Phenoxyphenyl Sulfone *N*-Formylhydroxylamines (Retrohydroxamates) as Potent, Selective, Orally Bioavailable Matrix Metalloproteinase Inhibitors

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A novel series of sulfone *N*-formylhydroxylamines (retrohydroxamates) have been investigated as matrix metalloproteinases (MMP) inhibitors. The substitution of the ether linkage of ABT-770 (**5**) with a sulfone group **13a** led to a substantial increase in activity against MMP-9 but was accompanied by a loss of selectivity for inhibition of MMP-2 and -9 over MMP-1 and diminished oral exposure. Replacement of the biphenyl P1′ substituent with a phenoxyphenyl group provided compounds that are highly selective for inhibition of MMP-2 and -9 over MMP-1. Optimization of the substituent adjacent to the retrohydroxamate center in this series led to the clinical candidate ABT-518 (**6**), a highly potent, selective, orally bioavailable MMP inhibitor that has been shown to significantly inhibit tumor growth in animal cancer models.

Introduction

The matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that are involved in the degradation of all components of the extracellular matrix. This family of enzymes plays an important role in remodeling and maintenance of normal tissue. It is the inappropriate activity of MMPs that has been implicated in a variety of pathologies such as arthritis, tumor metastasis, periodontal diseases, and multiple sclerosis, although the role of each MMP is not known for certain.[1−4]

MMP inhibitors possessing a range of potencies and selectivities have been evaluated in clinical studies (Chart 1).[5] They include hydroxamate-based compounds such as marimastat (**1**) and prinomastat (**2**) as well as compounds bearing thiol (BMS-275291, **3**) and carboxylate (BAY 12-9566, **4**) zinc binding groups. One of the findings from some of these studies was the onset of joint toxicity occurring predominantly in the upper limbs. In severe cases, upper limb range of motion was dramatically reduced ("frozen shoulder") requiring a dosing "holiday".[6] As a means of avoiding these effects, our efforts have focused on the discovery of subtype selective MMP inhibitors as antitumor agents. We targeted gelatinases A and B (MMP-2 and -9) since they have been consistently associated with tumor progression.[1,2] The substrate specificity of MMP-2 and -9 for type IV collagen, a major component of basement membranes, also supports their role in tumor progression. Significantly, MMP-2 and -9 deficient mice exhibit suppression of tumor growth and metastasis without gross developmental abnormalities.[7,8]

Selective inhibition of MMPs is possible due to differences in the depth of the S1′ pocket. From X-ray crystallographic and nuclear magnetic resonance (NMR)

Chart 1. MMP Inhibitors

1 marimastat

2 prinomastat

**3** BMS-275291

4 BAY 12-9566
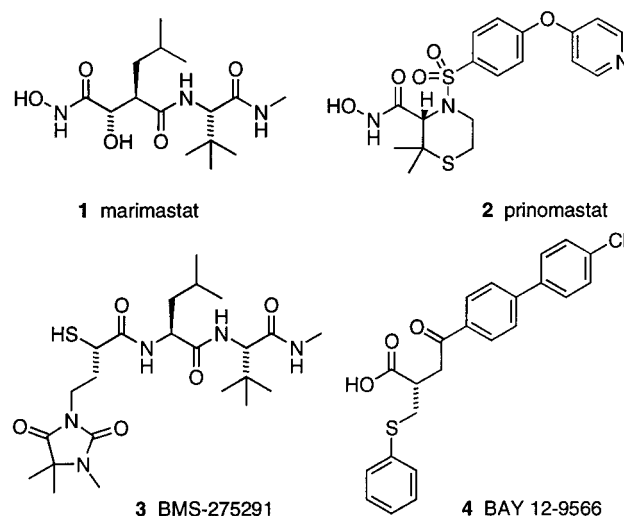
analysis and homology modeling, the MMPs may be classified into two broad structural classes, those with a relatively deep S1′ pocket (MMP-2, -3, -8, -9, and -13) and those with a shallow S1′ pocket (MMP-1 and -7).[9,10] Consequently, incorporation of an extended P1′ group (e.g., biphenyl) leads to selective inhibition, whereas the presence of smaller P1′ groups generally leads to broad spectrum inhibition.

Previously, we have disclosed the *N*-formylhydroxylamine (retrohydroxamate) **5** (Chart 2, ABT-770) as a potent MMP inhibitor with selectivity for inhibition of MMP-2 over MMP-1.[11,12] The replacement of the more typical hydroxamic acid zinc binding group with the retrohydroxamate and optimization of the α′ substituent (adjacent to the retrohydroxamate center) with a hydantoin group led to potent, long-lived, orally bioavailable MMP inhibitors.

To further probe the structure−activity relationship (SAR) of the retrohydroxamates as MMP inhibitors, we

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Chart 2. Ether and Sulfone Retrohydroxamates


5 ABT-770

6 ABT-518
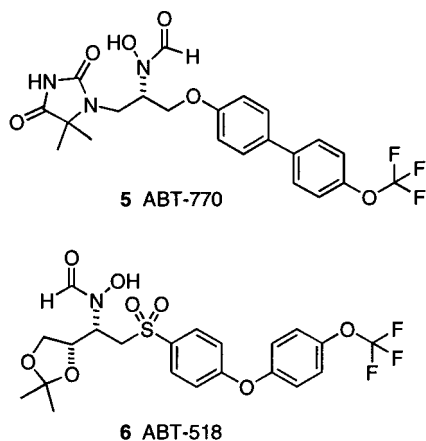
have investigated various replacements for the biaryl ether and hydantoin groups. Although **5** exhibits selective inhibition of MMP-2 over MMP-1, it is only moderately active against MMP-9. In our efforts to improve the inhibition of MMP-9, we have found that replacement of the ether linkage of **5** with a sulfone group (O→SO$_2$) led to a substantial increase in activity against MMP-9. Herein, we report the discovery of sulfone retrohydroxamates as potent, selective, orally bioavail-

able MMP inhibitors leading to the clinical candidate ABT-518 (**6**).[13]

Chemistry

The sulfone retrohydroxamates were synthesized by three general methods as shown in Schemes 1 and 2. Method A (Scheme 1) involves alkylation of an arylthiol with an α-bromo ketone (**7**) or an epoxide (**8**). The P1′ biaryl group may be installed from the onset by preparation of the appropriate biarylthiol via standard literature methods,[14−16] or it may be installed stepwise by alkylation of 4-bromothiophenol followed by a Suzuki coupling with the aryl bromide **9** (R′ = Br).[17] Reaction of the thiol with the α-bromo ketone in the presence of K$_2$CO$_3$ proceeded rapidly in dimethylformamide (DMF) at −5 °C (75−90% yield). In the case of ring opening of the epoxide, the reaction was heated at 100 °C. The resultant alcohol was then oxidized to the ketone by treatment with Dess−Martin periodinane.[18]

To install the retrohydroxamate group, a three step sequence was utilized, in most cases with purification only at the third step (50−80% overall yield). The ketones **9** and **12** were converted to the oximes by treatment with hydroxylamine hydrochloride in the presence of pyridine. The oxime was then reduced to the hydroxylamine using borane·pyridine/4 N HCl−

Scheme 1. Synthesis of Sulfone Retrohydroxamates via Arylthiols[a]
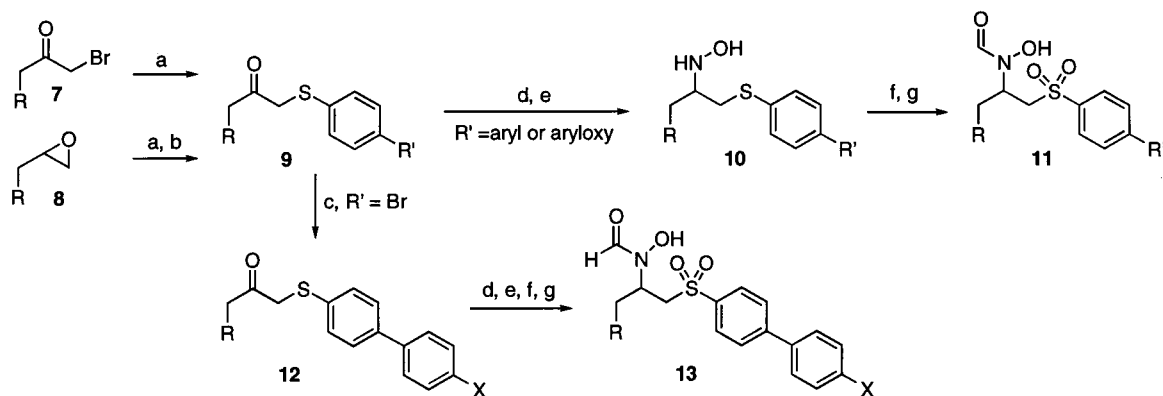
[a] Reagents: (a) K$_2$CO$_3$, HSAryl, DMF. (b) Dess−Martin. (c) ArylB(OR)$_2$, Pd(PPh$_3$)$_4$, NaOH. (d) HONH$_2$·HCl, pyridine, THF, EtOH. (e) BH$_3$·pyr. (f) Acetic formic anhydride, THF. (g) OXONE, MeOH, H$_2$O.

Scheme 2. Syntheses of Sulfone Retrohydroxamates via Aryl Methyl Sulfones

Method B[a]
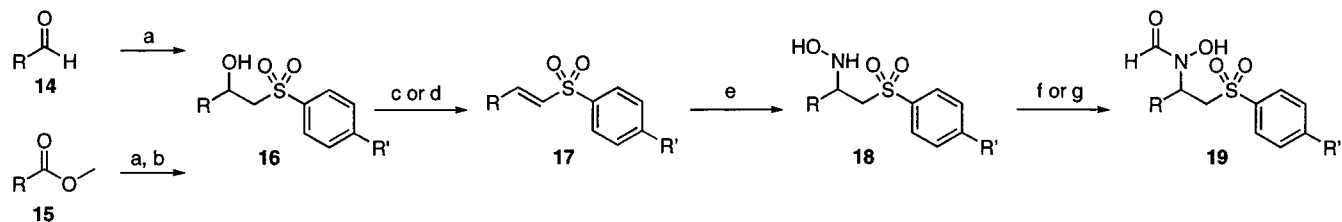
Method C[b]
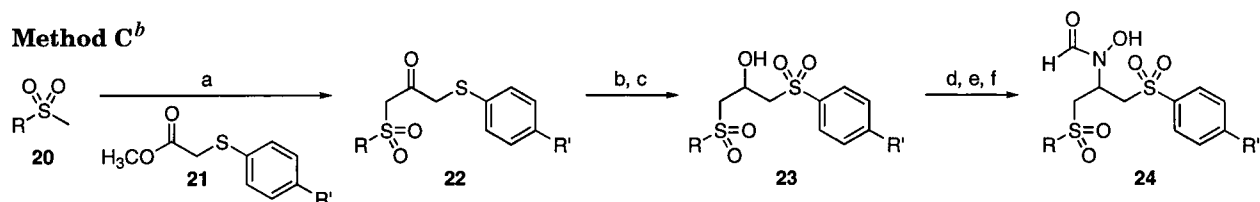
[a] Reagents: (a) ^{n}BuLi, H$_3$CSO$_2$Aryl, THF, −78 °C. (b) NaBH$_4$, MeOH, THF. (c) MsCl, Et$_3$N, CH$_2$Cl$_2$. (d) PPh$_3$, DEAD, THF. (e) HONH$_2$, THF. (f) Acetic formic anhydride. (g) Trifluoroethyl formate. [b] Reagents: (a) ^{n}BuLi, THF, −78 °C. (b) NaBH$_4$, MeOH, THF. (c) OXONE. (d) MsCl, Et$_3$N, CH$_2$Cl$_2$. (e) HONH$_2$, THF. (f) Trifluoroethyl formate.

Scheme 3. Synthesis of Sulfone Retrohydroxamate **6**[a]
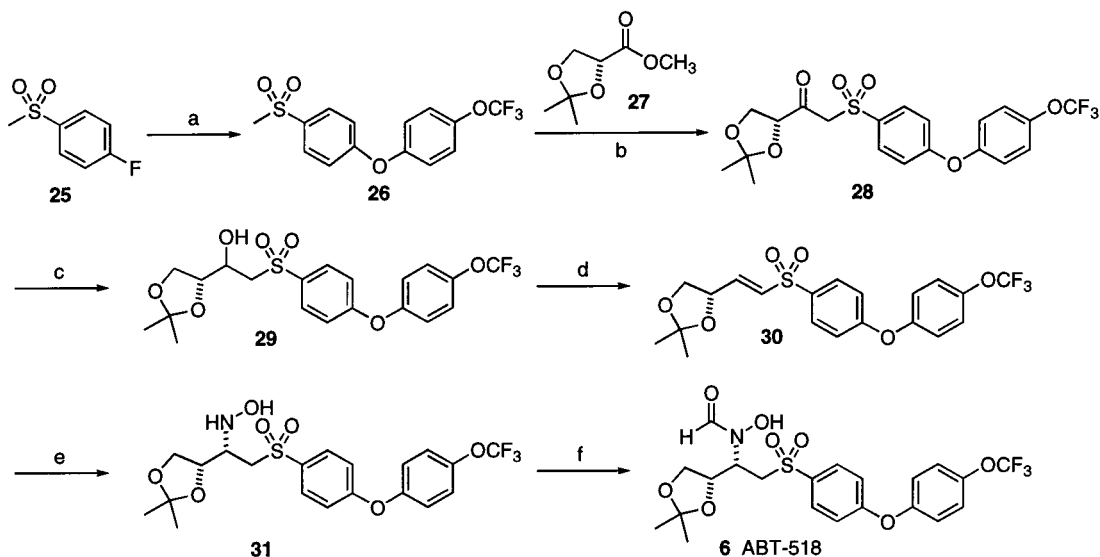
[a] Reagents: (a) 4-Trifluoromethoxyphenol, KOtBu, DMSO. (b) *n*BuLi, THF. (c) NaBH$_4$, EtOH. (d) MsCl, Et$_3$N, CH$_2$Cl$_2$. (e) HONH$_2$, THF. (f) Trifluoroethyl formate.

dioxane. We observed that using HCl in dioxane over aqueous HCl[19] gave consistently shorter reaction times for the reduction. Formylation of the hydroxylamine **10** was carried out with acetic formic anhydride at 0 °C in tetrahydrofuran (THF).[20] The final step of the synthesis was oxidation of the sulfide to the sulfone **11** or **13**, which was accomplished cleanly by treatment with OXONE in methanol/H$_2$O.

Method B (Scheme 2) involves addition of the lithium anion of a methyl sulfone to an aldehyde **14** or ester **15**. The biaryl methyl sulfones are readily prepared by nucleophilic aromatic substitution on 4-fluorophenyl methyl sulfone[21] or by Suzuki coupling between an arylboronic acid and a 4-bromophenyl methyl sulfone.[17] The lithium anion of the methyl sulfone was generated by treatment with *n*-butyllithium at −78 °C in THF to which was added the aldehyde at −78 °C to give the alcohol adduct **16**. Reaction of the methyl sulfone anion with the ester also proceeded at −78 °C. The resultant ketone was then reduced to the alcohol by treatment with sodium borohydride.

