benzyl ester (**38**). MS (DCI/NH₃) *m/e* 279 (M + H)⁺.

A solution of 4-bromothiophenol (4.72 g, 25.0 mmol) in DMF (20 mL) was treated with sodium hydride (1.10 g, 27.4 mmol), stirred for 30 min, treated with bromoethanol (1.95 mL, 27.4 mmol), stirred for 20 h, treated with aqueous ammonium chloride, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried (MgSO₄), filtered, and concentrated. The residue was purified on silica gel with 30% ethyl acetate/hexanes to provide 5.06 g (87%) of 2-(4-bromophenylsulfanyl)ethanol (**44a**). MS (DCI/NH₃) *m/e* 232 (M + H)⁺.

2-(4′-Chlorobiphenyl-4-ylsulfanyl)ethanol (**44b**) was prepared from **45a** using 4-chlorophenylboronic acid and the described conditions for procedure A. MS (DCI/NH₃) *m/e* 265 (M + H)⁺.

A solution of **44b** (0.50 g, 1.89 mmol) and triethylamine (0.39 mL, 2.84 mmol) in CH₂Cl₂ (10 mL) at 0 °C was treated with methanesulfonyl chloride (0.18 mL, 2.27 mmol). After 1 h, the reaction mixture was washed with 0.5 M HCl, water, and brine, dried (MgSO₄), filtered, and concentrated. The residue was dissolved in DMF (1 mL) and added to a solution of **38** (0.58 g, 2.08 mmol) and sodium hydride (0.087 g, 2.20 mmol) in DMF (6 mL) at 0 °C. The mixture was heated to 50 °C for 4 h, cooled, washed with brine, dried (MgSO₄), filtered, concentrated, and purified on silica gel using 20% ethyl acetate/hexanes to provide 0.49 g (50%) of 2-[2-(4′-chlorobiphenyl-4-ylsulfanyl)ethoxy]naphthalene-1-carboxylic acid benzyl ester (**45d**). MS (DCI/NH₃) *m/e* 525 (M + H)⁺.

A solution of **45d** (0.42 g, 0.75 mmol) and 3-chloroperoxybenzoic acid (0.65 g, 3.76 mmol) in methylene chloride (50 mL) was heated at reflux for 16 h, washed with aqueous sodium bisulfite, aqueous sodium bicarbonate, water, and brine, dried (MgSO₄), filtered, and concentrated. Recrystallization from ethyl acetate/hexanes provided 0.18 g (43%) of 2-[2-(4′-chlorobiphenyl-4-sulfonyl)ethoxy]naphthalene-1-carboxylic acid benzyl ester (**46d**). MS (DCI/NH₃) *m/e* 574 (M + NH₄)⁺.

A mixture of a solution of **46d** (0.18 g, 0.32 mmol) in 20% acetic acid−THF and 10% palladium−carbon (0.050 g) was stirred at room temperature under an atmosphere of hydrogen for 20 h, filtered, and concentrated to provide 0.086 g (58%) of 2-[2-(4′-chlorobiphenyl-4-sulfonyl)ethoxy]naphthalene-1-carboxylic acid (**47d**). MS (DCI/NH₃) *m/e* 484 (M + NH₄)⁺.

The carboxylate intermediate **47d** was converted to the titled compound **26** following procedure B. MS (DCI/NH₃) *m/e* 482 (M + H)⁺; ¹H NMR(DMSO-*d₆*) δ 4.87 (m, 2H), 4.46 (m, 2H), 7.41 (m, 2H), 7.56 (m, 4H), 7.78 (m, 3H), 7.98 (m, 5H), 9.20 (s, 1H), 11.02 (s, 1H). Anal. Calcd for C₂₅H₂₀ClNO₅S: C, 62.30; H, 4.18; Cl, 7.36; N, 2.91. Found: C, 61.96; H, 4.45; N, 2.66.

