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Orally Active MMP-1 Sparing α-Tetrahydropyranyl and α-Piperidinyl Sulfone Matrix Metalloproteinase (MMP) Inhibitors with Efficacy in Cancer, Arthritis, and Cardiovascular Disease

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α-Sulfone-α-piperidine and α-tetrahydropyranyl hydroxamates were explored that are potent inhibitors of MMP's-2, -9, and -13 that spare MMP-1, with oral efficacy in inhibiting tumor growth in mice and left-ventricular hypertrophy in rats and in the bovine cartilage degradation ex vivo explant system. α-Piperidine **19v** (SC-78080/SD-2590) was selected for development toward the initial indication of cancer, while α-piperidine and α-tetrahydropyranyl hydroxamates **19w** (SC-77964) and **9i** (SC-77774), respectively, were identified as backup compounds.

Introduction

Matrix metalloproteinases (MMPs[a]) are a family of zinc-dependent endopeptidases that are involved in the remodeling and degradation of all components of the extracellular matrix (ECM) and have key roles in development, morphogenesis, bone remodeling, wound healing, and angiogenesis.[1] The first matrix metalloproteinase, a collagenase, was discovered by Gross and Lapiere in 1962, explaining the metamorphosis of a tadpole into a frog.[2,3] However, inappropriate MMP activity has been implicated in a number of disease states including tumor growth and metastasis,[4−6] degradation of articular cartilage in arthritis,[7−9] and tissue remodeling and weakening of the left ventricular wall in congestive heart failure.[10−13] To ameliorate disease progression resulting from inappropriate matrix remodeling mediated by MMPs in these various disease states, MMP inhibitors (MMPi's) have been extensively explored.[4,5,14−16]

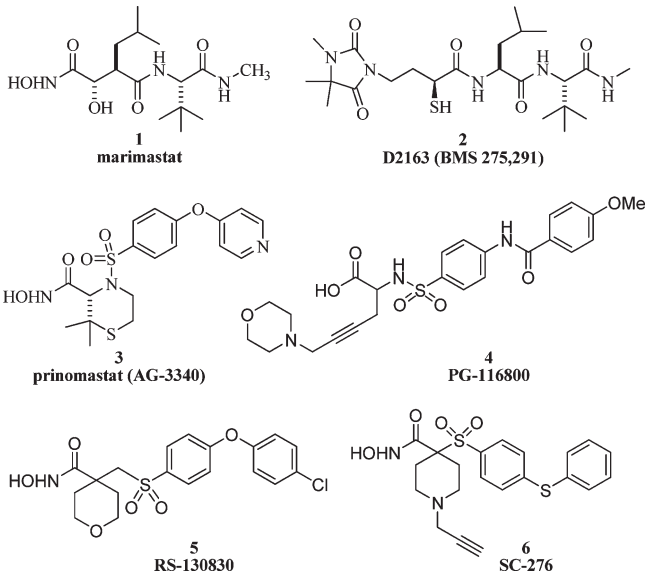

Figure 1. MMP Inhibitors.

However, patients dosed with broad-spectrum MMPi's including marimastat (**1**, Figure 1) suffer stiffening of the joints referred to as musculoskeletal syndrome (MSS)[12] and the broad-spectrum inhibitor marimastat induces joint fibroplasia in rats.[17] The underlying cause of MSS observed clinically with broad-spectrum inhibitors has been hypothesized to be due to inhibition of the constitutive interstitial collagenase MMP-1[18−21] or sheddases such as TACE[22] or a combination of those metalloproteinases. Hence, recent efforts have been toward the discovery and development of highly specific MMP inhibitors that spare off-target isozymes.[23−26]

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[a]Abbreviations: ADME, absorption, distribution, metabolism and excretion; API, active pharmaceutical ingredient; Ar, aryl; Arg, arginine; bid, twice daily; BNCD, bovine nasal cartilage degradation; CY, cyclophosphamide; DMAC, dimethylacetamide; DSC, differential scanning calorimetry; Dulbecco's Modified Eagle Medium; DMF, dimethylformamide; EA, ethyl acetate; EDC, 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride; ES, electrospray; F, female; Glu, glutamic acid; HOBt, *N*-hydroxybenzotriazole; HPLC, high pressure liquid chromatography; HRMS, high-resolution mass spectrometry; IL, interleukin; K_i, inhibition constant; LV, left ventricular; M, male; MI, myocardial infarction; MIR, multiple internal reflectance infrared spectroscopy; MMP, matrix metalloproteinase; MMPi, matrix metalloproteinase inhibitor; mpk, milligrams per kilogram; MSS, musculoskeletal syndrome; NMM, *N*-methylmorpholine; OA, osteoarthritis; PDB, Protein Data Bank; pk, pharmacokinetics; PyBroP, bromo-tris-pyrrolidino-phosphonium hexafluorophosphate; QD, once per day; rmsd, root-mean-square deviation; SAR, structure−activity relationship; SEM, standard error of the mean; THF, tetrahydrofuran; THP, tetrahydropyranyl; TIMP, tissue inhibitor of matrix metalloproteinase; TLC, thin-layer chromatography; TMS, tetramethylsilane.