To install the retrohydroxamate, the β-hydroxy sulfone **16** was first converted to the α,β-unsaturated sulfone **17** by either of two routes, formation of the mesylate followed by elimination or direct elimination of the alcohol under Mitsunobu conditions. Treatment of the α,β-unsaturated sulfone with aqueous hydroxylamine in THF gave the 1,4-Michael adduct **18** in good yield. Previous literature examples of the conjugate addition have used HONH$_2$·HCl and base.[22] Under those conditions, we observed substantial amounts of the bis-Michael adduct. The *N*-formylation was initially carried out by treatment with acetic formic anhydride at 0 °C in THF.[19] However, for certain substrates, substantial amounts of the *N,O*-bis formyl or *O*-formyl products were obtained. Investigation of several formylating reagents led to the use of trifluoroethyl formate[23] in refluxing THF or MTBE to give high yields of the desired *N*-formyl product **19**.[24]
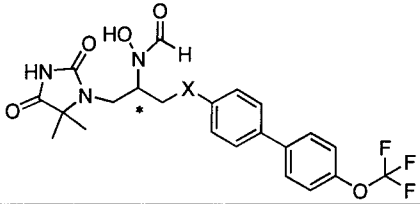
For compounds with ultimately two sulfone groups, a modification of method B was utilized, which es-

sentially reverses the functionality with respect to the addition of the methyl sulfone anion to the ester. In method C (Scheme 2), the ester functionality resides with the biaryl group **21**, and the α' substituent resides with the methyl sulfone **22**.

Synthesis of **6** was carried out using method B and is detailed in Scheme 3. The phenoxyphenyl methyl sulfone **26** was easily prepared by nucleophilic aromatic substitution between 4-fluoro-1-nitrobenzene and 4-trifluoromethoxyphenol. Treatment of the methyl sulfone **26** with *n*-butyllithium generated the lithium anion, to which was added the optically active methyl ester **27** at −78 °C in THF to give the ketone **28** in 79% yield (>99% ee). The ketone was then reduced with sodium borohydride to the alcohol **29**. Treatment of the alcohol with methanesulfonyl chloride and triethylamine led to elimination of the mesylate to give the α,β-unsaturated sulfone **30** as a 1:10 mixture of cis and trans isomers. The 1,4-addition of hydroxylamine to the olefin mixture proceeded with 4:1 selectivity in favor of the desired stereochemistry. The pure diastereomer **31** can be obtained by recrystallization and silica gel chromatography. Selective *N*-formylation of the hydroxylamine was accomplished by treatment with trifluoroethyl formate in refluxing MTBE to give **6** in 42% yield overall. Analysis of the final product by chiral high-performance liquid chromatography established the enantiomeric excess of **6** as >99%. This six step sequence has been optimized to give multikilogram quantities of **6** in 50% overall yield with >99% enantiomeric excess.[25]

Results and Discussion

Although the retrohydroxamate **5** (Table 1) is a potent and selective inhibitor of MMP-2 (IC$_{50}$ = 3.7 nM), it is only moderately active against MMP-9 (IC$_{50}$ = 120 nM). Replacement of the ether linkage of **5** with a sulfone group (O→SO$_2$) (**13a**, Table 1) led to a substantial increase in activity against MMP-9 (IC$_{50}$ = 0.86 nM). Unfortunately, this small change led to nearly complete loss of selectivity for inhibition of MMP-2 and -9 over
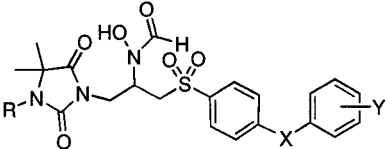
Table 1. Ether vs Sulfone Biaryl Retrohydroxamates

| cmpd | X | IC$_{50}$ (nM)^a | | | t1/2 (iv)/ |
		MMP-1	MMP-2	MMP-9	AUC (po)^b
5^c	O	4,600 ± 830 (3)	3.7 ± 1.6 (5)	120 ± 36 (3)	17.8 h/ 42 μM·h
13a	SO$_2$	82	0.86 ± 0.55 (2)	0.34	nd/ 5 μM·h

^{a} ± standard deviation (number of determinations). ^{b} Three mpk in cynomolgous monkey; $n = 1$ iv; $n = 2$ po. ^{c} S stereochemistry at * center.

MMP-1 (IC$_{50}$ MMP-1/MMP-2 < 10-fold) in addition to a significant decrease in exposure after oral dosing (AUC = 17.8 vs 5 μM·h, dose = 3 mpk).

Varying the substituent on the biphenyl sulfone had virtually no effect on the selectivity (**13b–d**, **19a**, **11a**; Table 2). Even a large *p*-butoxy group (**13b**) only increased the selectivity to 100-fold. One possible explanation is that the larger sulfone group perturbed the interaction of the P1′ substituent with the enzyme such that a large P1′ group could be accommodated by MMPs
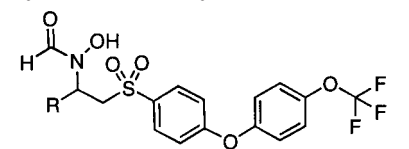
with either a deep or a shallow S1′ pocket. It was then proposed that introduction of another change in angle or increase in size of the P1′ group could alter the interaction with the enzyme to once again take advantage of the differences in size of the S1′ pocket. This was found to be the case when insertion of an ether linkage between the two aryl rings of the biphenyl group led to an improvement in selectivity (**11b–g**, Table 2). The direct phenoxyphenyl analogue **11b** containing a 5,5-dimethylhydantoin group and a *p*-trifluoromethoxy substituent had an IC$_{50}$ ratio for MMP-1/MMP-2 of >600. Methylation of the 1*N* of the hydantoin group led to a further increase in selectivity (**11e–g**, Table 2) with the *p*-trifluoromethoxy compound **11e** being the most selective (>27 000-fold). In contrast to the studies in the **5** ether series, we observed no *N*-dealkylation of the trimethylhydantoin in vivo.[26] Unfortunately, this series of hydantoin sulfone retrohydroxamates exhibited poor oral exposure (3 mpk in cynomolgous monkey, $n = 2$); the greatest exposure was obtained for the least selective *p*-Cl compounds **11d** and **11g**.

We continued to explore the SAR of the sulfone phenoxyphenyl retrohydroxamates with the intent of improving the oral exposure while maintaining the desired selectivity profile. The effect of substituting an aryl group for the hydantoin of **11b** is summarized in Table 3. In entries **19b–e**, the aryl group has a direct attachment with no alkyl or other spacer group. Selectivity was maintained. These compounds had no activity

Table 2. Hydantoin Sulfone Retrohydroxamates

| cmpd | R | X | Y | IC$_{50}$ (nM)^a | | | t1/2 (iv)^b | AUC (po)^b |
				MMP-1	MMP-2	MMP-9		
13a	H	-	*p*-OCF$_3$	82	0.86 ± 0.55 (2)	0.34	nd	5 μM·h
13b	H	-	*p*-Obutyl	240 ± 81 (2)	2.4 ± 1.6 (3)	6.2	nd	nd
13c	H	-	*p*-CF$_3$	44 ± 45 (2)	0.45	10	3.4 h	4 μM·h
13d	H	-	*m*-CH$_2$CN	78	0.35	0.91	0.5 h	nd
19a	H	-	*p*-SCH$_3$	2.9	0.67	1.1	nd	nd
11a	H	-	*p*-CN	36 ± 7.9 (2)	0.34 ± 0.14 (2)	4.1	1.1 h	nd
11b	H	O	*p*-OCF$_3$	820	1.3	2.0	nd	8 μM·h
11c	H	O	*p*-CN	990	0.93	3.9	nd	1 μM·h
11d	H	O	*p*-Cl	90	0.32	0.96	5.6 h	17 μM·h
11e	CH$_3$	O	*p*-OCF$_3$	>50,000	1.8	nd	0.7 h	1 μM·h
11f	CH$_3$	O	*p*-CN	2,500 ± 490 (3)	1.4	1.8	nd	nd
11g	CH$_3$	O	*p*-Cl	280	0.72 ± 0.46 (2)	1.4	11.7 h	13 μM·h

^{a} ± standard deviation (number of determinations). ^{b} Three mpk in cynomolgous monkey; $n = 1$ iv; $n = 2$ po.

Table 3. Aryl Sulfone Retrohydroxamates

cmpd	R	IC$_{50}$ (nM)[a]			AUC (po)[b]
		MMP-1	MMP-2	MMP-9	
19b	phenyl	>50,000	7.4 ± 2.3 (2)	4.1	0 μM•h
19c	2-pyridyl	>50,000	1.7	2.2	1 μM•h
19d	4-CF$_3$-phenyl	>50,000	62	37	nd
19e	N-methylindol-2-yl	>50,000	9.5	12	nd
19f	thiophen-2-yl-SCH$_2$	6,700	3.6	9.7	0 μM•h
19g	H$_3$CO$_2$C-phenyl-CH$_2$	>50,000	34 ± 5.1 (2)	0.98	nd
19h	HO$_2$C-phenyl-CH$_2$	>50,000	0.53 ± 0.20 (2)	0.53	16 μM•h
11h	uracil-CH$_2$	9,900 ± 1,700 (2)	0.91	1.4	11 μM•h

[a] ± standard deviation (number of determinations). [b] Three mpk in cynomolgous monkey; $n = 2$.

Table 4. Acyclic Sulfone Retrohydroxamates
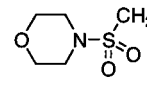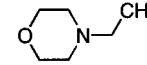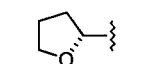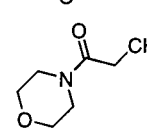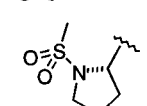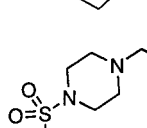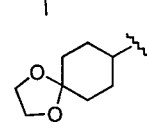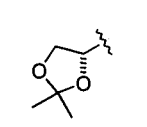
cmpd	R	IC$_{50}$ (nM)[a]			t1/2 (iv)/ AUC (po)[b]
		MMP-1	MMP-2	MMP-9	
24a	$CH_3SO_2N(CH_3)$-CH$_2$	6,600	0.098	7.2	nd / 4 μM•h
19i	$(CH_3)_2NCH_2$	5,200	1.3 ± 0.29 (5)	0.90	2.2/ 3 μM•h
19j	$CH_3SO_2N(CH_3)$-CH$_2$	2,000	12	1.7 ± 0.32 (2)	nd/nd
19k	HOCH$_2$	4,500	0.35	0.26	1.0 h/ nd
19l	H$_3$COCH$_2$	>50,000	2.4	0.90 ± 0.62 (2)	nd/ 0 μM•h
19m	HOCH$_2$CH$_2$OCH$_2$	>50,000	0.44	0.30	1.91 h/ nd
19n	(HO)$_2$CH-CH$_2$	>50,000	2.8	0.49	1.9 h/ 8 μM•h
19o[c]	HOCH$_2$CH(OH)-	>50,000	0.36	0.092	1 h/ 3 μM•h

[a] ± standard deviation (number of determinations). [b] Three mpk in cynomolgous monkey; $n = 1$ iv; $n = 2$ po. [c] S stereochemistry at * center.

against MMP-1 (IC$_{50}$ > 50 μM), but a slight decrease in potency against MMP-2 and -9 was observed (1.7–62 nM). The addition of a one or two methylene spacer group (**19f–h**, **11h**) resulted in a shift back to micromolar inhibition of MMP-1 and <10 nM inhibition of MMP-2 and -9. Overall, the exposure after oral (3 mpk in cynomolgous monkey, $n = 2$) or intravenous (iv, $n = 1$) dosing of this series of compounds showed no improvement, which may be attributed to their low solubility. This led to the investigation of the effect of basic or acidic functional groups. A pyridyl group (**19c**) had no effect on the oral exposure. A carboxylic acid group (**19h**) led to a highly potent (<1 nM) and selective (>10 000-fold) MMP inhibitor with a marginal increase in oral exposure. The corresponding methyl ester **19g** was nearly 100-fold less active against MMP-2.

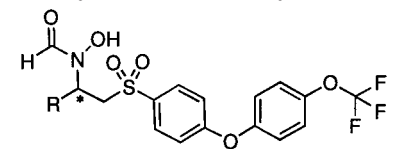Various polar groups were incorporated in hopes of improving the pharmacokinetics of the sulfone retrohydroxamates. Table 4 summarizes the effect of acyclic side chains varying from amines and sulfonamides to alcohols and ethers. All were potent (several subnanomolar) and selective (>1 000-fold), although some subtle differences were observed. Reversing the sulfonamide side chain (**19j** vs **24a**) leads to a reversal of potency against MMP-2 and -9. Compounds with ether side chains (**19l** and **19m**) and diol side chains (**19n** and **19o**) were the most selective for the inhibition of MMP-2 and -9 over MMP-1 with virtually no activity against MMP-1 (>50 μM). Also, within this series were several compounds (alcohols **19k**, **19m**, and **19o**) that possessed sub-nanomolar IC$_{50}$s against both MMP-2 and MMP-9. Unfortunately, no improvement in the pharmacokinetic properties was observed.

Cyclic variants of polar groups are summarized in Table 5. This series was found to be the most potent with the majority of compounds having sub-nanomolar IC$_{50}$s against MMP-2 and -9. The selectivity was also maintained (>2 900-fold). It was also in this series that we observed a marked improvement in the pharmacokinetic properties. Several compounds had oral AUCs greater than 20 μM·h (**6**, **19q**, and **19s–u**). In particular, the acetonide **6** dosed in cynomolgous monkeys had an oral AUC of 53 μM·h and an iv half-life of 16.8 h. The

Table 5. Heterocyclic Sulfone Retrohydroxamates

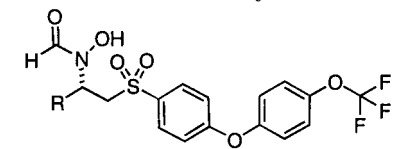| cmpd	R	IC$_{50}$ (nM)[a]			t1/2 (iv)/ AUC (po)[b]
		MMP-1	MMP-2	MMP-9	
24b		2,500	0.39	0.86	nd/ 3 μM•h
19p		>50,000	0.57	1.7	1.4 h/ 10 μM•h
19q[c]		>50,000	0.61	0.32	nd/ 26 μM•h
19r		>50,000	2.6	2.0	8.6 h/ nd
19s[c]		8,000	1.9	2.0	nd/ 24 μM•h
19t		>50,000	0.33	0.79	nd/ 41 μM•h
19u		>50,000	0.42	2.0	nd/ 28 μM•h
6[c]		8,900 ± 4,700 (2)	0.78 ± 0.20 (2)	0.50	16.8 h/ 53 μM•h
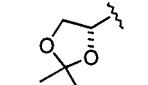
[a] ± standard deviation (number of determinations). [b] Three mpk in cynomolgous monkey; $n = 1$ iv; $n = 2$ po. [c] *S* stereochemistry at * center.

bioavailability of **6** was further evaluated in several species and was found to be >70% in rat, dog, and monkey. Compound **6** has excellent activity against MMP-2 and -9 (IC$_{50}$s = 0.78 and 0.50, respectively) and greater than 11 000-fold selectivity for the inhibition of MMP-2 and -9 over MMP-1 (IC$_{50}$ = 8900 nM).

Derivatives of acetonide **6** were also synthesized and tested as summarized in Table 6. The epimers **19v−x** were less potent inhibitors of MMP-2 and -9 (1.4−480 nM). Surprisingly, even small changes to the acetonide such as adding a methyl substituent (**19y,z**) or insertion of a methylene linker (**19aa**) also led to decreased activity and diminished oral exposure.