Synthesis of *N*-Hydroxy-2-[2-[[3′-(cyamomethyl)[1,1′-biphenyl]-4-yl]sulfonyl]ethoxy]-1-naphthalenecarboxamide (27, Scheme 5). The title compound was prepared according to the procedure described for the preparation of **22**, substituting 3-cyanomethylphenyl boronic acid in place of 4-methoxyboronic acid. MS (ESI +) *m/e* 487 (M + H)⁺; ¹H NMR (DMSO-*d₆*) δ 3.90 (d, *J* = 6 Hz, 2H), 4.13 (s, 2H), 4.47 (d, *J* = 6 Hz, 2H), 7.38−7.60 (m, 5H), 7.68−7.75 (m, 3H), 7.88 (d, *J* =

8 Hz, 1H); 7.92−7.98 (m, 3H), 8.06 (d, *J* = 8 Hz, 1H), 9.20 (d, *J* = 1.5 Hz, 1H). Anal. Calcd for $C_{27}H_{22}N_2O_5S\cdot0.2\ H_2O$: C, 66.16; H, 4.61;:N, 5.72. Found: C, 65.84; H, 4.64: N, 5.50.

Synthesis of *N*-Hydroxy-2-[[[4′-(trifluoromethoxy)[1,1′-biphenyl]-4-yl]sulfonylamino]methyl]-1-naphthalenecarboxamide (28, Scheme 7). A solution of 1-bromo-2-naphthaldehyde (2.12 g, 8.91 mmol) in MeOH under N_2 at 0 °C was treated with $NaBH_4$ (0.51 g, 13.4 mmol), stirred for 15 min, quenched with acetone, and concentrated. Purification on silica gel with 5% ethyl acetate/CH_2Cl_2 provided 1.95 g (92%) of (1-bromonaphthalen-2-yl)methanol (**50**) as a white solid. mp 101−102 °C; MS (DCI) *m/e* 256/254 (M + NH_4)$^+$; ^{1}H NMR (CDCl$_3$) δ 2.09 (br d, 1H), 5.00 (s, 2H), 7.50−7.70 (m, 3H), 7.85 (d, *J* = 8.8 Hz, 2H), 8.32 (d, *J* = 8.9 Hz, 1H).

A suspension of 4-bromophenylsulfonamide (3.5 g, 14.8 mmol) and di-*tert*-butyl dicarbonate (3.76 g, 17.0 mmol) in CH_2Cl_2 (100 mL) under nitrogen was treated with triethylamine (2.3 mL, 16.3 mmol) and DMAP (183 mg, 1.48 mmol) and stirred at room temperature for 12 h. The reaction mixture was washed with 1 M HCl (2 × 25 mL), H_2O (25 mL), and brine, dried (Na_2SO_4), filtered, and concentrated. Purification on silica gel with a gradient of 2% to 5% MeOH in CH_2Cl_2 afforded 4.46 g (90%) of *N*-Boc-4-bromobenzenesulfonamide as a white solid. mp 127−128 °C; MS (DCI) *m/e* 355/353 (M + NH_4)$^+$; ^{1}H NMR (CDCl$_3$) δ 1.41 (s, 9H), 7.16 (br s, 1H), 7.69 (d, 2H), 7.89 (d, 2H).

A mixture of *N*-Boc-4-bromobenzenesulfonamide (3.10 g, 9.22 mmol), 4-trifluoromethoxyphenylboronic acid (2.13 g, 10.14 mmol), absolute EtOH (15 mL), 2 M aqueous Na_2CO_3 (9.22 mL, 18.44 mmol), and toluene (65 mL) was sparged with N_2, treated with tetrakis(triphenylphosphine)palladium (538 mg, 0.461 mmol), and heated at reflux for 1.25 h. The reaction mixture was cooled, diluted with H_2O (50 mL) and ethyl acetate (100 mL), and acidified to pH 3 with HOAc. The organic phase was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated. Purification on silica gel with a gradient of CH_2Cl_2 to 2% MeOH/CH_2Cl_2 provided 3.40 g (88%) of *N*-Boc-4′-trifluoromethoxybiphenyl-4-sulfonamide (**51**) as a white solid. MS (DCI) *m/e* 435 (M + NH_4)$^+$; ^{1}H NMR (DMSO-d_6) δ 1.31 (s, 9H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.96 (s, 4H).