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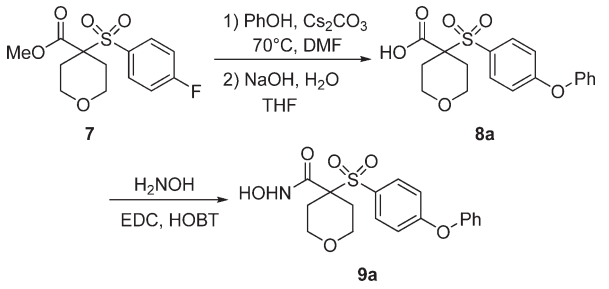
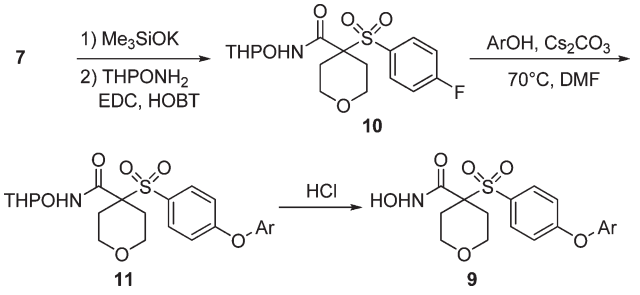
Several MMP inhibitors have been in clinical trials. Bramhall reported the first success in treating cancer with an MMPi in a placebo-controlled, double-blind study treating gastric cancer patients with the broad-spectrum inhibitor marimastat (**1**).[27] Marimastat afforded a survival rate similar to gemcitabine in patients with unresectable pancreatic cancer,[28] and a survival benefit was demonstrated in glioblastoma multiforme patients on marimastat in combination with Temozolomide,[29] although results with marimastat have been mixed and plagued with MSS.[30] Rebimastat (**2**, D2163/BMS-275291), a thiol-containing, broad-spectrum MMP inhibitor that does not inhibit sheddases, was added to systemic chemotherapy for the treatment of hormone-refractory prostate cancer with bone metastases[31] and for Kaposi sarcoma.[32] Encouragingly, rebimastat did not elicit joint toxicity in phase I studies at levels well above the targeted therapeutic range, but patients did suffer from general toxicities and lack of efficacy and the compound was therefore not advanced, In a phase II early stage breast cancer trial, the pattern of arthralgia in rebimastat-treated patients was consistent with MMPi-induced joint toxicity, although the differential incidence of arthralgia did not reach statistical significance.[33] A phase III study of **3** (Prinomastat/AG-3340) in nonsmall-cell lung cancer (NSCLC) did not show improvement in the outcome of chemotherapy in advanced cancer, and toxicities did include arthralgia, stiffness, and joint swelling.[34] Carboxylic acid **4** (PG-116800) is a broad-spectrum MMP inhibitor that elicited arthralgia despite sparing both MMP-1 and MMP-7, and the compound failed to show efficacy in preventing ventricular (LV) remodeling after myocardial infarction in humans over a course of 90 days of dosing,[35] despite impressive outcomes in preclinical animal studies where it significantly reduced LV volumes along with infarct zone collagen content in a post-MI porcine model.[36] Carboxylic acid **4** also induced musculoskeletal toxicity without clear benefit in patients with knee osteoarthritis in a 12-month, double-blind study.[37] Despite these setbacks, impressive efficacy in preclinical models, combined with advances in the understanding of MMP biology, improved parameters to adequately evaluate efficacy, and enhanced inhibitor design, underscore the perseverance toward safe and efficacious MMP inhibitors in the clinical setting.[4,5]

We previously described the synthesis and MMP inhibitory activity of β-sulfone hydroxamates[38,39] inspired by the Roche broad-spectrum MMP-inhibitor **5**, which was in the clinic for OA.[40,41] Our early β-sulfones potently inhibited MMP-2 and MMP-13 while sparing MMP-1 but suffered poor pk. We subsequently discovered that α-sulfone hydroxamates including **6** (SC-276) are superior to the β-sulfones in both MMP-1 sparing enzyme profile and ADME properties and exhibited excellent oral antitumor efficacy in vivo.[42] Hydroxamates tend to be rapidly metabolized, but we believe that the α-spiro moiety in combination with the α-sulfone moiety sterically hinder the metabolism of the otherwise labile hydroxamate moiety in vivo, leading to the outstanding pk properties of molecules of type **6**. Herein we highlight our further efforts in the exploration of α-sulfone α-piperidine and α-THP hydroxamates, resulting in the discovery of potent inhibitors of MMP's-2, -9, and -13 that spare MMP-1, with oral efficacy in inhibiting tumor growth in mice, cartilage degradation in vitro, and left-ventricular hypertrophy in rats, including the development candidate **19v** (SC-78080/SD-2590) as well as α-piperidine **19w** (SC-77964) and α-THP **9i** (SC-77774).

Scheme 1. Preparation of α-Tetrahydropyranyl-α-sulfone **9a**



Scheme 2. Synthesis of α-Tetrahydropyranyl-α-sulfones **9b**−**d**, **f**−**h**,**j**−**m**