The retrohydroxamate **6** was judged as the most promising candidate for further development due to its favorable combination of potency, selectivity, and bioavailability. Its activities against other MMPs are listed in Table 7. It is a potent inhibitor of MMP-3 (stromelysin), -8 (neutrophil collagenase), and -13 (collagenase-3) but does not inhibit MMP-7 (matrilysin). Retrohydroxamate **6** is a more potent inhibitor of MMP-2 and -9 than **4**. It is also more selective for the inhibition of MMP-2 and -9 over MMP-1 than **2**. Because **6** possesses

Table 6. Acetonide Sulfone Retrohydroxamates

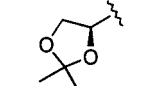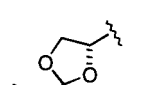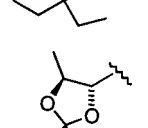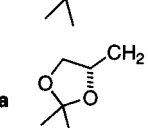| cmpd	R	IC$_{50}$ (nM)[a]			t1/2 (iv)/ AUC (po)[b]
		MMP-1	MMP-2	MMP-9	
6		8,900 ± 4,700 (2)	0.78 ± 0.20 (2)	0.50	16.8 h/ 53 μM•h
19v		>50,000	6.3	2.3	nd/nd
19w	ent-6	>50,000	25	1.4	nd/nd
19x	ent-19v	>50,000	260	480	nd/nd
19y		8,300	20	1.1	nd/ 5 μM•h
19z		>50,000	1.9	1.1	19.5 h/ 21 μM•h
19aa		>50,000	1.5	5.5	nd/ 2 μM•h

[a] ± standard deviation (number of determinations). [b] Three mpk in cynomolgous monkey; $n = 1$ iv; $n = 2$ po.

a metal chelating group, the ability of **6** to inhibit other metalloproteinases was also evaluated. Retrohydroxamate **6** does not inhibit LPS-stimulated TNFα (tumor necrosis factor) release from THP-1 cells suggesting a lack of functional inhibition of the ADAM class of metalloproteinases (Table 7). It also does not inhibit thermolysin, rat neprilysin, or leucine aminopeptidase (IC$_{50}$ > 100 μM).

The retrohydroxamate **6** was also evaluated in in vivo animal tumor models. The compound demonstrated antitumor activity when administered orally as a monotherapy in a murine syngenetic tumor growth model (B16 melanoma implanted subcutaneously in the flank of mice) (Figure 1). The compound or vehicle was administered orally twice daily on days 7−21. The inhibition of tumor growth was found to be dose-dependent with 48% inhibition of tumor growth to 2 g relative to control at 30 mpk.

Conclusion

We have reported that the replacement of the ether linkage of **5** with a sulfone group leads to increased inhibition of MMP-2 and -9 within a series of retrohydroxamates. Further exploration of the SAR of the sulfone retrohydroxamates led to orally bioavailable phenoxyphenyl sulfone retrohydroxamates, which are highly selective for the inhibition of MMP-2 and -9 over

Table 7. Inhibition of MMPs and Cellular TNFα Release

	MMP IC$_{50}$ (nM)[a]								
cmpd	MMP-1	MMP-2	MMP-1/MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-13	cellular TNFα release[b]
1	0.78	0.41	0.41	14	4.1	0.47	0.79	1.2	2100
2	5.7	0.048	119	3.5	72	0.54	0.048	0.20	8600
3[c]	25	41	0.61	157			25		
4[c]	>5000	11	>455	134			301		
6	8900 ± 4700 (2)	0.78 ± 0.20 (2)	11,400	12 ± 3.0 (3)	11 000	5.0	0.50	3.3	>50 000

[a] ± standard deviation (number of determinations). [b] Release of TNFα from LPS-stimulated THP-1 cells. [c] K_i literature values (ref 5).
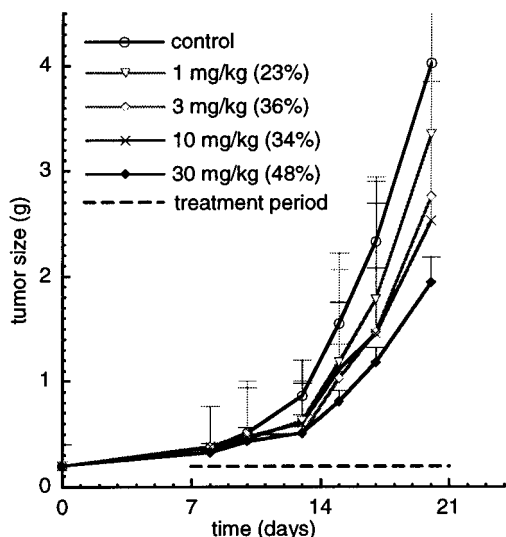

Figure 1. Effects of **6** on the growth of B16 melanoma cells implanted subcutaneously in the flank of mice (po, bid, d 7−21). Percent inhibition of control (2 g) in parentheses of legend.

MMP-1. Our research culminates in the discovery of the highly potent and selective MMP inhibitor **6**. Compound **6** possesses greater potency against MMP-2 and -9 than our previous biphenyl ether retrohydroxamate **5** and is more selective than the clinical candidate **2**. Compound **6** has pharmacokinetics consistent with once a day dosing. Additionally, **6** exhibits significant inhibition of tumor growth in animal cancer models and is currently undergoing phase I clinical trials in cancer patients.

Experimental Section

Chemistry. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a GE QE300 spectrometer, and chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane as an internal standard. Mass spectra were obtained on a Finnigan MAT SSQ700 instrument. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter with a continuous Na lamp (569 nM). Elemental analyses (C, H, N) were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Silica gel 60 (E. Merck, 230−400 mesh) was used for preparative column chromatrography. THF was freshly distilled from sodium benzophenone ketyl.

Method A. Preparation of 11a.

4′-[3-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)-2-oxo-propylsulfanyl]biphenyl-4-carbonitrile (9a). To a solution of 4′-hydroxybiphenyl-4-carbonitrile (10 g, 51.2 mmol) in 100 mL of DMF were added cesium carbonate (20 g, 61.4 mmol) and dimethylthiocarbamoyl chloride (7.6 g, 61.4 mmol). The reaction mixture was stirred at 23 °C for 16 h, partitioned between H$_2$O and EtOAc, extracted with EtOAc, washed with brine, dried over MgSO$_4$, filtered, and concentrated. The crude thiocarbamate was melted at 210 °C under argon for 10 min to effect the rearrangement. After the mixture was cooled to room temperature and the solid was dissolved in CH$_2$Cl$_2$, the

product was precipitated out by addition of ether and hexanes and collected by vacuum filtration. After purification by silica gel chromatography (10% hexanes/CH$_2$Cl$_2$ to 20% EtOAc/CH$_2$-Cl$_2$) (96% yield), 1.5 g (5.3 mmol) of the rearranged material was dissolved in 40 mL of methanol. NaOH(aq) (3 N, 3.5 mL, 10.6 mmol) was added, and the mixture was heated at reflux for 1.5 h. After the mixture was cooled to room temperature, some of the methanol was removed by rotary evaporation and the mixture was adjusted to pH 7 using 1 N HCl. The crude mixture was partitioned between EtOAc and H$_2$O, dried over MgSO$_4$, filtered, and concentrated to give the thiol, 4′-mercaptobiphenyl-4-carbonitrile, (0.98 g, 87%). ^{1}H NMR (DMSO-d_6): δ 7.92−7.84 (m, 4H), 7.66−7.63 (m, 2H), 7.44−7.40 (m, 2H), 5.65 (br, SH).

To a solution of the thiol (1.04 g, 4.9 mmol) in 50 mL of DMF at −5 °C were added K$_2$CO$_3$ (612 mg, 4.41 mmol) and the α-bromoketone, 3-(3-bromo-2-oxopropyl)-5,5-dimethylimidazolidine-2,4-dione (**7a**)[12] (1.3 g, 4.9 mmol). After 1 h at −5 °C, the reaction was quenched in H$_2$O, extracted with EtOAc, washed with H$_2$O and brine, dried over Na$_2$SO$_4$, filtered, and concentrated. Purification by silica gel flash chromatography (1:1 EtOAc/hexanes) gave the ketone **9a** in 86% yield (1.68 g). ^{1}H NMR (DMSO-d_6): δ 8.38 (br, NH), 7.94−7.87 (m, 4H), 7.73−7.69 (m, 2H), 7.45−7.41 (m, 2H), 4.51 (s, 2H), 4.26 (s, 2H), 1.30 (s, 6H). MS (ESI) m/z: 394 (M + H), 411 (M + NH$_4$), 416 (M + Na).

4′-[3-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)-2-hydroxyaminopropylsulfanyl]biphenyl-4-carbonitrile (10a). A solution of the ketone **9a** (1.67 g, 4.24 mmol) in 40 mL of 1:1 ethanol/THF was treated with hydroxylamine·hydrochloride (324 mg, 4.66 mmol) and pyridine (378 μL, 4.66 mmol), stirred at 23 °C for 16 h, and partitioned between EtOAc and saturated NaHCO$_3$. The organic layer was washed sequentially with water and brine, dried (Na$_2$SO$_4$), and concentrated to provide the oxime, (4′-[3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-hydroxyiminopropylsulfanyl]biphenyl-4-carbonitrile, which was used without further purification. ^{1}H NMR (DMSO-d_6): δ 11.28 (s, 0.5H), 11.25 (s, 0.5H), 8.42 (s, 0.5H), 8.30 (s, 0.5H), 7.94−7.87 (m, 4H), 7.74−7.70 (m, 2H), 7.51−7.45 (m, 2H), 4.30 (s, 1H), 4.20 (s, 1H), 3.90 (s, 1H), 3.72 (s, 1H), 1.30 (s, 3H), 1.27 (s, 3H). MS (ESI) m/z: 409 (M + H), 431 (M + Na).

A solution of the oxime (4.16 mmol) in 40 mL of 1:1 ethanol/THF was treated sequentially with borane·pyridine (1.26 mL, 12.48 mmol) and then dropwise with hydrochloric acid (6.25 mL, 25 mmol, 4 N in dioxane), stirred for 5 h at ambient temperature, poured into saturated NaHCO$_3$, and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), and concentrated. Purification on silica gel (2% methanol/CH$_2$Cl$_2$) provided the hydroxylamine **10a** in 65% yield (1.1 g). ^{1}H NMR (DMSO-d_6): δ 8.30 (br, NH), 7.93−7.86 (m, 4H), 7.72−7.69 (m, 2H), 7.45−7.41 (m, 2H), 7.23 (d, J = 3.0 Hz, OH), 5.81 (t, J = 3.0 Hz, NH), 3.57−3.54 (m, 2H), 3.24−3.13 (m, 2H), 2.98−2.91 (m, 1H), 1.27 (s, 6H). MS (ESI) m/z: 410 (M + H).

N-[1-(4′-Cyanobiphenyl-4-sulfonylmethyl)-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-N-hydroxyformamide (11a). A solution of the hydroxylamine **10a** (1.1 g, 2.7 mmol) in 25 mL of THF was cooled to 0 °C and treated with formic acetic anhydride (2.7 mL, 2.7 mmol, 1 M in THF), stirred for 30 min, and partitioned between saturated NaHCO$_3$ and EtOAc. The organic extracts were washed with H$_2$O and

brine, dried (Na_2SO_4), and concentrated. Purification on silica gel (2% methanol/CH_2Cl_2) provided the sulfide retrohydroxamate, *N*-[1-(4′-cyanobiphenyl-4-sulfanylmethyl)-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-*N*-hydroxyformamide, in 74% yield (877 mg). ^{1}H NMR (DMSO-d_6): δ 9.75 (s, 0.5H), 9.51 (s, 0.5H), 8.37 (s, 0.5H), 8.33 (s, 0.5H), 8.27 (s, 0.5H), 8.25 (s, 0.5H), 7.94−7.86 (m, 4H), 7.75−7.70 (m, 2H), 7.51−7.43 (m, 2H), 4.69−4.55 (m, 0.5H), 4.14−4.04 (m, 0.5H), 3.76−3.50 (m, 2H), 3.28−2.97 (m, 2H), 1.29 (s, 3H), 1.23 (s, 3H). MS (ESI) *m/z*: 437 (M − H)$^-$.

A solution of the sulfide (840 mg, 1.9 mmol) in 20 mL of 4:1 methanol/H_2O at 0 °C was treated with $NaHCO_3$ (399 mg, 4.75 mmol) and OXONE (489 mg, 4.75 mmol active O), stirred at 23 °C for 1 h, and partitioned between H_2O and EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified on silica gel (1−10% methanol/CH_2Cl_2) to give the sulfone retrohydroxamate **11a** in 54% yield (450 mg). ^{1}H NMR (DMSO-d_6): δ 9.66 (s, 0.5H), 9.51 (s, 0.5H), 8.38 (s, 0.5H), 8.34 (s, 0.5H), 8.10 (s, 0.5H), 8.07−7.96 (m, 8H), 7.74 (s, 0.5H), 4.94−4.86 (m, 0.5H), 4.58−4.50 (m, 0.5H), 3.80−3.37 (m, 4H), 1.23−1.20 (m, 6H). MS (ESI) *m/z*: 488 (M + NH_4). Anal. ($C_{22}H_{22}N_4O_6S$) C, H, N.

Method B. Preparation of 6.

4-(4′-Trifluoromethoxyphenoxy)phenyl Methyl Sulfone (26). A mixture of anhydrous potassium carbonate (159.0 g, 1.15 mol), 4-trifluoromethoxyphenol (150 mL, 1.16 mol), and 4-fluorophenyl methyl sulfone (200.0 g, 1.15 mol) in DMSO (1.5 L) was heated to 120 °C and stirred vigorously for 18 h. The mixture was cooled to room temperature, filtered through a glass wool plug with MTBE, and concentrated. The concentrate was diluted with water (1 L) and cooled to 0 °C. The resulting precipitate was collected by filtration, washed with water, and dried under vacuum at 50 °C. Recrystallization from MTBE/hexanes provided **26** in 89% yield; mp 71.5−72 °C. ^{1}H NMR (DMSO-d_6): δ 7.96−7.91 (m, 2H), 7.49−7.44 (9M, 2H), 7.31−7.26 (m, 2H), 7.24−7.19 (m, 2H), 3.20 (s, 3H). MS (ESI) *m/z*: 350 (M + 1).

1-((4R)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethanone (28). A solution of **26** (36.6 g, 0.11 mol) in THF (600 mL) at −78 °C was treated with *n*-butyllithium (2.5 M in hexanes, 48.0 mL, 0.12 mol) over 5 min and stirred for 1 h. The solution was transferred by cannula to a −78 °C solution of methyl (4*R*)-2,2-dimethyl-[1,3]dioxolane-4-carboxylate (**27**, 19.6 g, 0.12 mol) in THF (400 mL) over 30 min, stirred for 3 h, treated with 1 M H_2SO_4 (75 mL), and warmed to 0 °C. The aqueous phase was extracted with MTBE (500 mL), and the combined organic phases were washed with water and brine, dried (Na_2SO_4), and filtered. The solution was passed through a pad of silica gel (100 g), the pad was washed with MTBE, and the resulting solution was concentrated to one-fifth of the original volume, treated with hexanes (300 mL), and cooled to room temperature. The resulting precipitate was collected by filtration, washed with MTBE/hexanes, and dried to provide the desired product in 79% yield; mp 80−81 °C; [α]$_D^{25}$ + 49.9° (*c* 4.1, CH_2Cl_2). ^{1}H NMR (CDCl$_3$): δ 7.91−7.87 (m, 2H), 7.29−7.26 (m, 2H), 7.13−7.07 (m, 4H), 4.60 (d, *J* = 14.8 Hz, 1H), 4.54 (dd, *J* = 7.2, 5.1 Hz, 1H), 4.32 (d, *J* = 14.8 Hz, 1H), 4.16 (dd, *J* = 8.9, 7.2 Hz, 1H), 4.11 (dd, *J* = 8.9, 5.1 Hz, 1H), 1.45 (s, 3H), 1.38 (s, 3H). MS (ESI) *m/z*: 478 (M + NH_4), 483 (M + Na).