To a solution of **51** (3.37 g, 8.06 mmol) in THF (75 mL) under N_2 were added triphenylphosphine (5.34 g, 20.16 mmol), **50** (1.59 g, 6.72 mmol), and diethyl azodicarboxylate (DEAD) (2.8 mL, 16.80 mmol), and the reaction was allowed to stir for 24 h. The solvent was removed, and the material was purified on silica gel with a gradient of 50% to 40% hexanes/CH_2Cl_2 to provide 3.81 g (89%) of *N*-Boc-2-[(4′-trifluoromethoxy-biphenyl-4-sulfonylamino)methyl]-1-bromonaphthalene (**53a**). MS (APCI) *m/e* 655/653 (M + NH_4)$^+$; ^{1}H NMR (CDCl$_3$) δ 1.32 (s, 9H), 5.38 (s, 2H), 7.31−7.87 (m, 11H), 8.00 (d, *J* = 8.5 Hz, 2H), 8.32 (d, *J* = 8.5 Hz, 1H).

To a solution of **53a** (1.50 g, 2.36 mmol) in THF (25 mL) under N_2 at −78 °C was added *tert*-butyllithium (1.7 M in pentane, 3.0 mL, 5.10 mmol). The resulting reddish-purple solution was stirred for 30 min at the same temperature and then quenched with HOAc (0.56 mL, 9.77 mmol) and warmed to room temperature. The solvent was removed, and the resulting oil was dissolved in ethyl acetate (100 mL), washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated. Purification on silica gel with a gradient of 10% hexanes/CH_2Cl_2 to 3% ethyl acetate/CH_2Cl_2 provided 1.13 g (86%) of 2-{[methyl-(4′-trifluoromethoxybiphenyl-4-sulfonyl)amino]-methyl}naphthalene-1-carboxylic acid *tert*-butyl ester (**54a**). MS (DCI) *m/e* 575 (M + NH_4)$^+$; ^{1}H NMR (CDCl$_3$) δ 1.57 (s, 9H), 4.26 (d, *J* = 6.4 Hz, 2H), 5.32 (t, *J* = 6.4 Hz, 1H), 7.29−7.96 (m, 14H); HRMS (FAB) calculated 558.1562 for (M + H)$^+$ for $C_{29}H_{27}F_3NO_5S$. Found 558.1543.

A solution of example **54a** (1.255 g, 2.25 mmol) in DMF (20 mL) under N_2 at 0 °C was treated with NaH (60% dispersion in mineral oil, 180 mg, 4.50 mmol) and allowed to stir for 30 min. Benzyl chloroformate (0.68 mL, 4.50 mmol) was added, the mixture was allowed to stir for 2 h, and HOAc was added. The solvent was removed, and the residue was dissolved in

ethyl acetate (100 mL), washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated. Purification over silica gel with 30% hexanes/CH_2Cl_2 provided 1.19 g (77%) of *N*-Z-2-[(4′-trifluoromethoxybiphenyl-4-sulfonylamino)methyl]naphthalene-1-carboxylic acid *tert*-butyl ester (**55a**). MS (ESI) *m/e* 709 (M + NH_4)$^+$; ^{1}H NMR (CDCl$_3$) δ 1.71 (s, 9H), 5.13 (s, 2H), 5.38 (s, 2H), 7.05−7.40 (m, 8H), 7.47−7.62 (m, 6H), 7.75−7.86 (m, 4H), 8.01 (d, 1H); HRMS (FAB) calculated *m/e*=692.1930 for (M + H)$^+$ for $C_{37}H_{33}F_3NO_7S$. Found *m/e* = 692.1941.