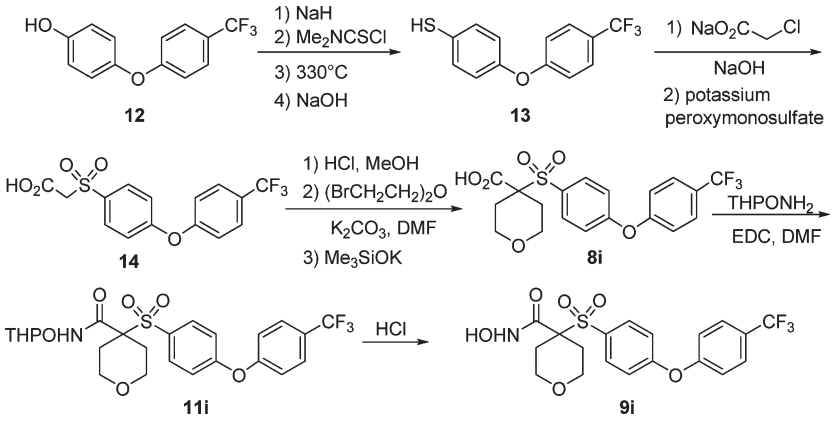


Chemistry

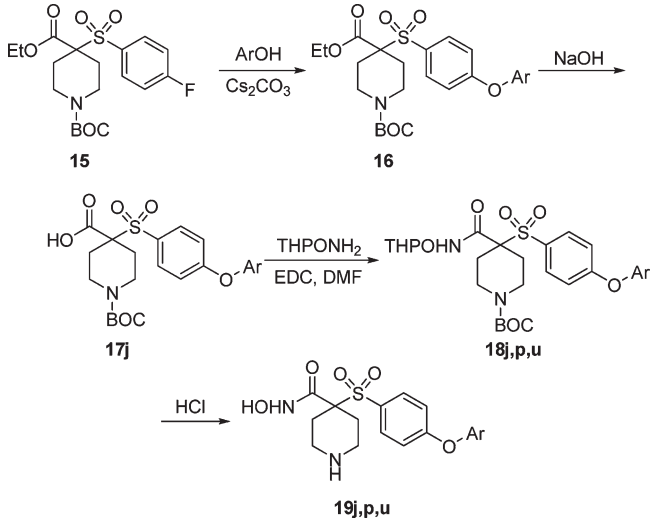
The preparation of α-sulfone hydroxamates **9a**−**m** and **19a**−**ee** is summarized in the following schemes. Phenyloxyphenyl α-tetrahydropyranyl sulfone hydroxamate **9a** was prepared as outlined in Scheme 1. 4-Fluorosulfone **7** was reacted with phenol in the presence of cesium carbonate to afford the diaryl ether, followed by saponification to yield carboxylic acid **8a**. Direct coupling with hydroxylamine employing EDC afforded hydroxamate **9a** after purification by reverse-phase chromatography. Other α-tetrahydropyranyl sulfone hydroxamates were prepared according to Scheme 2. *O*-Tetrahydropyranyl-protected hydroxamate **10** was prepared[42] by hydrolysis of the methyl ester of **6** with potassium trimethylsilanoate followed by EDC coupling with *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine. Nucleophilic aromatic substitution of the fluoride proceeded in the presence of cesium carbonate in DMF to afford THP-protected diaryl ethers **11**. Acidic removal of the THP group with HCl afforded the α-tetrahydropyranyl hydroxamates **9**. For the preparation of 4-hydroxyphenyloxyphenyl **9e**, the phenol employed was 4-(benzyloxy)phenol, yielding **11e** [Ar = 4-(benzyloxy)phenyl], which was deprotected as well as debenzylated with concentrated HCl in glacial acetic acid at 60 °C to afford **9e**.

The preparation of α-tetrahydropyranyl sulfone hydroxamate **9i** bearing the 4-trifluoromethyl group commenced with diaryl ether **12** (Scheme 3). According to the general method of Samaritoni,[43] phenol **12** was deprotonated with sodium hydride and the resulting sodium salt was then treated with dimethylthiocarbamoyl chloride. Pyrolysis and subsequent hydrolysis afforded thiophenol **13**, which was alkylated with sodium chloroacetate and oxidized with potassium peroxymonosulfate to yield sulfone **14**. Fischer esterification was followed by double alkylation with bis(2-bromoethyl)ether and hydrolysis with potassium trimethylsilanoate to afford carboxylic acid **8i**. Coupling with THP-protected hydroxylamine was accomplished with the water-soluble diimide

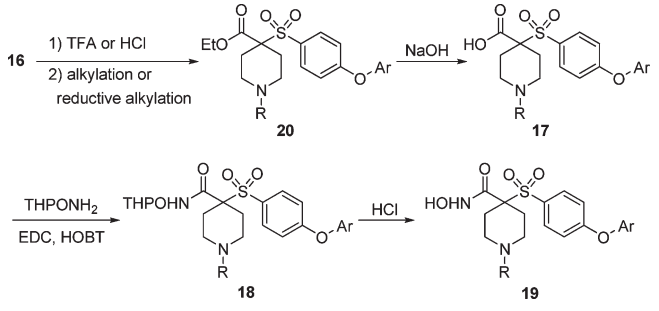
Scheme 3. Synthesis of α-Tetrahydropyranyl-α-sulfone **9i**



Scheme 4. Synthesis of Unsubstituted α-Piperidine Hydroxamates **19j,p,u**



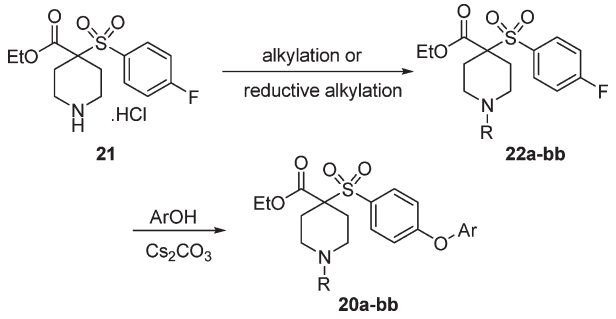
Scheme 5. Synthesis of *N*-Alkylated α-Piperidine Hydroxamates **19a**−**z**



reagent (EDC) to afford the protected hydroxamate **11i**, which was deprotected with HCl in 1,4-dioxane to afford hydroxamate **9i**.

The N-unsubstituted α-piperidines **19j**, **19p**, and **19u** were prepared as summarized in Scheme 4. Aryl fluoride **15** was subjected to nucleophilic aromatic substitution with the requisite phenol (ArOH) with cesium carbonate to afford the corresponding diaryl ether **16**. Saponification of the ethyl ester of **16** gave carboxylic acid **17j**, and coupling with tetrahydropyranyl-protected hydroxylamine using EDC gave the protected hydroxamate **18**. Removal of both the BOC and the tetrahydropyranyl protecting groups afforded α-piperidine hydroxamates **19**.