(4S)-2,2-Dimethyl-4-((E/Z)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethenyl)-[1,3]dioxolane (29). A suspension of **28** (37.3 g, 81 mmol) in ethanol (250 mL) at 23 °C was treated with sodium borohydride (1.40 g, 37 mmol), stirred for 30 min, treated dropwise with acetic acid (1 mL), and concentrated. The concentrate was partitioned between EtOAc and water, and the organic phase was washed sequentially with 1 M $NaHCO_3$, water, and brine, dried (Na_2SO_4), and filtered. The solution was passed through a pad of silica gel (200 g) using 3:2 hexanes/EtOAc, concentrated. The crude alcohol was carried on to the next reaction without further purification. ^{1}H NMR (DMSO-d_6): δ 7.93−7.87 (m, 2H), 7.50−7.46 (m, 2H), 7.28−7.18 (m, 4H), 5.39 (d, *J* = 6.5 Hz, OH),

3.91−3.77 (m, 3H), 3.37−3.33 (m, 2H), 1.21 (s, 3H), 1.21 (s, 3H). MS (ESI) *m/z*: 463 (M + 1), 480 (M + NH_4), 485 (M + Na).

(4S)-2,2-Dimethyl-4-((E/Z)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethenyl)-[1,3]dioxolane (30). The alcohol **29** was dissolved in CH_2Cl_2 (250 mL), treated with triethylamine (31.1 mL, 222 mmol), cooled to 0 °C, and treated with methanesulfonyl chloride (8.0 mL, 103 mmol) over 40 min. The mixture was stirred for 15 min, warmed to room temperature, stirred for 1 h, washed sequentially with water, 1 M HCl, water, 1 M $NaHCO_3$, water, and brine, dried (Na_2SO_4), and filtered. The concentrate was purified by flash column chromatography on silica gel using 98:2 CH_2Cl_2/EtOAc. The purified concentrate was recrystallized from MTBE/hexanes to provide the desired product as a mixture of cis and trans isomers (1:10) in 91% yield from **28**. Trans ^{1}H NMR (DMSO-d_6): δ 7.91−7.86 (m, 2H), 7.49−7.46 (m, 2H), 7.32−7.26 (m, 2H), 7.24−7.18 (m, 2H), 6.88 (m, 2H), 4.77−4.71 (m, 1H), 4.15 (dd, *J* = 8.5, 6.8 Hz, 1H), 3.70 (dd, *J* = 8.5, 6.5 Hz, 1H), 1.33 (s, 3H), 1.29 (s, 3H). MS (ESI): 445 (M + 1), 462 (M + NH_4), 467 (M + Na). Cis ^{1}H NMR (DMSO-d_6): δ 7.95−7.90 (m, 2H), 7.50−7.47 (m, 2H), 7.34−7.28 (m, 2H), 7.25−7.20 (m, 2H), 6.71 (dd, *J* = 11.4, 1.4 Hz, 1H), 6.41 (dd, *J* = 11.4, 7.7 Hz, 1H), 5.53−5.46 (m, 1H), 4.23 (dd, *J* = 8.4, 7.0 Hz, 1H), 3.66 (dd, *J* = 8.4, 6.2 Hz, 1H), 1.36 (s, 3H), 1.32 (s, 3H).

(4S)-4-((1S)-1-(Hydroxyamino)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl)-2,2-dimethyl-[1,3]dioxolane (31). A solution of **30** (28.6 g, 64.3 mmol) in THF (800 mL) at −35 °C was treated with 50% aqueous hydroxylamine (6.4 g, 193 mmol), held at −10 °C for 5 h, and concentrated. The concentrate was dissolved in MTBE, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was recrystallized from MTBE/hexanes to provide a 9:1 mixture of two diastereomers, which were separated by flash column chromatography on silica gel using 70:30 hexanes/EtOAc to provide the desired product in 69% yield. ^{1}H NMR (DMSO-d_6): δ 7.94−7.89 (m, 2H), 7.50−7.46 (m, 2H), 7.41 (d, *J* = 3.0 Hz, OH), 7.31−7.26 (m, 2H), 7.25−7.20 (m, 2H), 5.60 (t, *J* = 3.0 Hz, NH), 4.27−4.21 (m, 1H), 3.92 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.68 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.56−3.49 (m, 1H), 3.25−3.17 (m, 2H), 1.27 (s, 3H), 1.22 (s, 3H). MS (ESI) *m/z*: 478 (M + 1), 500 (M + Na).

N-[(1S)-1-((4S)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-2-(4-(4-(trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]-N-hydroxyformamide (6). A solution of **31** (21.6 g, 45.2 mmol) in MTBE (200 mL) was treated with trifluoroethyl formate reagent (8.9 M, 50 mL, 443 mmol), heated to reflux, stirred for 20 h, and slowly cooled to room temperature. The mixture was cooled to 0 °C, and the resulting precipitate was collected by filtration, washed with cold MTBE, and dried to provide the desired product in 96% yield; mp 127.5−128.5 °C; [α]$_D^{25}$ + 4.85° (*c* 2.14, CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ 1.20 (s, 1.2H), 1.23 (s, 1.8H), 1.26 (s, 1.2H), 1.30 (s, 1.8H), 3.32 (t, *J* = 7.5 Hz, 0.6H), 3.59−3.76 (m, 2.1H), 3.92−4.15 (m, 3H), 4.57 (t, *J* = 8.4 Hz, 0.4H), 7.18−7.32 (m, 4H), 7.48 (d, *J* = 9.6 Hz, 2H), 7.82 (s, 0.6H), 7.88 (d, *J* = 9.6 Hz, 0.8H), 7.94 (d, *J* = 9.6 Hz, 1.2H), 8.13 (s, 0.4H), 9.63 (s, 0.6H), 10.00 (s, 0.4 H). MS (APCI) *m/z*: 506 (M + H). Anal. ($C_{21}H_{22}F_3NO_8S$) C, H, N.

Method C. Preparation of 24a.

Methyl (4-(4-Trifluoromethoxyphenoxy)phenylsulfanyl)acetate (21a). A solution of the intermediate xanthate, dithiocarbonic acid *O*-ethyl ester *S*-(4-(4-trifluoromethoxyphenoxy)phenyl)ester, (5.0 g, 13.95 mmol, see **11b**), and powdered KOH (2.0 g, 35.71 mmol) in 50 mL of ethanol was heated at 80 °C for 2 h and cooled to room temperature. Another 1.0 g of KOH and bromo acetate (1.94 g, 13.95 mmol) were added. The reaction mixture was stirred for 16 h at 23 °C, heated at 80 °C for 3 h, cooled to 0 °C, acidified to pH 2−3 using 1 N HCl, partitioned between H_2O and EtOAc, extracted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The oil was dissolved in 50 mL of methanol, and the solution was cooled to 0 °C. Thionyl chloride (1.5 mL, 20.9 mmol) was added. The reaction mixture was stirred for 16 h at 23 °C, quenched with H_2O, extracted with

EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (8:1 hexanes/EtOAc) gave 2.93 g (59%) of the methyl ester. ^1H NMR (CDCl$_3$): δ 7.46−7.41 (m, 2H), 7.21−7.18 (m, 2H), 7.03−6.98 (m, 2H), 6.97−6.92 (m, 2H), 3.72 (s, 3H), 3.60 (s, 2H).

2-Oxo-3-(4-(4-trifluoromethoxyphenoxy)phenylsulfanyl)propane-1-sulfonic Acid Dimethyl Amide (22a). To a solution of *N*,*N*-dimethylmethanesulfonamide (**20a**, 560 mg, 4.47 mmol) in 25 mL of THF at −25 °C was added *n*-butyllithium (2.0 mL, 4.92 mmol, 2.5 M in hexanes). The reaction mixture was stirred at −25 °C for 1.5 h and then cooled to −78 °C. A solution of **21a** (1.6 g, 4.47 mmol) in 15 mL of THF was added. The reaction mixture was stirred for 16 h, quenched with saturated NH$_4$Cl and H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (2:1 hexanes/EtOAc) gave 0.917 g (46%) of the ketone. ^1H NMR (CDCl$_3$): δ 7.37 (d, J = 6.6 Hz, 2H), 7.20 (d, J = 9.0 Hz, 2H), 7.01 (d, J = 6.6 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 4.22 (s, 2H), 3.90 (s, 2H), 2.88 (s, 6H). MS (ESI) *m/z*: 450 (M + H), 450 (M + Na).

2-Hydroxy-3-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)propane-1-sulfonic Acid Dimethyl Amide (23a). To a solution of **22a** (888 mg, 1.98 mmol) in 20 mL of methanol at 0 °C was added portionwise NaBH$_4$ (90 mg, 2.38 mmol). The reaction mixture was stirred at 0 °C for 1 h, quenched with acetone, concentrated, diluted with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the crude alcohol, 2-hydroxy-3-(4-(4-trifluoromethoxyphenoxy)phenylsulfanyl)propane-1-sulfonic acid dimethyl amide. ^1H NMR (DMSO-d_6): δ 7.44 (d, J = 9.0 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.11 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 5.55 (d, J = 5.7 Hz, 1H), 4.02 (m, 1H), 3.30−3.02 (m, 4H), 2.74 (s, 6H).

To a solution of the alcohol (880 mg, 1.95 mmol) in 50 mL of methanol were added 25 mL of H_2O, NaHCO$_3$ (410 mg, 4.88 mmol), and OXONE (3.0 g, 4.88 mmol). The suspension was stirred at 23 °C for 16 h, diluted with H_2O, extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the crude sulfone. ^1H NMR (DMSO-d_6): δ 7.91 (d, J = 9.3 Hz, 2H), 7.49 (d, J = 9.3 Hz, 2H), 7.28 (d, J = 9.3 Hz, 2H), 7.22 (d, J = 9.3 Hz, 2H), 5.58 (d, J = 6.6 Hz, 1H), 4.36 (m, 1H), 3.61 (dd, J = 14.4, 4.5 Hz, 1H), 3.50 (dd, J = 14.4, 7.5 Hz, 1H), 3.28 (dd, J = 14.4, 4.5 Hz, 1H), 3.19 (dd, J = 14.4, 7.5 Hz, 1H), 2.73 (s, 6H). MS (ESI) *m/z*: 484 (M + H), 501 (M + NH$_4$).

2-(Formylhydroxyamino)-3-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)propane-1-sulfonic Acid Dimethylamide (24a). To a solution of the β-hydroxy sulfone **23a** (920 mg, 1.90 mmol) in 20 mL of CH$_2$Cl$_2$ at 0 °C were added triethylamine (398 μL, 2.86 mmol) and methanesulfonyl chloride (177 μL, 2.29 mmol). The reaction mixture was stirred at 0 °C for 1.5 h, diluted with CH$_2$Cl$_2$, washed with 1 N HCl and H_2O, dried over $MgSO_4$, filtered, and concentrated to give a mixture of the mesylate, 1-dimethylsulfamoylmethyl-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl methansulfonate and the corresponding elimination product alkene.

To a solution of the mesylate/alkene (960 mg, 1.71 mmol) in 20 mL of THF was added aqueous hydroxylamine (1 mL, 17.1 mmol, 50 wt %). The reaction mixture was heated at reflux for 1 h, cooled to room temperature, concentrated, diluted with H_2O, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the crude hydroxylamine, 2-hydoxyamino-3-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)propane-1-sulfonic acid dimethyl amide. ^1H NMR (DMSO-d_6): δ 7.92 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 3.3 Hz, 1H), 7.48 (d, J = 9.9 Hz, 2H), 7.29 (d, J = 9.3 Hz, 2H), 7.24 (d, J = 9.0 Hz, 2H), 5.71 (t, J = 3.3 Hz, 1H), 3.62−3.46 (m, 2H), 3.47−3.18 (m, 2H), 2.74 (s, 6H). MS (ESI) *m/z*: 499 (M + H).

The hydroxylamine was carried on to the title compound as described for the conversion of **31** to **6**: mp 124.5−125.5 °C. ^1H NMR (DMSO-d_6): δ 2.74−2.69 (2 s, 6H), 3.44−3.25 (m,

2H), 3.83−3.56 (m, 2H), 4.51 (m, 0.5H), 5.04 (m, 0.5H), 7.30−7.20 (m, 4H), 7.48 (d, 2H, J = 9.0 Hz), 7.85 (s, 0.5H), 7.91 (dd, 2H, J = 9.0, 3.0 Hz), 8.10 (s, 0.5H), 9.89 (s, br, 0.5H), 10.08 (s, br, 0.5H). MS (ESI) *m/z*: 527 (M + H), 544 (M + NH$_4$). Anal. (C$_{19}$H$_{21}$F$_3$N$_2$O$_8$S$_2$) C, H, N.

Compounds Prepared by Method A.

N-[2-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)ethyl]-*N*-hydroxyformamide (11b).** To a solution of 4-trifluoromethoxyphenol (5 g, 28 mmol) in 75 mL of DMSO were added potassium *t*-butoxide (3.36 g, 30 mmol) and a solution of 1-fluoro-4-nitrobenzene (2 mL, 19 mmol) in 25 mL of DMSO. The reaction mixture was heated at 100 °C for 1 h, cooled to room temperature, partitioned between CH$_2$Cl$_2$ and 1 N NaOH, washed with 1 N NaOH and brine, dried over $MgSO_4$, filtered, and concentrated. The nitro group was then reduced to the amine by treatment of the crude material with 840 mg of 10% Pd−C under 4 atm of H$_2$ in 200 mL of methanol for 3 h followed by filtration and concentration. To a cooled (ice bath) mixture of concentrated HCl (3.4 mL) and ice (4.9 g) was added the amine. A solution of NaNO$_2$ (1.3 g, 19 mmol) in 7.4 mL of H_2O was added dropwise. After 30 min, the mixture was added slowly to a solution of potassium ethyl xanthate (6 g, 38 mmol) in 7.4 mL of H_2O at 70 °C. The reaction mixture was heated for 1 h at 70 °C, cooled to room temperature, adjusted to pH 8 using 1 N HCl, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated. The crude dithiocarbonate was dissolved in 30 mL of ethanol and treated with KOH (4.7 g, 85 mmol) and heated at reflux for 2 h. The reaction mixture was cooled to room temperature, adjusted to pH 7 using 1 N HCl, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated to give the thiol, 4-(4-trifluoromethoxyphenoxy)benzenethiol. ^1H NMR (DMSO-d_6): δ 7.39−7.32 (m, 4H), 7.09−7.06 (m, 2H), 7.00−6.97 (m, 2H), 5.49 (br, SH).

The thiol was carried on to the title compound **11b** as described for the conversion of **7a** to **11a**. ^1H NMR (DMSO-d_6): δ 9.64 (s, 0.5H), 9.45 (s, 0.5H), 8.35 (d, 1H, J = 12.2 Hz), 8.10 (s, 0.5H), 7.91 (dd, 2H, J = 8.9, 2.8 Hz), 7.68 (s, 0.5H), 7.47 (d, 2H, J = 9.2 Hz), 7.30−7.21 (m, 4H), 4.88−4.77 (m, 0.5H), 4.51−4.40 (m, 0.5H), 3.73−3.38 (m, 4H), 1.24 (s, 3H), 1.22 (s, 3H). MS (ESI) *m/z*: 546 (M + H), 568 (M + Na), 544 (M − H). Anal. (C$_{22}$H$_{22}$N$_3$O$_8$SF$_3$) C, H, N.

N-[1-(4-(4-Cyanophenoxy)phenylsulfonylmethyl)-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-*N*-hydroxyformamide (11c).** Compound **11c** was prepared as described for **11b**, except the thiol was prepared using 4-cyanophenol and Fe/NH$_4$Cl in methanol/H_2O for the reduction of the nitro group to the amine. ^1H NMR (DMSO-d_6): δ 9.70 (s, 0.5H), 9.50 (s, 0.5H), 8.39 (s, 0.5H), 8.34 (s, 0.5H), 8.10 (s, 0.5H), 7.98−7.91 (m, 4H), 7.68 (s, 0.5H), 7.37−7.27 (m, 4H), 4.88−4.77 (m, 0.5H), 4.52−4.41 (m, 0.5H), 3.78−3.39 (m, 4H), 1.24−1.22 (m, 6H). MS (ESI) *m/z*: 487 (M + 1). Anal. (C$_{22}$H$_{22}$N$_4$O$_7$S) C, H, N.