A solution of **55a** (1.19 g, 1.72 mmol) in CH_2Cl_2 (35 mL) under N_2 at −20 °C was treated with trifluoroacetic acid (13.3 mL, 0.172 mol) and allowed to stir at 0 °C for 1 h and then quenched with 2.6 M Na_2CO_3 (50 mL). The reaction mixture was reacidified to pH 3 with 1 M aq HCl and extracted with ethyl acetate. The combined oranic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated (chasing with anhydrous toluene) to provide 1.096 g (100%) of 2-[(4′-trifluoromethoxybiphenyl-4-sulfonylamino)methyl]naphthalene-1-carboxylic acid (**56a**). MS (APCI) *m/e* 653 (M + NH_4)$^+$, 636 (M + H)$^+$; ^{1}H NMR (CDCl$_3$) δ 5.09 (s, 2H), 5.41 (s, 2H), 7.05−7.25 (m, 5H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.52−7.65 (m, 5H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.88 (m, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 8.16 (d, 1H); HRMS (FAB) calculated 636.1304 for (M + H)$^+$ for $C_{33}H_{25}F_3NO_7S$. Found 636.1318.

To an ice cold solution of **56a** (1.096 g, 1.72 mmol) in CH_2Cl_2 (12 mL) under N_2 were added DMF (5 drops) and oxalyl chloride (0.30 mL, 3.45 mmol), and the reaction was allowed to stir at room temperature for 1 h. The solvent was then removed by rotary evaporation chasing with anhydrous toluene (5 mL), and the residue was taken up in CH_2Cl_2 (7 mL) and added to a 0 °C solution of hydroxylamine hydrochloride (1.21 g, 0.017 mol) and triethylamine (2.9 mL, 0.021 mol) in THF/H_2O (2:1 v/v, 12 mL). After allowing the reaction mixture to stir at room temperature for 3 h, ethyl acetate (100 mL) and H_2O (25 mL) were added, the layers were separated, and the organic phase was washed with 1 M HCl (2 × 10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was triturated with CH_2Cl_2 (75 mL) and vacuum filtered to remove a solid impurity. The filtrate was concentrated and the residue purified on silica gel (1.9 × 6 cm) with a gradient of CH_2Cl_2 to 3% MeOH/CH_2Cl_2 + 0.5% concentrated NH_4OH to obtain 0.459 g (41%) of *N*-hydroxy-2-[[[[4′-(trifluoromethoxy)[1,1′-biphenyl]-4-yl]sulfonyl](phenylmethoxycarbonyl)amino]methyl]-1-naphthalenecarboxamide. MS (ESI) *m/e* 668 (M + NH_4)$^+$, 651 (M + H)$^+$; ^{1}H NMR (CDCl$_3$) δ 5.05 (s, 2H), 5.22 (br s, 2H), 7.04 (d, *J* = 7.3 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 2H), 7.28−7.39 (m, 3H), 7.42 (d, *J* = 7.7 Hz, 2H), 7.50−7.60 (m, 4H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.84−8.02 (m, 3H), 9.19 (br s, 1H); HRMS (FAB) calculated 651.1413 for (M + H)$^+$ for $C_{33}H_{26}F_3N_2O_7S$. Found 651.1418.

A mixture of benzyl ester (0.456 g, 0.70 mmol) and 5% Pd−C (100 mg) in MeOH (10 mL) at 0 °C was hydrogenated under 1 atm of hydrogen for 2 h. The catalyst was removed by vacuum filtration through a 0.5 m poly(tetrafluoroethylene) (PTFE) membrane, and the filtrate was concentrated. Recrystallization from ethyl acetate/hexane provided 0.19 g (52%) of **28** as a white solid. MS (ESI) *m/e* 539 (M + Na)$^+$, 534 (M + NH_4)$^+$, 517 (M + H)$^+$; ^{1}H NMR (CD$_3$OD) δ 4.29 (s, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.47−7.60 (m, 3H), 7.70−7.79 (m, 4H), 7.81−7.90 (m, 3H), 7.95 (d, *J* = 8.1 Hz, 2H). Anal. Calcd for $C_{25}H_{19}F_3N_2O_5S$: C, 58.13; H, 3.71; N, 5.42. Found: C, 57.88; H, 3.75; N, 5.39.