Scheme 6. Alternate Synthesis of *N*-Alkylated α-Piperidine Ethyl Esters **20a-bb**

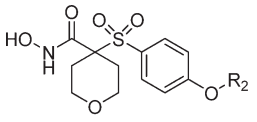


Scheme 5 outlines the general synthesis of N-substituted α-piperidine sulfonamide hydroxamates **19**. *N*-BOC ethyl ester diaryl ether **16** was deprotected with trifluoroacetic acid to afford the secondary amine, which was then alkylated or subjected to reductive alkylation to give *N*-alkyl piperidines **20**. Saponification then gave carboxylic acids **17**, which was coupled with *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine to give the THP-protected hydroxamates **18**. Removal of the THP with HCl gave the free hydroxamate as the hydrochloride salts **19**. For the specific preparation of *N*-acetyl trifluoromethoxyphenyloxyphenyl sulfone derivative **19x**, *N*-BOC carboxylic acid **17a** was deprotected with HCl and then acetylated with acetyl chloride to afford acetamide **17x**, which was then converted to the hydroxamate **19x** via the THP-protected intermediate. Alternatively, for the preparation of hydroxamates **19**, *N*-alkylation of piperidine **21**[42] may be carried out first to afford *N*-alkylpiperidines **22**, followed by nucleophilic displacement of the aryl fluoride to yield diaryl ethers **20** (Scheme 6), which are then converted to hydroxamates **19** according to Scheme 5.

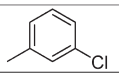
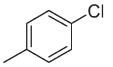
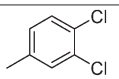
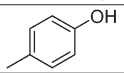
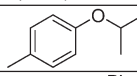
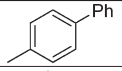
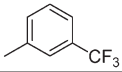
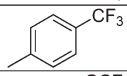
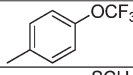
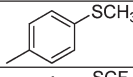
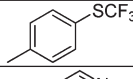
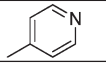
Results and Discussion

The synthesized α-tetrahydropyranyl (THP) and α-piperidine hydroxamates were tested for inhibitory potency versus MMP-1, -2, -3, -7, -8, -9, -13, and -14 (Tables 1 and 2, respectively). Selected analogues were assayed for pharmacokinetic profiles in rats to assess potential for further development. Rats metabolize hydroxamates quite rapidly, so using the rat as a filter was a high bar that we expected would improve the quality of compounds selected for advancement within

Table 1. IC_{50} Values (nM) versus MMPs for α-Tetrahydropyranyl Sulfones



9a-m

Cmpd	R_2	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-13	MMP-14	clogP[a]	C_{max} (ng/mL)	C6h (ng/mL)	$t_{1/2}$ (h)	BA (%)
9a		268	0.1	7.0	-	0.4	0.4	0.1	-	0.80	872	50	1.74	5.8
9b		1800	0.3	18.1	-	1.8	2.9	0.45	4.5	1.51	-	-	-	-
9c[b]		435	<0.1	18.1	-	1.2	0.3	0.15	5.6	1.51	3119	506	1.5	45.8
9d		3600	0.35	35	-	4.0	5.0	0.8	47	2.10	-	-	-	-
9e		400	0.2	-	-	-	<0.1	0.3	1.71	0.13	-	-	-	-
9f		300	<0.1	-	-	-	<0.1	0.1	10.5	1.56				
9g		1400	0.1	50	-	2.4	1.7	0.25	20	2.69	-	-	-	-
9h		>10K	0.8	55.3	-	30	42.5	0.8	24	1.68	1143	257	1.12	18.3
9i		8000	0.1	22	>10K	9,4	1.2	0.4	64	1.68	4304	1154	2.68	33.0
9j		1140	<0.1	35	-	0.9	0.2	<0.1	10.6	1.83	8584	1172	1.87	35.9
9k		2500	<0.1	-	-	-	<0.1	<0.1	3.63	1.36	-	-	-	-
9l		5000	0.4	20	-	0.4	0.25	0.25	200	2.47	7272	3113	1.71	49.0
9m		5000	0.6	-	-	-	-	1.0	-	-0.47	1610	3	0.25	42.3

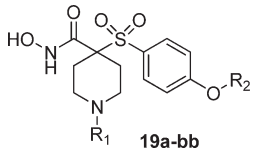
[a] Calculated by ACD Laboratories. [b] Some data for **9c** previously reported.[42]

the series. Moreover, the post-MI left-ventricular hypertrophy efficacy assay was performed in the rat (vida infra), and therefore it was essential to have good oral exposure in this species. As noted above, the α-spiro, α-sulfone moiety that was optimized in our earlier work[42] was maintained because of its beneficial effect on pharmacokinetic properties of the analogues, apparently through sterically limiting access to the hydroxamate by metabolic enzymes, in addition to improving enzyme potency and selectivity. Intermediate carboxylic acid of all hydroxamates were also tested but failed to show any significant inhibitory potency for the MMP isozymes tested.

The α-THP series was generally employed for rapidly screening the P_1' (diaryl ether) moieties for enzyme inhibitory potency and selectivity because synthesis via common intermediate **10** (Scheme 2) enabled rapid analogue production. Most analogues in Table 1 were prepared via this method. This strategy of rapidly screening α-THP analogues, in some cases employing parallel medicinal chemistry (PMC), also enabled the discovery of compounds with more selective enzyme profiles, some of which have now been reported.[44,45] In most cases, the α-piperidines exhibited greater exposure than the α-THP analogues.