N-[1-(4-(4-Chlorophenoxy)phenylsulfonylmethyl)-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-*N*-hydroxyformamide (11d).** Compound **11d** was prepared as described for **11b**, except the thiol was prepared using 4-chlorophenol and Fe/NH$_4$Cl in methanol/H_2O for the reduction of the nitro group to the amine. ^1H NMR (DMSO-d_6): δ 9.67 (s, 0.5H), 9.50 (s, 0.5H), 8.36 (d, 1H, J = 13.2 Hz), 8.10 (s, 0.5H), 7.90 (dd, 2H, J = 8.8, 3.0 Hz), 7.68 (s, 0.5H), 7.53 (d, 2H, J = 8.8 Hz), 7.20 (d, 4H, J = 8.8 Hz), 4.89−4.77 (m, 0.5H), 4.52−4.40 (m, 0.5H), 3.68−3.38 (m, 4H), 1.25−1.21 (m, 6H). MS (ESI) *m/z*: 496 (M + H), 513 (M + NH$_4$), 494 (M − H). Anal. (C$_{21}$H$_{22}$ClN$_3$O$_7$S).

N-Hydroxy-*N*-[1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)-2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]formamide (11e).** Compound **11e** was prepared as described for **11b**, except using 3-(3-bromo-2-oxopropyl)-1,5,5-trimethylimidazolidine-2,4-dione (**7b**).^{12} ^1H NMR (DMSO-d_6): δ 9.51 (s, 0.5H), 9.70 (s, 0.5H), 8.09 (s, 0.5H), 7.91 (dd, J = 8.9, 3.1 Hz, 2H), 7.68 (s, 0.5H), 7.47 (d, 2H, J = 9.2 H, 2 Hz), 7.31−7.21 (m, 4H), 4.90−4.78 (m, 0.5H), 4.51−4.40 (m, 0.5H), 3.74−3.40 (m, 4H), 2.76 (d, J = 1.7 Hz, 3H), 1.27−

1.22 (m, 6H). MS (ESI) *m/z*: 558 (M − H), 560 (M + H), 577 (M + NH₄), 582 (M + Na). Anal. ($C_{23}H_{24}F_3N_3O_8S$) C, H, N.

***N*-[1-(4-(4-Cyanophenoxy)phenylsulfonylmethyl)-2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-*N*-hydroxyformamide (11f).** Compound **11f** was prepared as described for **11b**, except the thiol was prepared using 4-cyanophenol and Fe/NH₄Cl in methanol/H₂O for the reduction of the nitro group to the amine and using 3-(3-bromo-2-oxopropyl)-1,5,5-trimethylimidazolidine-2,4-dione (**7b**) in place of **7a**. ¹H NMR (DMSO-*d₆*): δ 9.74 (br, 0.5H), 9.52 (br, 0.5H), 8.10 (s, 0.5H), 7.97−7.90 (m, 4H), 7.68 (s, 0.5H), 7.36−7.28 (m, 4H), 4.89−4.79 (m, 0.5H), 4.52−4.42 (m, 0.5H), 3.76−3.37 (m, 4H), 2.76 (s, 1.5H), 2.76 (s, 1.5H), 1.26−1.23 (m, 6H). MS (ESI) *m/z*: 501 (M + 1). Anal. ($C_{23}H_{24}N_4O_7S$) C, H, N.

***N*-[1-(4-(4-Chlorophenoxy)phenylsulfonylmethyl)-2-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-*N*-hydroxyformamide (11g).** Compound **11g** was prepared as described for **11b**, except the thiol was prepared using 4-chlorophenol and Fe/NH₄Cl in methanol/H₂O for the reduction of the nitro group to the amine and using 3-(3-bromo-2-oxopropyl)-1,5,5-trimethylimidazolidine-2,4-dione (**7b**) in place of **7a**. ¹H NMR (DMSO-*d₆*): δ 9.78−9.71 (m, 0.5H), 9.58−9.49 (m, 0.5H), 8.09 (s, 0.5H), 7.89 (dd, *J* = 5.8, 2.9 Hz, 2H), 7.68 (s, 0.5H), 7.53 (d, *J* = 9.2 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 4H), 4.88−4.78 (m, 0.5H), 4.50−4.38 (m, 0.5H), 3.72−3.40 (m, 4H), 2.76 (s, 1.5H), 2.76 (s, 1.5H), 1.26−1.22 (m, 6H). MS (ESI) *m/z*: 510 (M + H), 527 (M + NH₄), 508 (M − H). Anal. ($C_{22}H_{24}ClN_3O_7S$) C, H, N.

***N*-Hydroxy-*N*-[2-(3-methyl-2,6-dioxo-3,6-dihydro-2*H*-pyrimidin-1-yl)-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)ethyl]formamide (11h).** To a solution of 1-methyl-1*H*-pyrimidine-2,4-dione (440 mg, 3.49 mmol) in 17 mL of methanol were added epibromohydrin (3 mL, 35 mmol) and potassium carbonate (482 mg, 3.49 mmol). The reaction mixture was stirred at room temperature for 16 h, diluted with CH₂Cl₂, filtered, and concentrated to give the epoxide, 1-methyl-3-oxiranylmethyl-1*H*-pyrimidine-2,4-dione (**8a**). MS (ESI): 183 (M + 1), 200 (M + NH₄). ¹H NMR (DMSO-*d₆*): δ 7.70 (dd, *J* = 7.8, 0.8 Hz, 1H), 5.69 (d, *J* = 7.8, 1.4 Hz, 1H), 4.06 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.86 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.00 (s, 3H), 3.15−3.09 (m, 1H), 2.70 (t, *J* = 4.6 Hz, 1H), 2.53−2.51 (m, 1H).

To a solution of the thiol, 4-(4-trifluoromethoxyphenoxy)benzenethiol prepared as described in **11b**, (1.19 g, 4.16 mmol) in 17 mL of DMF were added K₂CO₃ (478 mg, 3.46 mmol) and the epoxide **8a** (630 mg, 3.46 mmol). The reaction mixture was heated at 100 °C for 16 h, cooled to room temperature, partitioned between H₂O and EtOAc, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated. Purification by silica gel chromatography (1:1 to 1:4 EtOAc/hexanes) gave 735 mg (45%) of the alcohol, 1-methyl-3-[2-hydroxy-3-(4-trifluoromethoxyphenoxy)phenylsulfonyl]propyl]-1*H*-pyrimidine-2,4-dione. MS (ESI) *m/z*: 469 (M + 1). ¹H NMR (DMSO-*d₆*): δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.40−7.37 (m, 4H), 7.13−7.08 (m, 2H), 7.03−6.99 (m, 2H), 5.65 (d, *J* = 7.8 Hz, 1H), 5.16 (d, *J* = 5.4 Hz, OH), 4.01−3.84 (m, 3H), 3.27 (s, 3H), 3.03−2.88 (m, 2H).

The alcohol (730 mg, 1.56 mmol) was dissolved in 15 mL of CH₂Cl₂. The solution was cooled to 0 °C and treated with Dess−Martin periodinane (991 mg, 2.34 mmol). After the solution was stirred for 3 h at 23 °C, the reaction was quenched with 1:1 saturated NaHCO₃/10% NaHSO₃, extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and concentrated. Purification by silica gel flash chromatography (1:1 EtOAc/hexanes) gave 625 mg (86%) of the ketone, 1-methyl-3-[2-oxo-3-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)propyl]-1*H*-pyrimidine-2,4-dione (**9h**). MS (ESI) *m/z*: 467 (M + 1). ¹H NMR (DMSO-*d₆*): δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.45−7.38 (m, 4H), 7.14−7.09 (m, 2H), 7.04−6.99 (m, 2H), 5.72 (d, *J* = 8.1 Hz, 1H), 4.87 (s, 2H), 4.11 (s, 2H), 3.29 (s, 3H).

The ketone **9h** was converted to the title compound **11h** as described for the conversion of **9a** to **11a**. ¹H NMR (DMSO-*d₆*): δ 9.52 (br, 0.5H), 9.42 (br, 0.5H), 8.04 (s, 0.5H), 7.89−7.85 (m, 2H), 7.73 (s, 0.5H), 7.70−7.66 (m, 1H), 7.49−7.46 (m,

2H), 7.31−7.26 (m, 2H), 7.22−7.18 (m, 2H), 5.64 (d, *J* = 7.8 Hz, 1H), 4.99−4.90 (m, 0.5H), 4.43−4.34 (m, 0.5H), 4.03−3.87 (m, 2H), 3.75−3.63 (m, 1H), 3.52−3.41 (m, 1H), 3.17 (s, 3H). MS (ESI): 544 (M + 1). Anal. ($C_{22}H_{20}F_3N_3O_8S$) C, H, N.

***N*-[2-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)-1-(4′-tri-fluoromethoxybiphenyl-4-sulfonylmethyl)ethyl]-*N*-hydroxyformamide (13a).** Compound **13a** was prepared as described for the preparation of **13d**, except using 4-(trifluoromethoxy)phenylboronic acid; mp 195−197 °C. ¹H NMR (DMSO-*d₆*): δ 9.62 (bs, 1H), 8.29−8.43 (c, 1H), 8.10 (s, 1/2H), 7.95−8.05 (c, 4H), 7.92 (d, 1H, *J* = 3 Hz), 7.88 (d, 1H, *J* = 3 Hz), 7.74 (s, 1/2H), 7.54 (s, 1H), 7.49 (s, 1H), 4.87−4.99 (c, 1/2H), 4.50−4.63 (c, 1/2H), 3.43−3.80 (c, 4H), 1.22 (s, 6H). MS (ESI) *m/z*: 530 (M + H), 547 (M + NH₄), 552 (M + Na), 1076 (2M + NH₄), 1081 (2M + Na). Anal. ($C_{22}H_{22}F_3N_3O_7S$) C, H, N.

***N*-[1-(4′-Butoxybiphenyl-4-sulfonylmethyl)-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-*N*-hydroxyformamide (13b).** Compound **13b** was prepared as described for the preparation of **13d**, except using 4-butoxyphenylboronic acid. ¹H NMR (DMSO-*d₆*): δ 0.92−0.97 (t, 3H, *J* = 7.5 Hz), 1.20, 1.22 (s+s, 6H), 1.42−1.52 (m, 2H), 1.68−1.77 (m, 2H), 3.41−3.72 (m, 3.5H), 4.02−4.06 (t, 2H, *J* = 6.6 Hz), 4.52 (m, 0.5H), 4.89 (m, 0.5H), 7.05−7.08 (d, 2H, *J* = 8.4 Hz), 7.70−7.74 (2H), 7.91 (s, 3.5H), 8.10 (s, 0.5H), 8.32−8.35 (d, 1H, *J* = 9.6 Hz), 9.48 (s, 0.5H), 9.62 (s, 0.5H). MS (ESI) *m/z*: 518 (M + H), 535 (M + NH₄), 516 (M − H), 552 (M + Cl). Anal. ($C_{25}H_{31}N_3O_7S·0.25H_2O$) C, H, N.

***N*-[2-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)-1-(4′-tri-fluoromethylbiphenyl-4-sulfonylmethyl)ethyl]-*N*-hydroxyformamide (13c).** Compound **13c** was prepared as described for the preparation of **13d**, except using 4-(trifluoromethyl)phenylboronic acid. ¹H NMR (DMSO-*d₆*): δ 1.19−1.27 (m, 6H), 3.38−3.79 (m, 5H), 7.75 (s, 0.5H), 7.87−7.94 (m, 2H), 7.97−8.08 (m, 6H), 8.10 (s, 0.5H), 8.35 (s, 0.5H), 8.38 (s, 0.5H), 9.51 (s, 0.5H), 9.67 (s, 0.5H). MS (ESI) *m/z*: 514 (M + H), 531 (M + NH₄), 512 (M − H). Anal. ($C_{22}H_{22}F_3N_3O_6S·0.75H_2O$) C, H, N.

***N*-[1-(3′-Cyanomethylbiphenyl-4-sulfonylmethyl)-2-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)ethyl]-*N*-hydroxyformamide (13d).** The ketone, 3-(3-(4-bromophenylsulfanyl)-2-oxopropyl)-5,5-dimethylimidazolidine-2,4-dione, was prepared as described for **9a** except using 4-bromothiophenol. The ketone (1.0 g, 2.69 mmol) was treated with the pinacol boronate, [3-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)phenyl]acetonitrile (785 mg, 3.23 mmol), Pd(PPh₃)₄ (311 mg, 0.269 mmol), and 1 N NaOH (5.38 mL, 5.38 mmol) in 30 mL of 1,2-dimethoxyethane at 90 °C for 3 h. The reaction mixture was cooled to room temperature, quenched with saturated NH₄Cl, extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and concentrated. Purification by silica gel chromatography (20% EtOAc, CH₂Cl₂) gave 217 mg (20%) of the biaryl ketone, [4′-(3-(4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-oxopropylsulfanyl)biphenyl-3-yl]acetonitrile (**12d**). ¹H NMR (DMSO-*d₆*): δ 1.49 (s, 6H), 3.75 (s, 2H), 3.81 (s, 2H), 4.55 (s, 2H), 5.30 (s, 1H), 7.29−7.34 (m, 1H), 7.42−7.55 (m 7H). MS (APCI) *m/z*: 408 (M + H), 425 (M + NH₄), 406 (M − H), 442 (M + Cl).

The biaryl ketone **12d** was carried on to the title compound **13d** as described for the conversion of **9a** to **11a**. ¹H NMR (DMSO-*d₆*): δ 1.21−1.23 (6H), 3.35−3.78 (m, 5H), 4.47−4.60 (m, 0.5H), 4.86−4.96 (m, 0.5H), 7.45−7.47 (d, 1H, *J* = 7.5 Hz), 7.54−7.59 (t, 1H, *J* = 8.4 Hz), 7.74−7.77 (m, 2.5H), 7.94−8.02 (m, 4H), 8.09 (s, 0.5H), 8.33−8.36 (d, 1H, *J* = 9.6 Hz), 9.48 (s, 0.5H), 9.63 (s, 0.5H). MS (ESI) *m/z*: 485 (M + H), 502 (M + NH₄), 507 (M + Na), 483 (M − H). Anal. ($C_{23}H_{24}N_4O_6S·0.4Et_2O H_2O$).

Compounds Prepared by Method B.

***N*-[2-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)-1-(4′-methylsulfanylbiphenyl-4-sulfonylmethyl)ethyl]-*N*-hydroxyformamide (19a).** To a solution of 4-(thiomethyl)phenylboronic acid (6.72 g, 39.99 mmol) and 4-bromophenyl methyl sulfone (9.41 g, 40.03 mmol) in 140 mL of DMF were added PdCl₂(dppf) (1.63 g, 2 mmol) and cesium carbonate (39.1 g, 120 mmol). The mixture was heated at 65 °C for 5.5 h, cooled to room temperature, partitioned between EtOAc and 1:1

brine/H_2O, and extracted with EtOAc. The combined extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (5−10% EtOAc/hexanes) gave the biphenyl methyl sulfone, 4-methanesulfonyl-4′-methylsulfanylbiphenyl, in 93% yield (10.39 g). ¹H NMR (DMSO-d_6): δ 2.54 (s, 3H), 3.09 (s, 3H), 7.34−7.37 (d, J = 8.4 Hz, 2H), 7.53−7.56 (d, J = 8.7 Hz, 2H), 7.74−7.76 (d, J = 8.4 Hz, 2H), 7.98−8.01 (d, J = 8.4 Hz, 2H). MS (APCI) m/z: 279 (M + H), 296 (M + NH_4).