Synthesis of 2-[2-[(4′-Chloro[1,1′-biphenyl]-4-yl)sulfonyl]ethyl]-*N*-hydroxy-1-naphthalenecarboxamide (29, Scheme 9). A solution of 4-chloro-4′-methyl sulfone biphenyl (0.24 g, 0.88 mmol) in THF (25 mL) was treated with *n*-BuLi (0.35 mL, 0.88 mmol) and stirred and −78 °C for 15 min to produce the lithiosulfone. A solution of **61** (0.25 g, 0.88 mmoL)[19] in THF (5 mL) was added dropwise to the lithiosulfone and stirred at ambient temperature for 16 h, poured into water, and extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification on silica gel with 20% ethyl acetate/

hexanes provided 0.12 g (29%) of 2-[2-[(4′-chloro[1,1′-biphenyl]-4-yl)sulfonyl]ethyl]-1-naphthalenecarboxylic acid methyl ester (**62**).

To a solution of **62** (0.12 g, 0.26 mmoL) in MeOH (3 mL), H_2O (3 mL), and THF (15 mL) was added LiOH·H_2O (0.17 g, 3.84 mmoL). The mixture was stirred at 80 °C for 16 h, poured into H_2O, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification on silica gel with 2% MeOH/CH_2Cl_2 provided 0.02 g (20%) of 2-[2-[(4′-chloro[1,1′-biphenyl]-4-yl)sulfonyl]ethyl]-1-naphthalenecarboxylic acid (**63**).

The carboxylate intermediate **63** was converted to the titled compound **29** following procedure B. mp 115 °C; MS (ESI) *m/e* 534 (M − H)$^+$, 536 (M + H)$^+$, 558 (M + Na)$^+$; ^{1}H NMR (DMSO-d_6) δ 10.98 (s, 1H), 9.30 (s, 1H), 8.04−7.39 (m, 14H), 3.74−3.68 (m, 2H), 3.11−3.01 (m, 2H); HRMS Calculated for $C_{25}H_{21}NO_4ClS$: 536.0880. Found: 536.0880.

Synthesis of *N*-Hydroxy-2-[4-(4′-methoxy[1,1′-biphenyl]-4-yl)-3-oxopropyl]-1-naphthalenecarboxamide (30, Scheme 8). **58a** was converted to **30** as described for the conversion of **58b** to **25**. MS (APCI) *m/e* 426 (M + H)$^+$, 448 (M + Na)$^+$; ^{1}H NMR (DMSO-d_6) δ 3.00−3.11 (t, 2H, *J* = 9 Hz), 3.40−3.50 (m, 2H), 3.81 (s, 0.8H), 3.89 (s, 0.2H), 7.02−7.09 (d, 2H, *J* = 9 Hz), 7.23−7.97 (10H), 8.79−8.06 (d, 2H, *J* = 3 Hz), 9.31 (s, 1H), 11.05 (s, 1H). Anal. Calcd for $C_{27}H_{23}NO_4$·0.75 MeOH, C, 74.14; H, 5.83; N, 3.11. Found: C, 74.08; H, 5.83; N, 2.73.

References

(1) Docherty, A. J. P.; O'Connell, J.; Crabbe, T.; Angal, S.; Murphy, G. The Matrix Metalloproteinases and their Natural Inhibitors: Prospects for Treating Degenerative Tissue Diseases. *Trends Biotechnol.* **1992**, *10*, 200−207.

(2) Beckett, R. P.; Davidson, A. H.; Drummond, A. H.; Huxley, P.; Whittaker, M. Recent Advances in Matrix Metalloproteinase Inhibitor Research. *Drug Discovery Today* **1996**, *1*, 16−26.

(3) Beckett, R. P.; Whittaker, M. Matrix Metalloproteinase Inhibitors 1998. *Exp. Opin. Ther. Patents* **1998**, *8*, 259−282.

(4) Steward, W. P. Marimistat (BB2516): Current Status of Development. *Cancer Chemother. Pharmacol.* **1999**, *43*, S56−60.

(5) Shalinsky, D. R.; Brekken, J.; Zou, H.; McDermott, C. D.; Forsyth, P. et al. Broad Antitumor and Antiangiogenic Activities of AG3340, a Potent and Selective MMP inhibitor Undergoing Advanced Oncology Clinical Trials. *Ann. N. Y. Acad. Sci.* **1999**, *878*, 236−270.