Simple phenyloxyphenyl derivative **9a** exhibited subnanomolar potency for MMPs-2, -3, -9, and -13. Potency for MMP-1 was 268 nM, with selectivity for MMP-13 relative to MMP-1 at approximately 2700×, but we sought an even wider therapeutic window (> 10000×) with respect to MMP-1 to avoid any inhibition of this isozyme at C_{max}. We had noted previously that unsubstituted phenyloxyphenyl ethers were more potent but less selective than phenylthiophenyl ethers of type **6** but turned our attention away from the more metabolically labile thioethers to the oxygen-linked analogues described herein, relying on aryl substitution on the distal ring to afford greater selectivity. Unsubstituted phenyl ether **9a** had only 5.8% bioavailability in the rat, presumably due to the availability of the para position in the distal ring to metabolism, combined with the low clogP of 0.8, given the optimal logP for oral bioavilability of ~2,[46] which was consistent with our findings in this series. Thus, our strategy in analogue preparation was to improve potency and selectivity with aryl substituents and to block metabolism at the 4-position, but given the narrowness of the P1′ pocket, we were essentially limited to substituents in the 3- and/or 4-positions in the distal ring. Substitution with a chlorine on the 3-position (**9b**) raised the clogP to 1.51 but reduced the potency for all MMP

Table 2. IC_{50} Values (nM) and Oral Rat PK Data of α-Piperidine Sulfones (20 mpk Suspension)



19a-bb

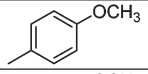
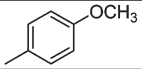
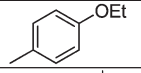
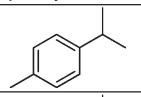
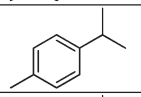
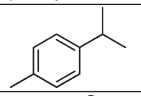
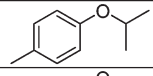
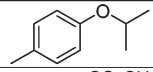
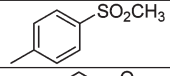
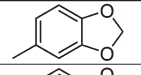
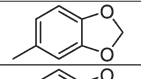
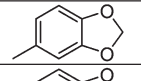
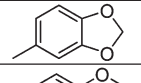
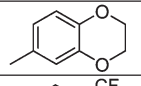
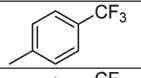
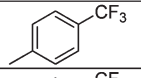
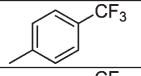
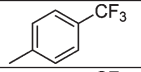
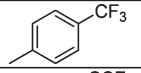
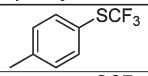
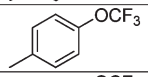
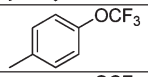
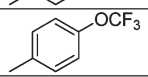
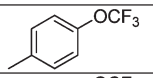
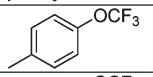
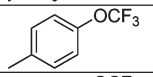
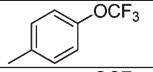
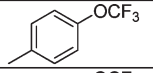
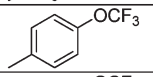
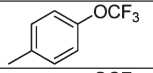
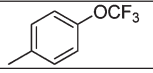
Cmpd	R_1	R_2	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-13	MT1-MMP	clogP[b]	C_{max} (ng/mL)	C6h (ng/mL)	$t_{1/2}$ (h)	BA (%)
6[a]	propargyl	-	8660	0.33	13.0	>10K	1.8	1.5	0.40	19.1	2.04	13630	281	1.1	28
19a	propargyl		3600	0.4	0.2	-	10	1.1	0.4	-	1.57	27158	192	1.01	36.9
19b	2-pyridylmethyl		4500	0.2	20.6	-	1.9	0.1	0.3	3.1	1.44	8551	160	-	-
19c			1000	0.1	-	-	-	0.2	0.25	6.8	2.00	-	-	-	-
19d[c]	propargyl		>10K	0.1	32.6	-	1.6	2.0	0.25	53.9	3.08	5312	21	0.73	23.8
19e	methoxyethyl		10K	0.1	-	-	-	-	0.2	-	2.83	-	-	-	-
19f			>10K	1.0	22.5	-	1.8	2.2	2.7	159	3.49	-	-	-	-
19g	methoxyethyl		2000	0.3	-	-	-	-	0.5	25.8	2.16	-	-	-	-
19h			770	0.1	-	-	-	0.21	0.1	13.3	2.31	-	-	-	-
19i	propargyl		>10K	3.3	-	-	-	82.3	2.9	3486	0.01	-	-	-	-
19j	H		4400	0.4	35	-	2.4	3.8	1.9	83.0	0.74	1548	128	-	-
19k	propargyl		2000	0.2	18.1	-	1.3	0.3	0.6	14.9	1.62	18,474	134	0.843	30.1
19l	methoxyethyl		2400	0.25	20	-	1.2	0.27	0.2	4.0	1.37	-	-	-	-
19m			1000	0.5	-	-	-	<0.1	0.3	0.73	1.51	13079	206	-	-
19n			6000	0.2	21.5	-	1.5	1.9	0.5	49.4	1.47	9460	15	3.30	16.6
19o[c]			>10K	0.1	76.8	>10K	1.3	2.3	0.2	500	2.43	8316	631	1.48	36.3
19p	H		>10K	1.7	64.7	-	2.0	4.0	1.2	160	1.66	540	150	1.88	12.4
19q	N-morpholinyl-ethyl		>10K	0.3	-	-	-	0.1	0.35	7.4	1.41	147	73	0.94	2.6
19r			>10K	0.3	40	-	1.4	1.9	5.5	58.6	2.95	5118	429	2.08	48.3
19s	ethyl		>10K	0.2	36.9	-	1.4	1.5	0.6	100.5	2.64	-	-	-	-
19t	methoxyethyl		>10K	0.2	23.9	9000	1.9	0.25	0.2	108	3.08	32938	14078	2.99	34.1
19u	H		10K	<0.1	21.5	-	0.7	0.22	0.1	53.3	1.81	630	223	1.78	6.7
19v	methoxyethyl		>10K	<0.1	28.7	7000	1.7	0.18	<0.1	13	2.44	29634	20521	2.94	67.9
19w			4000	<0.1	22	7000	1.2	0.15	0.1	4.6	2.58	4160	440	2.85	23.0