The methyl sulfone was treated with *n*-butyllithium and methyl (4,4-dimethyl-2,5-dioxoimidazolidin-1-yl)acetate and carried on to the final product **19a** as described for the conversion of **28** to **6**; mp 215.3−217.7 °C. ¹H NMR (DMSO-d_6): δ 1.20−1.23 (m, 6H), 2.53 (s, 3H), 3.34−3.76 (m, 4H), 4.47−4.60 (m, 0.47H), 4.84−4.95 (m, 0.53H), 7.38−7.41 (d, J = 8.4 Hz, 2H), 7.71−7.75 (dd+s, J = 2.7, 8.7 Hz, 2.47H), 7.94−7.95 (d, J = 1.8 Hz, 4H), 8.10 (s, 0.53H), 8.26−8.32 (d, J = 9.6 Hz, 1H), 9.50 (s, 0.47H), 9.65 (s, 0.53H). MS (ESI) m/z: 492 (M + H), 509 (M + NH_4), 514 (M + Na), 490 (M − H)⁻. Anal. ($C_{22}H_{25}N_3O_6S$) C, H, N.

N-Hydroxy-N-[1-phenyl-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]-formamide (19b). To a solution of the methyl sulfone **26** (1 g, 3 mmol) in 50 mL of THF at −78 °C was added dropwise *n*-butyllithium (1.2 mL, 3.6 mmol, 2.5 M in hexanes). The reaction mixture was stirred for 1.5 h at −78 °C. Benzaldehyde (0.48 g, 4.5 mmol) was added. The reaction mixture was stirred for 4 h at −78 °C, quenched with saturated NH_4Cl, extracted with ethyl acetate, dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography gave 1.9 g (90%) of the alcohol, 1-phenyl-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethanol (**16b**). ¹H NMR (DMSO-d_6): δ 7.91−7.86 (m, 2H), 7.51−7.46 (m, 2H), 7.32−7.24 (m, 7H), 7.18−7.12 (m, 2H), 5.64 (d, 4.8 Hz, OH), 5.02−4.96 (m, 1H), 3.71 (dd, J = 14.7, 8.5 Hz, 1H), 3.55 (dd, J = 14.7, 3.7 Hz, 1H).

The alcohol **16b** was carried on to the final product **19b** as described for the conversion of **29** to **6**. ¹H NMR (DMSO-d_6): δ 10.06 (s, 0.5H), 9.96 (s, 0.5H), 8.18−8.11 (m, 1H), 7.87−7.85 (m, 2H), 7.50−7.47 (d, J = 8.8 Hz, 2H), 7.30−7.24 (m, 5H), 7.15−7.13 (d, J = 8.5 Hz, 2H), 5.78 (s, 0.5H), 5.41 (s, 0.5H), 4.24−4.04 (m, 3H). MS (ESI) m/z: M − H (480). Anal. ($C_{22}H_{18}F_3NO_6S$) C, H, N.

N-Hydroxy-N-[1-pyridin-2-yl-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]formamide (19c). Compound **19c** was prepared as described for **6**, except using nicotinic acid methyl ester in place of **27**; mp 116.4−117.6 °C. ¹H NMR (DMSO-d_6): δ 3.88−4.04 (m, 1H), 4.28−4.36 (dd, J = 4.5, 15 Hz, 1H), 5.50 (br, 0.5H), 5.84 (br, 0.5H), 7.12−7.44 (m, 6H), 7.44−7.50 (d, J = 9 Hz, 2H), 7.74−7.95 (m, 2H), 8.18 (s, 0.5H), 8.25 (s, 0.5H), 8.47 (1H), 9.66 (s, 0.5H). MS (ESI) m/z: 483 (M + H), 505 (M + Na), 481 (M − H), 517 (M + Cl). Anal. ($C_{21}H_{17}F_3N_2O_6S$).

N-Hydroxy-N-[2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)-1-(4-trifluoromethylphenyl)ethyl]formamide (19d). Compound **19d** was prepared as described for **19b**, except using 4-trifluoromethylbenzaldehyde in place of benzaldehyde. ¹H NMR (DMSO-d_6): δ 10.25 (s, 0.5H), 9.70 (s, 0.5H), 8.25−8.1 (m, 1H), 7.90−7.85 (d, J = 8.6 Hz, 2H), 7.77−7.70 (d, J = 8.8 Hz, 2H), 7.65 (s, 1H), 7.52−7.46 (d, J = 8.7 Hz, 2H), 7.23−7.10 (d, J = 8 Hz, 2H), 5.87 (s, 0,5H), 5.55 (s, 0.5H), 4.20−4.00 (m, 3H). MS (ESI) m/z: 548 (M − H). Anal. ($C_{23}H_{17}F_6NO_6S$·1.25 EtOAc) C, H, N.

N-Hydroxy-N-[1-(1-methyl-1H-indol-2-yl-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]formamide (19e). Compound **19e** was prepared as described for **6**, except using 1-methyl-1H-lindole-2-carboxylic acid methyl ester in place of **27**. ¹H NMR (DMSO-d_6): δ 9.95 (s, 0.5H), 9.56 (s, 0.5H), 8.13 (s, 0.5H), 7.90−7.85 (d, J = 8.9 Hz, 2H), 7.50−7.40 (m, 4H), 7.2−7.0 (m, 6H), 6.53 (s, 1H), 6.1 (s, 0.5H), 5.70 (s, 0.5H), 4.15 (m, 2H), 3.7−3.65 (m, 4H). MS (ESI) m/z: 533 (M − H). Anal. ($C_{25}H_{21}F_3N_2O_6S$) C, H, N.

N-Hydroxy-N-[2-(thiophen-2-ylsulfanyl)-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)ethyl]formamide (19f). Compound **19f** was prepared as described for **6**,

except using (thiophen-1-ylsulfanyl)acetic acid methyl ester in place of **27**; mp 120−122 °C. ¹H NMR (DMSO-d_6): δ 10.12 (bs, 1/2H), 9.80 (bs, 1/2H), 8.35 (s, 1/2H), 7.89−7.98 (m, 2.5H), 7.73−7.79 (m, 1H), 7.55−7.63 (m, 2H), 7.34−7.42 (m, 2H), 7.23−7.32 (m, 3H), 7.11−7.20 (m, 1H), 4.72−4.82 (m, 1/2H), 4.04−4.13 (m, 1/2H), 3.63−3.88 (m, 2H), 2.99−3.19 (m, 2H). MS (ESI) m/z: 533 (M + NH_4 − H_2O), 550 (M + NH_4), 555 (M + Na). Anal. ($C_{21}H_{18}F_3NO_6S_3$) C, H, N.

Methyl 4-[3-(Formylhydroxyamino)-4-(4-(4-tirfluoromethoxyphenoxy)phenylsulfonyl)butyl]benzoate (19g). Compound **19g** was prepared as described for **6**, except using 4-(2-methoxycarbonylethyl)benzoic acid methyl ester in place of **27**; mp 153−154 °C. ¹H NMR (DMSO-d_6): δ 9.84−10.09 (m, 1/2H), 9.55−9.73 (m, 1/2H), 8.21 (s, 1/2H), 7.83−7.94 (m, 4H), 7.80 (s, 1/2H), 7.42−7.52 (m, 2H), 7.23−7.34 (m, 4H), 7.13−7.23 (m, 2H), 4.52−4.61 (m, 1/2H), 4.04−4.15 (m, 1/2H), 3.83 (s, 3H), 3.57−3.74 (m, 1H), 3.44−3.55 (m, 1H), 2.43−2.68 (m, 2H), 1.86−2.01 (m, 1H), 1.71−1.83 (m, 1H). MS (APCI) m/z: 568 (M + H), 585 (M + NH_4). Anal. ($C_{26}H_{24}F_3NO_8S$) C, H, N.

4-[3-(Formylhydroxyamino)-4-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)butyl]benzoic Acid (19h). To a solution of the methyl ester **19g** (609 mg, 1.1 mmol) in 5 mL of 1:1 THF/methanol was added KOH (73 mg, 1.3 mmol) in 1.2 mL of H_2O. The reaction mixture was stirred at 23 °C for 16 h, diluted with H_2O, acidified to pH 3, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated. The crude material was recrystallized from EtOAc/hexanes to give the title compound (420 mg, 71%); mp 189−191 °C. ¹H NMR (DMSO-d_6): δ 9.50−9.85 (m, 1/2H), 8.21 (s, 1/2H), 7.82−7.94 (m, 4H), 7.79 (s, 1/2H), 7.44−7.52 (m, 2H), 7.23−7.32 (m, 4H), 7.15−7.23 (m, 2H), 4.52−4.62 (m, 1/2H), 4.04−4.14 (m, 1/2H), 3.58−3.74 (m, 1H), 3.46−3.55 (m, 1H), 2.42−2.66 (m, 2H), 1.85−2.01 (m, 1H), 1.72−1.83 (m, 1H). MS (APCI) m/z: 554 (M + H), 571 (M + NH_4). Anal. ($C_{25}H_{22}F_3NO_8S$) C, H, N.

N-[2-Dimethylamino-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)ethyl]-N-hydroxyformamide (19i). Compound **19i** was prepared as described for **6**, except using ethyl dimethylaminoacetate in place of **27**. ¹H NMR (DMSO-d_6): δ 2.04 (s, 3H), 2.10 (s, 3H), 2.21−2.39 (m, 2H), 3.40−3.48 (m, 1H), 3.53−3.63 (m, 1H), 4.05−4.17 (m, 0.5H), 4.62−4.72 (m, 0.5H), 7.19−7.30 (m, 4H), 7.47 (d, J = 9.0 Hz, 2H), 7.86 (s, 0.5H), 7.87−7.94 (m, 2H), 8.10 (s, 0.5H), 9.45 (bs, 0.5H), 9.85 (bs, 0.5H). MS (ESI) m/z: 463 (M + H), 485 (M + Na). Anal. ($C_{19}H_{21}F_3N_2O_6S$) C, H, N.

N-[2-(Formylhydroxyamino)-3-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)propyl]-N-methylmethanesulfonamide (19j). The BOC-protected amino alcohol, *tert*-butyl (2-hydroxy-3-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)propyl)methylcarbamate, was prepared from methyl (*t*-butoxycarbonylmethylamino)acetate as described for the conversion of **26** to **29**. The BOC-amine (2 g, 4 mmol) was dissolved in 10 mL of 4 N HCl/dioxane. The reaction mixture was stirred at 23 °C for 2 h, concentrated, taken up in saturated $NaHCO_3$ and EtOAc, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated to give the amino alcohol, 1-methylamino-3-(4-(4-trifluoromethoxyphenoxy)-phenylsulfonyl)propan-2-ol (**16j**). ¹H NMR (CDCl₃): δ 7.92 (s, 1H), 7.89 (s, 1H), 7.29 (s, 1H), 7.26 (s, 1H), 7.06−7.16 (m, 4H), 4.19−4.31 (m, 1H), 3.18−3.40 (m, 2H), 2.57−2.80 (m, 2H), 2.42 (s, 3H), 2.05 (bs, 2H). MS (DCI) m/z: 406 (M + H).

To a solution of the amino alcohol **16j** (1.59 g, 3.6 mmol) in 100 mL of CH_2Cl_2 at 0 °C were added triethylamine (1.62 mL, 11.6 mmol) and methanesulfonyl chloride (730 μL, 9.4 mmol). The reaction mixture was stirred at 23 °C for 1 h. DBU (934 μL, 6.25 mmol) was added. The reaction mixture was heated at reflux 1 h, cooled to room temperature, washed with H_2O, 1 N HCl, and saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (3−8% EtOAc/hexanes) gave 1.2 g (71%) of the alkene *N*-methyl-*N*-[3-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)allyl]-methanesulfonamide (**17j**). ¹H NMR (CDCl₃): δ 7.86 (t, J = 3 Hz, 1H), 7.83 (t, J = 3 Hz, 1H), 7.29 (s, 1H), 7.26 (s, 1H), 7.05−7.15 (m, 4H), 6.90 (dt, J = 15, 6 Hz, 1H), 6.61 (dt, J = 12, 3

Hz, 1H), 3.97 (dd, $J = 4.5, 3$ Hz, 2H), 2.88 (s, 3H), 2.85 (s, 3H). MS (DCI) *m/z*: 483 (M + NH$_4$).

The α,β-unsaturated sulfone **17j** was carried on to the title compound **19j** as described for the conversion of **30** to **6**; mp 135−138 °C. ^{1}H NMR (CDCl$_3$): δ 8.28 (s, 1/2H), 7.95 (s, 1/2H), 7.82−7.90 (m, 2H), 7.23−7.31 (m, 2H), 7.05−7.14 (m, 2H), 5.02−5.12 (m, 1/2H), 4.45 (bs, 1/2H), 3.42−3.75 (m, 2H), 3.23−3.40 (m, 2H), 2.80−2.95 (m, 6H). MS (ESI) *m/z*: 525 (M − H)$^-$. Anal. (C$_{19}$H$_{21}$F$_3$N$_2$O$_8$S$_2$) C, H, N.

N-Hydroxy-N-[2-hydroxy-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)ethyl]formamide (19k). The TBDMS-protected alcohol, *N*-[2-(*tert*-butyldimethylsilanyloxy)-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)-ethyl]-*N*-hydroxyformamide, was prepared as described for **19a**, except using (*tert*-butyldimethylsilanyloxy)acetaldehyde in place of benzaldehdye. To a solution of the silyl-protected alcohol (250 mg, 455 μmol) in 10 mL of THF at 0 °C was added tetrabutylammonium fluoride (910 μL, 1 M in THF, 910 μmol). The reaction mixture was stirred at 0 °C for 1.5 h, partitioned between ether and brine, dried over MgSO$_4$, filtered, and concentrated. Purification by silica gel chromatography (5% 2-propanol/CH$_2$Cl$_2$ to 10% methanol/CH$_2$Cl$_2$) followed by re-crystallization from ether gave 69 mg (35%) of the title compound **19k**; mp 115−117 °C. ^{1}H NMR (DMSO-d_6): δ 3.30−3.62 (m, 4H), 3.93−4.03 (m, 0.5H), 4.51−4.61 (m, 0.5H), 4.95−5.06 (m, 1H), 7.22 (d, $J = 9.0$ Hz, 2H), 7.25−7.32 (m, 2H), 7.48 (d, $J = 9.0$ Hz, 2H), 7.76 (s, 0.5H), 7.86−7.94 (m, 2H), 8.13 (s, 0.5H), 9.41 (bs, 0.5H), 9.82 (bs, 0.5H). MS (ESI) *m/z*: 436 (M + H), 453 (M + NH$_4$), 458 (M + Na). Anal. (C$_{17}$H$_{16}$F$_3$NO$_7$S) C, H, N.

N-Hydroxy-N-[2-methoxy-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)ethyl]formamide (19l). The alcohol, 1-methoxy-3-(4-(4-trifluoromethoxyphenoxy)-phenylsulfonyl)propan-2-ol, was prepared as described for **29**, except using ethyl methoxyacetate in place of **27**. To a solution of the alcohol (610 mg, 1.53 mmol) in 10 mL of THF at 23 °C were added triphenylphosphine (482 mg, 1.84 mmol) and DEAD (291 μL, 1.84 mmol). The reaction mixture was stirred at 23 °C for 1 h and concentrated. Purification by silica gel chromatography (30% EtOAc/hexanes) gave 530 mg (90%) of a 1.8:1 trans/cis mixture of alkenes 1-methoxy-3-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)-2-propene (**17l**). ^{1}H NMR (DMSO-d_6): δ 7.94−7.85 (m, 2H), 7.50−7.45 (m, 2H), 7.33−7.26 (m, 2H), 7.23−7.18 (m, 2H), 6.90 (dt, $J = 15.3, 3.5$ Hz, 0.64H), 6.77 (dt, $J = 15.3, 1.9$ Hz, 0.64H), 6.63 (dt, $J = 11.5, 2.2$ Hz, 0.36H), 6.45 (dt, $J = 11.5, 5.3$ Hz, 0.36H), 4.49 (dd, $J = 5.3, 2.2$ Hz, 0.72 H), 4.12 (dd, $J = 3.5, 1.9$ Hz, 1.28H), 3.28 (s, 1.92H), 3.26 (s, 1.08H).