(6) MacPherson, L. J.; Bayburt, E. K.; Capparelli, M. P.; Carroll, B. J.; Goldstein, R. L. et al. Discovery of CGS 27023A, A Nonpeptidic, Potent, and Orally Active Stromelysin Inhibitor

(7) Singh, J.; Conzentino, P.; Cundy, P.; Gainor, J. A.; Gilliam, C. L. et al. Relationship Between Structure and Bioavailability in a Series of Hydroxamate Based Metalloprotease Inhibitors. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 337−342.

(8) Summers, J. B.; Gunn, B. P.; Mazdiyasni, H.; Goetze, A. M.; Young, P. R. et al. *J. Med. Chem.* **1987**, *30*, 2121−2126.

(9) Peng, S. X.; Strojnowski, M. J.; Hu, J. K.; Smith, B. J.; Eichhold, T. E. et al. Gas Chromatographic-Mass Spectrometric Analysis of Hydroxylamine for Monitoring Hydrolysis of Metalloprotease Inhibitors in Rat and Human Liver Microsomes. *J. Chromatogr. B* **1999**, *724*, 181−187.

(10) Hajduk, P. J.; Gomtsyan, A.; Didomenico, S.; Cowart, M.; Bayburt, E. K. et al. Design of Adenosine Kinase Inhibitors from the NMR−Based Screening of Fragments. *J. Med. Chem.* **2000**, *43*, 4781−4786.

(11) Hajduk, P. J.; Sheppard, G.; Nettesheim, D. G.; Olejniczak, E. T.; Shuker, S. B. et al. Discovery of Potent Nonpeptide Inhibitors of Stromelysin Using SAR by NMR. *J. Am. Chem. Soc.* **1997**, *119*, 5818−5827.

(12) Michaelides, M.; Dellaria, J.; Gong, J.; Holms, J.; Bouska, J. et al. Biaryl ether retrohydroxamates as potent, long-lived, orally bioavailable MMP inhibitors. *Biorg. Med. Chem. Lett.* **2001**, *11*, 1553−1556.

(13) Wada, C. K.; Holms, J. H.; Curtin, M. L.; Dai, Y.; Florjancic, A. S. et al. Phenoxyphenyl Sulfone *N*-Formylhydroxylamines (Retrohydroxamates) as Potent, Selective, Orally Bioavailable Matrix Metalloproteinase Inhibitors. *J. Med. Chem.* **2002**, *45*, 219−232.

(14) Migdalof, B. H.; Antonaccio, M. J.; McKinstry, D. N.; Singhvi, S. M.; Lan, S.-J. et al. Captopril: Pharmacology, Metabolism, and Disposition. *Drug. Metab. Rev.* **1984**, *15*, 841−869.

(15) It should be noted that the inhibitory activity observed in the blood during the PK studies cannot formally be attributed to the parent compound, as an active metabolite could also contribute to enzymatic inhibition. However, the most likely metabolite would be the corresponding carboxylic acid, which would be predicted to have little or no activity (See ref 2). In fact, the carboxylic analogue of the initial inhibitor **3** exhibited a more than 100-fold loss in potency compared to the hydroxamate-containing parent (ref 12).

(16) Shuker, S. B.; Hajduk, P. J.; Meadows, R. P.; Fesik, S. W. Discovering High-Affinity Ligands for Proteins: SAR by NMR. *Science* **1996**, *274*, 1531−1534.

(17) Hajduk, P. J.; Boyd, S.; Nettesheim, D.; Nienaber, V.; Severin, J. et al. The Identification of Novel Inhibitors of Urokinase Using NMR−Based Screening. *J. Med. Chem.* **2000**, *43*, 3862−3866.

(18) Meadows, R. P.; Hajduk, P. J. A genetic algorithm-based protocol for docking ensembles of small ligands using experimental restraints. *J. Biomol. NMR* **1995**, *5*, 41−47.

(19) Brunger, A. T. *X-PLOR Version 3.1.*; Yale University Press: New Haven and London, 1992.