Table 2. Continued

Cmpd	R_1	R_2	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-13	MT1-MMP	clogP[b]	C_{max} (ng/mL)	C6h (ng/mL)	$t_{1/2}$ (h)	BA (%)
19x	2-pyridylmethyl		6000	0.2	115	>10K	0.6	0.2	<0.1	4.1	2.54	36810	1850	1.25	46.8
19y	3-pyridylmethyl		4600	<0.1	42.5	>10K	1.5	0.6	0.2	3.7	2.54	52640	1900	1.05	49.8
19z	ethoxyethyl		5900	<0.1	-	-	-	0.1	<0.1	9.5	2.82	3130	3040	1.66	14.7
19aa	hydroxyethyl		4500	<0.1	-	-	-	-	<0.1	-	1.68	1380	570	1.39	21.9
19bb	acetyl		3600	0.1	18.1	-	1.6	0.1	0.2	9.0	0.85	159	72	1.06	4.0
19cc	propargyl		2600	<0.1	-	-	-	<0.1	0.2	1.33	2.68	-	-	-	-
19dd	methyl		>10K	<0.1	-	-	-	0.18	0.6	24.9	2.25	-	-	-	-
19ee			>10K	<0.1	-	-	0.4	<0.1	<0.1	7.1	3.09	-	-	-	-

[a] Data for **6** taken from Becker et al.[42] except for MMP-14. [b] Calculated by ACD Laboratories. [c] Some hemolysis was observed as evidenced by blood in the urine after iv dosing.

isozymes tested by several fold. Chlorine substitution on the 4-position (**9c**), however, maintained robust potency and dramatically enhanced the oral exposure in rat, giving an excellent bioavailability of 46%, consistent with blocking metabolism at the electron-rich 4-position of the phenyl ether. Interestingly, hydroxamate **9c** is the α-sulfone analogue of *β*-sulfone **5** that was advanced by Roche Bio-Science to phase II clinical trials for osteoarthritis.[41] We had directly compared **9c** with RS-130,830 (**5**) in our earlier report[42] to demonstrate the superiority of α-sulfones over *β*-sulfones in both potency and pk. 3,4-Dichloro substitution led to approximately an order of magnitude loss of potency (**9d**), given the steric demand of the two chlorine atoms. 3,5-Disubstitution with either two chlorines or two methoxy substituents led to compounds that were much less potent for MMP-13 (83 and 230 nM, respectively; these compounds are not exemplified in the tables). Introduction of an H-bond donor/acceptor 4-hydroxy group in phenol **9e** gave excellent potency for desired isozymes but surprisingly a relatively potent MMP-1 inhibition of 400 nM. As part of our strategy, we turned to ethers of phenol **9e** to extend the P1′ substituent even further while blocking the 4-position without introducing metabolically labile benzylic hydrogens. Introduction of the more bulky isopropyloxy in compound **9f** and the biphenyl moiety in **9g** gave potent compounds and slightly reduced potency for MMP-1 (>1000 nM) by biphenyl **9g**. Installation of a trifluoromethyl group in the 3-position gave more selective compound **9h** (12500× for MMP-13 over MMP-1) and modest pk in the rat. Moving the trifluoromethyl group to the para position in **9i** improved both potency and selectivity (20000× for MMP-13 vs MMP-1) and dramatically enhanced the pk, with $t_{1/2}$ = 2.68 h and BA = 33%. Similarly, 4-trifluoromethoxyphenyl ether **9j** was several times more potent and also exhibited excellent pk in the rat. These two trifluoromethyl-containing compounds (**9i** and **9j**) had the best overall profiles that we had seen among the MMP-1 sparing α-THP sulfones, with greater exposures and half-lives than those of 4-chloro derivative **9c** and rivaling those of α-piperidine **6** (cf. Table 2). Methylthio derivative **9k** also had excellent potency, as did trifluoromethylthio derivative **9l**, which also had a noteworthy pk profile, boasting a bioavailability of 49%. The latter two compounds were de-emphasized due to modest concerns that the sulfur linkages might present a metabolic liability, and trifluormethylthio moiety of **9l** raised concerns about a high cost of goods. 4-Pyridine derivative **9m** was an order of magnitude less potent at MMP-13 than several other α-THPs and had low exposure upon oral dosing in the rat, with a $t_{1/2}$ of only 0.25 h and the plasma concentration approaching 0 ng/mL after 6 h, possibly due to oxidation of the pyridine nitrogen as well as its dramatically lower clogP of −0.47.

Table 2 summarizes the MMP inhibitory potency and rat pharmacokinetics of selected α-piperidine sulfone hydroxamates. Among these α-piperidines, we employed N-substituted piperidines of varying basicity with the expectation of optimizing pk through modulating physicochemical properties and affecting membrane-crossing potential.[47] The crystal structure of (vide infra) showed that the piperidine N-substituent projects into solvent, so this moiety generally had little impact on potency and selectivity, at least for the smaller substituents, and provided a handle for modulating pk. An *N*-methoxyethyl substituent lowers the basicity of the piperidine nitrogen inductively[48] and substitution with an *N*-cyclopropyl substituent, introduced by the procedure of Gillaspy, lowers the basicity of a substituted amine by 1−2 log units (per cyclopropyl substituent) as she has shown.[49] Varying the substituents at the distal phenyl 3- and 4-positions affected potency and selectivity more profoundly, and also affected pk in the α-THPs, and limited the selection of aryl substituents selected for installation in the α-piperidines, ultimately pointing to trifluoromethyl-containing derivatives in the 4-position of the distal phenyl ring as having optimal properties overall. Substitution with a 4-methoxy group on the distal phenyl ring (R_2 = 4-MeOPh) combined with an *N*-propargyl substituent on the piperidine gave **19a**, which exhibited good potency and selectivity and a very high C_{max} but a modest half-life of 1.0 h. Hydroxamate **19b** with a bulky *N*-2-pyridylmethyl substituent on the α-piperidine exhibited comparable potencies at MMPs-1, -2 and -13 but lost 2 orders of magnitude