The α,β-unsaturated sulfone **17l** was converted to the title compound **19l** as described for the conversion of **30** to **6**. ^{1}H NMR (DMSO-d_6): δ 3.20 (s, 3H), 3.23−3.45 (m, 3H), 3.52−3.65 (m, 1H), 4.16−4.27 (m, 0.5H), 4.70−5.02 (m, 0.5H), 7.21 (dd, $J = 3,9$ Hz, 2H), 7.28 (dd, $J = 6,9$ Hz, 2H), 7.47 (d, $J = 9$ Hz, 2H), 7.81 (s, 0.5H), 7.90 (dd, $J = 3,9$ Hz, 2H), 8.12 (s, 0.5H), 9.56 (bs, 0.5H), 9.91 (bs, 0.5H). MS (ESI) *m/z*: 448 (M − H)$^-$. Anal. (C$_{18}$H$_{18}$F$_3$NO$_7$S·0.25 EtOAc) C, H, N.

N-Hydroxy-N-[2-(2-hydroxyethoxy)-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)ethyl]formamide (19m). Compound **19m** was prepared as described for **19k**, except using (2-*tert*-butyldimethylsilanyloxy)ethoxy)acetaldehyde in place of (*tert*-butyldimethylsilanyloxy)acetaldehyde. ^{1}H NMR (DMSO-d_6): δ 3.4−3.63 (m, 6H), 4.13−4.26 (m, 0.5H), 4.63 (s, 1H), 4.69−4.8 (m, 0.5H), 7.23 (d, $J = 9$ Hz, 2H), 7.29 (d, $J = 9$ Hz, 2H), 7.48 (d, $J = 9$ Hz, 2H), 7.8 (s, 0.5H), 7.91 (dd, $J = 9.1,8.8$ Hz, 2H), 8.14 (s, 0.5H), 9.54 (s, 0.5H), 9.92 (s, 0.5H). MS (ESI) *m/z*: 478 (M − H)$^-$. Anal. (C$_{19}$H$_{20}$F$_3$NO$_8$S) C, H, N.

N-Hydroxy-N-[3-hydroxy-2-hydroxymethyl-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)propyl]-formamide (19n). The acetonide-protected diol hydroxyl-amine, *N*-[1-(2,2-dimethyl[1,3]dioxan-5-yl)-2-(4-(4-trifluoro-methoxyphenoxy)phenylsulfonyl)ethyl]hydroxylamine, was prepared as described for the conversion of **26** to **31**, except using ethyl 2,2-dimethyl[1,3]dioxane-5-carboxylate in place of **27**.

The acetonide (598 mg, 1.22 mmol) was dissolved in 40 mL of THF and treated with 2.3 mL of 3 N HCl at 23 °C for 2.5 h. The reaction mixture was partitioned between EtOAc and saturated NaHCO$_3$, washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated to give the diol hydroxylamine, 2-[1-hydroxyamino-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)-ethyl]propane-1,3-diol (**18n**, 533 mg, 97%). ^{1}H NMR (DMSO-d_6): δ 7.93−7.88 (m, 2H), 7.49−7.45 (m, 2H), 7.31−7.26 (m, 2H), 7.24−7.19 (m, 2H), 5.5 (br, 1H), 4.45 (t, $J = 4.8$ Hz, OH), 4.39 (t, $J = 4.8$ Hz, OH), 3.51−3.42 (m, 6H). MS (APCI) *m/z*: 452 (M + 1), 486 (M + Cl).

The hydroxylamine **18n** was treated with acetic formic anhydride as described for the preparation of **11a** to give the title compound **19n**; mp 129.2−131.3 °C. ^{1}H NMR (DMSO-d_6): δ 1.69−1.79 (m, 1H), 3.57−3.80 (m, 2H), 3.24−3.51 (m, overlapped with solvent H), 4.13−4.19 (dt, $J = 1.5, 8.4$ Hz, 1H), 4.64−4.70 (1H), 7.19−7.30 (m, 4H), 7.45−7.48 (d, $J = 9$ Hz, 2H), 7.678 (s, 0.7H), 7.86−7.90 (m, 2H), 8.04 (s, 0.3H). MS (ESI) *m/z*: 480 (M + H), 502 (M + Na), 981 (2M + Na), 478 (M − H)$^-$, 957 (2M − H)$^-$. Anal. (C$_{19}$H$_{20}$F$_3$NO$_8$S·0.25 H$_2$O) C, H, N.

(1S,2S)-N-[2,3-Dihydroxy-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)propyl]-N-hydroxyform-amide (19o). Compound **19o** was prepared as described for **19n**, except using methyl (4*R*)-2,2-dimethyl[1,3]dioxolane-4-caboxylate; mp 137−138 °C; $[\alpha]_D^{25} + 4.2°$ (MeOH). ^{1}H NMR (DMSO-d_6): δ 3.30−3.60 (m, 4H), 3.65−3.78 (m, 1H), 3.90−3.90 (m, 0.5H), 4.53−4.62 (m, 0.5H), 4.78 (bs, 1H), 4.94 (bs, 1H), 7.21 (d, $J = 9.0$ Hz, 2H), 7.25−7.32 (m, 2H), 7.47 (d, $J = 8.60$ Hz, 2H), 7.70 (s, 0.5H), 7.84−7.92 (m, 2H), 8.09 (s, 0.5H), 9.30 (bs, 0.5H), 9.65 (bs, 0.5H). MS (ESI) *m/z*: 466 (M + H), 483 (M + NH$_4$), 488 (M + Na). Anal. (C$_{18}$H$_{18}$F$_3$NO$_8$S) C, H, N.

N-Hydroxy-N-[2-morpholin-4-yl-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)ethyl]formamide (19p). Compound **19p** was prepared as described for **6**, except using methyl 3-(morpholin-4-yl)propionate in place of **27**; mp 139.1−140.5 °C. ^{1}H NMR (DMSO-d_6): δ 1.58−2.40 (m, 4H), 2.90−3.20 (br, 2H), 3.40−3.75 (m, 4H), 3.85−4.08 (br, 0.6H), 4.60−4.70 (br, 0.4H), 7.21−7.29 (m, 4H), 7.46−7.49 (d, $J = 8.4$ Hz, 2H), 7.80 (s, 0.6H), 7.89−7.92 (d, $J = 8.7$ Hz, 2H), 8.10 (s, 0.4H), 9.63 (s, 0.6H), 10.1 (br, 0.4H). MS (ESI) *m/z*: 519 (M + H), 541 (M + Na), 517 (M − H)$^-$, 553 (M + Cl). Anal. (C$_{22}$H$_{25}$F$_3$N$_2$O$_7$S·H$_2$O) C, H, N.

(1S)-N-Hydroxy-N-[1-(2R)-tetrahydrofuran-2-yl)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]-formamide (19q). Compound **19q** was prepared as described for **6**, except using methyl (2*R*)-tetrahydrofuran-2-carboxylate in place of **27**. ^{1}H NMR (DMSO-d_6): δ 1.37−1.45 (m, 1H), 1.71−1.82 (m, 2H), 1.88−1.99 (m, 1H), 3.28 (m, 0.6H), 3.56−3.73 (m, 4H), 3.81−3.91 (m, 2H), 4.46 (t, $J = 10.0$ Hz, 0.4H), 7.22 (d, $J = 9.0$ Hz, 2H), 7.25−7.29 (m, 2H), 7.46 (d, $J = 8.5$ Hz, 2H), 7.77 (s, 0.6H), 7.90 (d, $J = 9.0$ Hz, 2H), 7.93 (d, $J = 8.5$ Hz, 2H), 8.12 (s, 0.4H), 9.45 (s, br, 0.6H), 9.82 (s, br, 0.4H). MS (ESI) *m/z*: 476 (M + H), 493 (M + NH$_4$). Anal. (C$_{20}$H$_{20}$F$_3$-NO$_7$S) C, H, N.

N-Hydroxy-N-[3-morpholin-4-yl-3-oxo-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)propyl]-formamide (19r). Compound **19r** was prepared as described for **6**, except using methyl 4-(morpholin-4-yl)-4-oxobutyrate in place of **27**. ^{1}H NMR (DMSO-d_6): δ 1.64−1.86 (m, 2H), 2.17−2.31 (m, 2H), 3.40−3.71 (m, 10H), 4.10−4.23 (m, 0.5H), 4.52−4.63 (m, 0.5H), 7.22 (d, $J = 9$ Hz, 2H), 7.28 (d, $J = 8.9$ Hz, 2H), 7.47 (d, $J = 9.1$ Hz, 2H), 7.74 (s, 0.5H), 7.85 (d, $J = 9$ Hz, 2H), 8.11 (s, 0.5H), 9.48 (s, 0.5H), 9.82 (s, 0.5H). MS (ESI) *m/z*: 545 (M − H)$^-$. Anal. (C$_{23}$H$_{25}$F$_3$N$_2$O$_8$S) C, H, N.

(1S)-N-Hydroxy-N-[1-(1-(2S)-methanesulfonylpyrrolidin-2-yl)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]formamide (19s). Compound **19s** was pre-pared as described for **6**, except using methyl (2*S*)-1-methanesulfonylpyrrolidine-2-carboxylate in place of **27**. ^{1}H NMR (DMSO-d_6): δ 1.65−1.78 (m, 3H), 1.93−2.08 (m, 1H), 2.85 (s, 0.4H), 2.88 (s, 0.6H), 3.12−3.45 (m, 3H), 3.71−3.79 (m, 0.6H), 4.23−4.28 (m, 0.4H), 7.19−7.29 (m, 4H), 7.43−7.46

(d, $J = 8.7$ Hz, 2H), 7.80 (s, 0.6H), 7.86−7.92 (m, 2H), 8.17 (s, 0.4H), 9.48 (s, 0.6H), 9.71 (s, 0.4H). MS (ESI) m/z: 553 (M + H), 570 (M + NH$_4$), 551 (M − H). HRMS (APCI) calcd for C$_{21}$H$_{24}$F$_3$N$_2$O$_8$S$_2$ (M + 1) m/z: 553.0926; found, 553.0930.

N-Hydroxy-N-[3-(4-methanesulfonylpiperazin-1-yl)-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)-propyl]formamide (19t). Compound **19t** was prepared as described for **19j**, except using *tert*-butyl 4-(2-ethoxycarbonylethyl)piperazine-1-carboxylate in place of **27**; mp 165.9−167.2 °C. ^{1}H NMR (DMSO-d_6): δ 1.61−1.74 (m, 2H), 2.10−2.46 (m, 6H), 2.87 (s, 3H), 2.94−3.13 (m, 4H), 3.44−3.72 (2H), 4.10−4.22 (m, 0.7H), 4.63−4.73 (m, 0.3H), 7.21−7.30 (m, 4H), 7.46−7.49 (d, $J = 8.4$ Hz, 2H), 7.78 (s, 0.7H), 7.89−7.92 (2H), 8.10 (s, 0.3H), 9.56 (s, 0.7H), 10.09 (s, 0.3H). MS (ESI) m/z: 596 (M + H), 618 (M + Na), 594 (M − H) Anal. (C$_{23}$H$_{28}$F$_3$N$_3$-O$_8$S$_2$) C, H, N.

N-[1-(1,4-Dioxaspiro[4.5]dec-8-yl)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]-N-hydroxyformamide (19u). Compound **19u** was prepared as described for **6**, except using ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate in place of **27**; mp 139.5−141.2 °C. ^{1}H NMR (DMSO-d_6): δ 0.93−1.70 (m, 11H), 3.51−3.65 (m, 1H), 3.81−3.82 (s+s, 4H), 4.02−4.10 (m, 0.5H), 4.57−4.67 (m, 0.5H), 7.19−7.31 (m, 4H), 7.46−7.49 (d, $J = 9.3$ Hz, 2H), 7.88−7.93 (m, 2.5H), 8.11 (s, 0.5H), 9.50 (s, 0.5H), 9.85 (s, 0.5H). MS (ESI) m/z: 560 (M + H), 577 (M + NH$_4$), 582 (M + Na), 558 (M − H), 594 (M + Cl). Anal. (C$_{25}$H$_{28}$F$_3$NO$_8$S) C, H, N.

(1S)-N-[1-((4R)-2,2-Dimethyl[1,3]dioxolan-4-yl)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]-N-hydroxyformamide (19v). Compound **19v** was prepared as described for **6**, except using (4S)-2,2-dimethyl-1,3-dioxolane-4-carboxylate in place of **27**. The major product, (4R)-4-((1S)-1-(hydroxyamino)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl)-2,2-dimethyl[1,3]dioxolane (**18v**), from the conjugate addition of hydroxylamine (3:1 ratio) was carried on to the title compound. ^{1}H NMR (DMSO-d_6): δ 1.05 (s, 1.5H), 1.14 (s, 1.5H), 1.20 (s, 1.5H), 1.23 (s, 1.5H), 3.3−3.4 (m, 1H), 3.5−4.1 (m, 4.5H), 4.3−4.4 (m, 0.5H), 7.2−7.3 (m, 4H), 7.48 (d, 2H), 7.8−8.0 (m, 2.5H), 8.15 (s, 0.5H), 9.68 (br s, 0.5H), 10.10 (br s, 0.5H). MS (ESI) m/z: 506 (M + 1), 523 (M + 18).

(1R)-N-[1-((4R)-2,2-Dimethyl[1,3]dioxolan-4-yl)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]-N-hydroxyformamide (19w). Compound **19w** was prepared as described for **19v**, utilizing the minor product (4R)-4-((1R)-1-(hydroxyamino)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl)-2,2-dimethyl[1,3]dioxolane (**18w**) from the conjugate addition of hydroxylamine. ^{1}H NMR (DMSO-d_6): δ 1.21 (s, 1.5H), 1.23 (s, 1.5H), 1.26 (s, 1.5H), 1.30 (s, 1.5H), 3.3−3.4 (m, 1H), 3.60−3.75 (m, 2H), 3.9−4.1 (m, 2.5H), 4.5−4.6 (m, 0.5H), 7.2−7.3 (m, 4H), 7.48 (d, $J = 8.7$ Hz, 2H), 7.81 (s, 0.5H), 7.85−7.95 (m, 2H), 8.13 (s, 0.5H), 9.63 (br s, 0.5H), 10.0 (br s, 0.5H). MS (ESI) m/z: 506 (M + 1), 523 (M + NH$_4$). Anal. (C$_{21}$H$_{22}$F$_3$NO$_8$S) C, H, N.

(1R)-N-[1-((4S)-2,2-Dimethyl[1,3]dioxolan-4-yl)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]-N-hydroxyformamide (19x). Compound **19x** was prepared as described for **6**. The minor product (4S)-4-((1R)-1-(hydroxyamino)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl)-2,2-dimethyl[1,3]dioxolane (**18x**) from the conjugate addition of hydroxylamine was carried on to the title compound; mp 149−150 °C. ^{1}H NMR (DMSO-d_6): δ 1.04 (s, 1.5H), 1.13 (s, 1.5H), 1.20 (s, 1.5H), 1.23 (s, 1.5H), 3.57−4.11 (m, 5.5H), 4.39 (t, $J = 9.80$ Hz, 0.5H), 7.19−7.30 (m, 4H), 7.49 (d, $J = 8.70$ Hz, 2H), 7.86−7.97 (m, 2.5H), 8.15 (s, 0.5H), 9.71 (bs, 0.5H), 10.20 (s, 0.5H). MS (ESI) m/z: 506 (M + H), 523 (M + NH$_4$), 528 (M + Na). Anal. (C$_{21}$H$_{22}$F$_3$NO$_8$S) C, H, N.