potency versus MMP-3 while gaining an order of magnitude potency at MMPs-8 and -9. Meanwhile, the exposure in the rat was roughly a third of the exposure of the corresponding α-piperidine *N*-propargyl analogue. Hydroxamate **19c** with an *N*-cyclopropylpiperidine and bearing a 4-ethoxy group in P1′ had comparable potencies at target MMPs while losing some selectivity toward MMP-1. *para*-Isopropylphenyl ether **19d** exhibited good potencies and selectivity, though losing some potency for MMP-9. In the rat, a fairly high initial C_{max} of 5300 ng/mL was due in part to the higher clogP of 3.08, yet the compound was rapidly cleared by 6 h, with a $t_{1/2}$ of less than 1 h, presumably due to metabolism of the isopropyl group. Some hemolysis was apparent with this compound as judged by blood observed in the urine. Isopropylphenyl compound **19e** had good potency for MMPs-2 and -13 and selectivity versus MMP-1, while isopropylphenyl *N*-isopropylpiperidine **19f** was surprisingly somewhat less potent at target isozymes, although solubility may have been an issue, given the higher clogP of 3.49. These 4-isopropylphenyl derivatives were not advanced due to concern about the hemolysis observed in the iv arm with **19d**. Extension of the 4-substituent as isopropyl ethers **19g** and **19h** showed potency for target isozymes, but these derivatives were also unexpectedly more potent versus MMP-1, in particular **19h**, with a potency of 770 versus MMP-1. 4-Methylsulfone **19i** backed off on potency versus MMP-13 by almost 30× relative to some analogues. Interestingly, whereas most analogues did not spare the nontarget MT1-MMP (MMP-14) enzyme, **19i** was 1200× selective for MMP-13 over MT1-MMP. This elicited some excitement later on, when our focus shifted to dual MMP-1/14 sparing compounds but was not initially considered as a criterion for advancement. The sesamol-derived 1,3-benzodioxole derivative **19j** with a free piperidine NH was slightly less potent than *N*-alkyl piperidines, and its oral exposure in the rat was modest, as we had seen for N-unsubstituted piperidines in the first-generation series. The poor pk of the unsubstituted piperidines may be due to the lower logP (clogP = 0.74 for **19j**) or the first-pass metabolism of the free piperidine NH, or both. Sesamol-substituted *N*-propargyl piperidine **19k** exhibited a very high exposure when dosed orally, as judged by the high C_{max} of over 18000 ng/mL, but the half-life was less than 1 h. *N*-Methoxyethyl piperidine **19l** was virtually identical to propargyl derivative **19k** based on the enzyme profile. Installation of an *N*-cyclopropyl substituent on the piperidine gave hydroxamate **19m**, which was potent and selective, with moderate exposure in the rat. The ring-expanded 1,4-benzodioxane **19n** displayed good potency and selectivity but had a moderate bioavailability of 16.6%.

The 4-trifluoromethylphenyl ether **19o** bearing an *N*-cyclopropyl piperidine was a very promising compound, with subnanomolar potency for MMPs-2 and -13, excellent selectivity versus MMP-1, and attenuated potency for MT1-MMP. Oral exposure in the rat was good, with a bioavailability of 36% and a half-life of nearly 1.5 h, although slight hemolysis was detected after iv administration of the compound. Free piperidine **19p** again suffered a loss of potency and reduced oral exposure as for piperidine **19j** above, and the *N*-morpholinyl-ethyl piperidine **19q** had minimal exposure in the rat and only 2.6% bioavailability, demonstrating that the additional basic site in this analogue is counterproductive. *N*-Isopropyl piperidine **19r** exhibited excellent pk in the rat with a half-life of greater than 2 h and a BA of almost 50%, but the enzyme potency was attenuated, particularly for target enzyme MMP-13. The enzyme profile of *N*-ethyl piperidine **19s** was very comparable to *N*-methoxyethylpiperidine **19t** bearing the trifluorothiophenyl ether, but the methoxyethyl derivative was chosen for pk due to the reduced basicity of its piperidine nitrogen, which we believe to be advantageous for oral exposure. The profile of trifluoromethylthioether **19t** was deemed worthy of promotion, with one of the highest concentrations at 6 h observed overall (14078 ng/mL), a half-life of approximately 3 h, and a good bioavailability of 34%, yet higher cost of goods concerns and perhaps a bias against the somewhat less common trifluoromethylthio functionality limited its advancement; a trifluoromethoxy group is present in the approved drug riluzole, but there are no trifluormethylthiophenyl ethers approved or in testing.[50] In contrast, the 4-trifluoromethoxyphenyl ether contributed to overall spectacular profiles within the series and was installed in a number of analogues, including all subsequent analogues in Table 2, with varying piperidine *N*-substituents. Nonetheless, unsubstituted piperidine **19u** bearing the 4-trifluoromethoxy group in P1′ suffered from limited exposure and low bioavailability of only 6.7%, nearly identical to the rat pk of trifluoromethylphenyl ether **19p**. On the other hand, *N*-methoxyethylpiperidine **19v** bearing the 4-trifluoromethoxyphenyl ether distinguished itself with exceptional inhibitory potency and 10^6-fold selectivity versus MMP-1, combined with unmatched exposure after oral dosing in the rat with a BA of 68%, a half-life of almost 3 h, and a concentration of > 20000 ng/mL 6 h after dosing. Thus, *N*-methoxyethylpiperidine hydroxamate **19v** was selected for development as a 50 pM K_i inhibitor of the gelatinases (MMP-2 and MMP-9) with 100000-fold selectivity over MMP-1. The other top-performing piperidine N-substituent, the cyclopropyl, was also incorporated, giving rise to *N*-cyclopropylpiperidine **19w**, with an enzyme profile nearly identical to **19v**, and with a very good pk profile in the rat including a similar $t_{1/2}$ to **19v** of just under 3 h and lower but acceptable BA of 23%. This compound was selected as the development back-up to **19v**. *N*-2-Pyridylmethyl and *N*-3-pyridylmethylpiperidine analogues **19x** and **19y** were very attractive compounds from the perspective of potency and selectivity and also in consideration of their high exposures and bioavailabilities of ca. 47% and 50%, respectively, although their half-lives in the rat were just over 1 h. The shorter half-lives were a concern for these two pyridylmethyl derivatives, as well as higher the protein binding, as indicated by 110-fold and 123-fold shifts in MMP-2 inhibitory potency, respectively, in the presence of human plasma in a classic plasma-shift assay,[51] compared with the somewhat lower 69-fold and 38-fold for **19v** and **19w**, respectively. *N*-Ethoxyethyl- and *N*-hydroxyethyl- piperidines **19z** and **19aa** were potent and selective, with good exposure in the rat but with only a 14.7% bioavailability for **19z** and a 1.39 h half-life for **19aa**. Acetamide derivative **19bb** maintained excellent potency and selectivity, but the pk in the rat dropped precipitously to only 4% BA and very low plasma concentrations. *N*-Propargyl piperidine hydroxamate **18cc** was potent and selective and bears the same piperidine substituent as first-generation MMP-1 sparing hydroxamate **6**. We shied away from propargyl substituent as it did not afford any advantages over *N*-methoxyethyl or *N*-cyclopropyl (among other substituents), and we observed that it forms 1−2% of a vinyl chloride impurity in the final API upon HCl deprotection of the THP-protected hydroxamate. *N*-Methyl and *N*-isopropyl piperidine derivatives **19dd** and **19ee** were potent and selective and should have favorable pk profiles in the rat but were not advanced.