(1S)-N-[1-((4S)-2,2-Diethyl[1,3]dioxolan-4-yl)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]-N-hydroxyformamide (19y). Compound **19y** was prepared as described for **6**, except using methyl (4R)-2,2-diethyl[1,3]-dioxolane-4-carboxylate in place of **27**. ^{1}H NMR (DMSO-d_6): δ 0.7−0.8 (m, 6H), 1.4−1.6 (m, 4H), 3.2−3.3 (m, 1H), 3.45−3.55 (m, 1H), 3.69 (dd, $J = 8.7$, 15.6 Hz, 1H), 3.95−4.15 (m, 2.5H), 4.5−4.6 (m, 0.5H), 7.2−7.3 (m, 4H), 7.47 (d, $J = 8.4$

Hz, 2H), 7.81 (s, 0.5H), 7.85−7.95 (m, 2H), 8.14 (s, 0.5H), 9.66 (br s, 0.5H), 10.11 (br s, 0.5H). MS (ESI) m/z: 534 (M + 1), 551 (M + NH$_4$). Anal. (C$_{23}$H$_{26}$F$_3$NO$_8$S) C, H, N.

(1S)-N-Hydroxy-N-[2-(4-(4-trifluoromethoxyphenoxy)-phenylsulfonyl)-1-((4S)-2,2,5-trimethyl[1,3]dioxolan-4-yl)ethyl]formamide (19z). Compound **19z** was prepared as described for **6**, except using methyl (4R)-2,2,5-trimethyl[1,3]-dioxolane-4-carboxylate in place of **27**. ^{1}H NMR (DMSO-d_6): δ 1.2−1.3 (m, 9H), 3.3−3.5 (m, 2H), 3.6−3.9 (m, 3H), 4.1−4.2 (apparent t, $J = 5.0$ Hz, 0.5H), 4.6−4.7 (apparent t, $J = 5.0$ Hz, 0.5H), 7.2−7.3 (m, 4H), 7.48 (d, $J = 9.0$ Hz, 2H), 7.85−8.00 (m, 2.5H), 8.15 (s, 0.5H), 9.69 (s, 0.5H), 9.95 (s, 0.5H). MS (ESI) m/z: 520 (M + 1), 537 (M + NH$_4$). Anal. (C$_{22}$H$_{24}$F$_3$-NO$_8$S) C, H, N.

(1S)-N-[2-((4S)-2,2-Dimethyl[1,3]dioxolan-4-yl)-1-(4-(4-trifluoromethoxyphenoxy)phenylsulfonylmethyl)ethyl]-N-hydroxyformamide (19aa). Compound **19aa** was prepared as described for **6**, except using methyl (4S)-(2,2-dimethyl[1,3]dioxolan-4-yl)acetate in place of **27**. ^{1}H NMR (DMSO-d_6): δ 1.18−1.27 (m, 6H), 1.56−1.74 (m, 1H), 1.74−1.93 (m, 1H), 3.26−3.71 (m, 3H), 3.81−3.94 (m, 2H), 4.12−4.23 (m, 0.5H), 4.66−4.76 (m, 0.5H), 7.19−7.31 (m, 4H), 7.48 (d, $J = 9.0$ Hz, 2H), 7.76 (s, 0.5H), 7.87−7.94 (m, 2H), 8.12 (s, 0.5H), 9.59 (s, 0.5H), 9.88 (s, 0.5H). MS (ESI) m/z: 520 (M + H), 537 (M + NH$_4$). Anal. (C$_{22}$H$_{24}$F$_3$NO$_8$S) C, H, N.

Compounds Prepared by Method C.

N-Hydroxy-N-[1-(morpholine-4-sulfonylmethyl)-2-(4-(4-trifluoromethoxyphenoxy)phenylsulfonyl)ethyl]-formamide (24b). Compound **24b** was prepared as described for **24a**, except using 4-methansulfonylmorpholine in place of **20a**; mp 123−125 °C. ^{1}H NMR (DMSO-d_6): δ 3.03−3.15 (m, 4H), 3.37−3.41 (m, 1H), 3.43−3.82 (m, 7H), 4.51 (m, 0.5H), 5.04 (m, 0.5H), 7.21−7.30 (m, 4H), 7.48 (d, $J = 9.0$ Hz, 2H), 7.86 (s, 0.5H), 7.90 (dd, $J = 9.0$, 3.0 Hz, 2H), 8.12 (s, 0.5H), 9.82 (s, br, 0.5H), 10.12 (s, br, 0.5H). MS (ESI) m/z: 569 (M + H), 586 (M + NH$_4$), 591 (M + Na). Anal. (C$_{21}$H$_{23}$F$_3$N$_2$O$_9$S$_2$) C, H, N.

Biological Methods. In Vitro Enzyme Assay. The IC$_{50}$ values were determined using fluorimetric assays for MMP enzyme inhibition as detailed by Marcotte and Davidsen in ref 27. The IC$_{50}$ values for all compounds except as noted are from a single determination done in triplicate (variability < 2-fold).

Other metalloproteinase IC$_{50}$s were determined as detailed by Marcotte et al. in ref 28.

Cellular Assay. TNFα release assays were performed as detailed by Glaser et al. in ref 29.

In Vivo Tumor Model. The murine tumor growth model was conducted as detailed by Chirivi et al. in ref 30 and Albert and Davidsen in ref 31.

References

(1) Foda, H. D.; Zucker, S. Matrix Metalloproteinases in Cancer Invasion, Metastasis and Angiogenesis. *Drug Discovery Today* **2001**, *6* (9), 478−482.

(2) Hidalgo, M.; Eckhardt, S. G. Development of Matrix Metalloproteinase Inhibitors in Cancer Therapy. *J. Natl. Cancer Inst.* **2001**, *93* (7), 178−193.

(3) Michaelides, M. R.; Curtin, M. L. Recent Advances in Matrix Metalloproteinase Inhibitors Research. *Curr. Pharm. Des.* **1999**, *5* (10), 787−819.

(4) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. Design and Therapeutic Application of Matrix metalloproteinase Inhibitors. *Chem. Rev.* **1999**, *99* (9), 2735−2776.

(5) Brown, P. D. Ongoing Trials with Matrix Metalloproteinase Inhibitors. *Expert Opin. Invest. Drugs* **2000**, *9* (9), 2167−2177. Since this review, the clinical trials of marimastat (**1**) have been suspended (www.britbio.co.uk).

(6) Hutchinson, J. W.; Tierney, G. M.; Parsons, S. L.; Davis, T. R. C. Dupuytren's Disease and Frozen Shoulder Induced by Treatment with a Matrix Metalloproteinase Inhibitor. *J. Bone Jt. Surg., B* **1998**, *80* (5), 907−908.

(7) Itoh, T.; Tanioka, M.; Matsuda, H.; Nishimoto, H.; Yoshioka, T.; Suzuki, R.; Uehira, M. Experimental Metastasis is Suppressed in MMP-9-deficient Mice. *Clin. Exp. Metastasis* **1999**, *17* (2), 177−181.

(8) Itoh, T.; Tanioka, M.; Yoshida, H.; Yoshioka, T.; Nishimoto, H.; Itohara, S. Reduced Angiogenesis and Tumor Progression in Gelatinase A-deficient Mice. *Cancer Res.* **1998**, *58* (5), 1048–1051.

(9) Lovejoy, B.; Cleasby, A.; Hassell, A. M.; Longley, K.; Luther, M. A.; Weigl, D.; McGeehan, G.; McElroy, A. B.; Drewry, D.; Lanbert, M. H.; Jordan, S. R. Structure of the Catalytic Domain of Fibroblast Collagenase Complexed with an Inhibitor. *Science* **1994**, *263*, 375–377.

(10) Gooley, P. R.; O'Connell, J. F.; Marcy, A. I.; Cuca, G. C.; Salowe, S. P.; Bush, B. L.; Hermes, J. D.; Esser, C. K.; Hagmann, W. K.; Springer, J. P.; Johnson, B. A. The NMR Structure of the Inhibited Catalytic Domain of Human Stromelysin-1. *Struct. Biol.* **1994**, *1*, 111–118.

(11) Morgan, D. W.; Albert, D. H.; Magoc, T.; Tapang, P.; Marcotte, P.; Elmore, I.; Glaser, K.; Pease, L.; Li, J.; Michaelides, M.; Curtin, M.; Holms, J.; Davidsen, S. K. ABT-770: A Novel, Selective Gelatinase A Inhibitor with Antitumor Activity in Preclinical Models of Tumor Growth. Presented at the 1999 AACR–NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Washington, DC, November 1999; Paper 0764.

(12) Curtin, M. L.; Florjancic, A. S.; Heyman, H. R.; Michaelides, M. R.; Garland, R. B.; Holms, J. H.; Steinman, D. H.; Dellaria, J. F.; Gong, J.; Wada, C. K.; Guo, Y.; Elmore, I. B.; Tapang, P.; Albert, D. H.; Magoc, T. J.; Marcotte, P. A.; Bouska, J. J.; Goodfellow, C. L.; Bauch, J. L.; Marsh, K. C.; Margon, D. W.; Davidsen, S. K. Discovery and Characterization of the Potent, Selective and Orally Bioavailable MMP Inhibitor ABT-770. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1557–1560.

(13) Albert, D. H.; Morgan, D. W.; Magoc, T.; Tapang, P.; Kherzai, A.; Marcotte, P.; Elmore, I.; Glaser, K.; Pease, L.; Li, J.; Leal, J.; Michaelides, M.; Curtin, M.; Holms, J.; Wada, C.; Dai, Y.; Davidsen, S. K. Preclinical pharmacology of ABT-518, a Novel and Potent Inhibitor of Gelatinase A and B with Antitumor Activity. *Abstract of Papers*, 11th NCI EORTC AACR Symposium on New Drugs in Cancer Therapy, November 2000; Abstract 301; published as a supplement to *Clin. Cancer Res.* **2000**, *6*, 4525s.

(14) Hori, M.; Kataoka, T.; Shimizu, H.; Ban, M.; Matsushita, H. 10-Thiaanthracenes. Part 3. A Re-Examination of the Reaction of 9-Phenylthioxanthylium Salt and Phenyllithium. *J. Chem. Soc., Perkin Trans. 1* **1987**, 187–194.

(15) Klemm, L. H.; Karchesy, J. J. The Insertion and Extrusion of Heterosulfur Bridges. VI. Comparative Desulfurizations of Dibenzothiophene and Biphenylthiols. *J. Heterocycl. Chem.* **1978**, *15*, 281–284.

(16) Tarbell, D. S.; Fukushima, D. K. m-Thiocresol. *Org. Synth.* **1947**, *27*, 81–83 (Coll. **1955**, *3*, 809).

(17) Miyaura, N.; Suzuki, A. Palladium-catalyzed Cross-coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457–2483.

(18) Dess, D. B.; Martin, J. C. Readily Accessible 12-I-5 Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(19) Kawase, M.; Kikugawa, Y. Chemistry of Amine-boranes. Part 5. Reduction of Oximes, *O*-Acyl-oximes, and *O*-Alkyl-oximes with Pyridine-borane in Acid. *J. Chem. Soc., Perkin Trans. 1* **1979**, 643–645.

(20) Krimen, L. I. Acetic Formic Anhydride. *Org. Synth.* **1970**, *50*, 1–3 (Coll. **1988**, *VI*, 8–9).

(21) Markley, L. D.; Tong, Y. C.; Dulworth, J. K.; Steward, D. L.; Goralski, C. T.; Johnston, H.; Wood, S. G.; Vinogradoff, A. P.; Bargar, T. M. Antipicornavirus Activity of Substituted Phenoxybenzenes and Phenoxypyridines. *J. Med. Chem.* **1986**, *29*, (3), 427–433.

(22) Ku, Y.-Y.; Patel, R. R.; Roden, B. A.; Sawick, D. P. Synthesis of Substituted Heterocycles. Simple Method for the Introduction of the *N*-Hydroxyurea Functionality. *Tetrahedron Lett.* **1994**, *35* (33), 6017–6020.

(23) Zayia, G. H. First General Method for Direct Formylation of Kinetically generated Ketone Enolates. *Org. Lett.* **1999**, *1* (7), 989–991.

(24) Hill, D. R.; Hsiao, C.-N.; Kurukulasuriya, R.; Wittenberger, S. J. 2,2,2-Trifluoroethyl Formate: A Versatile and Selective Reagent for the Formylation of Alcohols, Amines and *N*-Hydroxylamines. *Org. Lett.*, submitted for publication.

(25) Gupta, A.; Hill, D.; Chang, S. J.; Fernando, D.; Wittenberger, S.; King, S. Efficient Large Scale Synthesis of Matrix Metalloprotease Inhibitor, ABT-518. Presented at the 221st National Meeting of the American Chemical Society, San Diego, CA, April 2001; Paper ORGN 327.

(26) Michaelides, M. R.; Dellaria, J. F.; Gong, J.; Holms, J. H.; Bouska, J. J.; Stacey, J.; Wada, C. K.; Heyman, H. R.; Curtin, M. L.; Guo, Y.; Goodfellow, C. L.; Elmore, I. B.; Albert, D. H.; Magoc, T. J.; Marcotte, P. A.; Morgan, D. W.; Davidsen, S. K. Biaryl Ether Retrohydroxamates as Potent, Long-lived, Orally Bioavailable MMP Inhibitors. *Bioorg. Med. Chem. Lett.* **2001**, *11* (12), 1553–1556.

(27) Marcotte, P. A.; Davidsen, S. K. Characterization of Matrix Metalloproteinase Inhibitors: Enzymatic Assays. In *Current Protocols in Pharmacology*; Enna, S. J., Williams, M., Ferkany, J. W., Kenakin, T., Porsolt, R. D., Sullivan, J. P., Eds.; John Wiley & Sons: New York, 2001; pp 3.7.1–3.7.14.

(28) Marcotte, P. A.; Elmore, I. N.; Guan, Z.; Magoc, T. J.; Morgan, D. H.; Curtin, M. L.; Garland, R. B.; Guo, Y.; Heyman, H. R.; Holms, J. H.; Sheppard, G. S.; Steinman, D. H.; Wada, C. K.; Davidsen, S. K. Evaluation of the Inhibition of Other Metalloproteinases by Matrix Metalloproteinase Inhibitors. *J. Enzyme Inhib.* **1999**, *14* (6), 425–435.

(29) Glaser, K. B.; Pease, L.; Li, J.; Morgan, D. W. Enhancement of the Surface Expression of Tumor Necrosis Factor α (TNFα) But Not the p55 TNFα Receptor in the THP-1 Monocytic Cell Line by Matrix Metalloprotease Inhibitors. *Biochem. Pharm.* **1999**, *57*, 291–302.

(30) Chirivi, R. G. S.; Garofalo, A.; Crimmin, M. J.; Bawden, L. J.; Stoppacciaro, A.; Brown, P. D.; Giavazzi, R. Inhibition of the Metastatic Spread and Growth of B16-BL6 Murine Melanoma by a Synthetic Matrix Metalloproteinase Inhibitor. *Int. J. Cancer* **1994**, *58*, 460–464.

(31) Albert, D. H.; Davidsen, S. K. In *Current Protocols in Pharmacology*; Enna, S. J., Williams, M., Ferkany, J. W., Kenakin, T., Porsolt, R. D., Sullivan, J. P., Eds.; John Wiley & Sons: New York, 2001; pp 5.23.1–5.23.11.