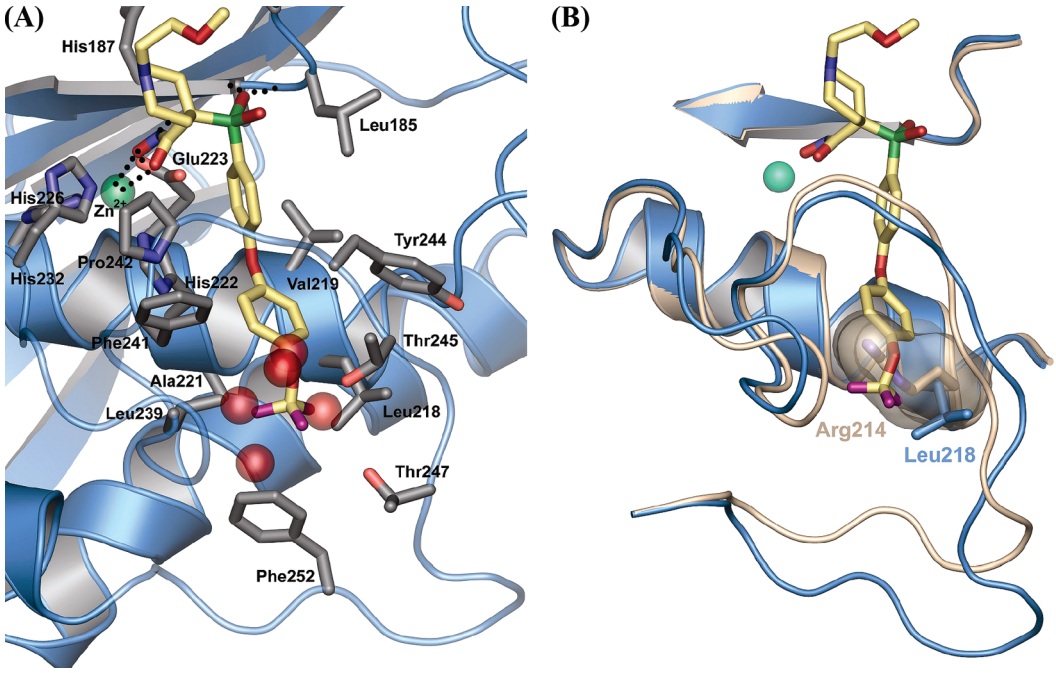


Figure 2. Structure of **19v** and origins of its selectivity. (A) Complex of **19v** bound at the MMP-13 active site. Hydrogen bonds and metal (green sphere) coordination is depicted as dotted lines. Solvent molecules are shown as red spheres. (B) Superposition of the catalytic domains of MMP-1 (PDB accession code: 1HFC) and the **19v**:MMP-13 complex. The molecular surface for Arg214 of MMP-1 is drawn to demonstrate its steric blockade of inhibitors with sufficient length of their S1′ substituents.

Thus, preparation of the α-THP derivatives enabled rapid exploration of SAR, but these compounds generally had poorer pk profiles than the corresponding α-piperidines. The trifluoromethyl-substituted analogues **9i**, **9j**, and **9l** are notable exceptions, with excellent pk profiles, and these P1′ substituents performed well in the α-piperidine series as well. We believe that this is the result of blocking metabolism at the para position of the terminal phenyl ring of the diaryl ether as well as enhanced membrane penetration due to fluorine substitution.[52] *N*-Methoxyethylpiperidine **19v** and *N*-cyclopropylpiperidine **19w**, both bearing the distal trifluoromethoxyphenyl group in P1′, were promoted for full efficacy evaluation, and α-THP **9i** was also considered a top priority compound to augment the structural diversity of the leads and spread the risk among different chemistries.

Crystallography. The crystal structure of MMP-13 in complex with **19v** was determined at 1.9 Å resolution (R_{free} = 25.6%; PDB accession code: 3KRY) and shows the compound forming an intricate web of contacts to the catalytic zinc ion and surrounding amino acids (Figure 2). Two hydrogen bonds are made between an oxygen atom of the sulfone moiety and the protein backbone, and an additional hydrogen bond is made from the nitrogen of the hydroxamate function to the protein backbone (Figure 2A). The two oxygen atoms of the hydroxamate coordinate to the metal, and an additional interaction is formed with the side chain of Glu223. For that close interaction (2.8 Å), it is assumed that either the Glu residue or the hydroxamate oxygen is protonated. The diphenyl ether tail of the compound protrudes deeply into the S1′ subsite, which is in an open conformation. Five ordered solvent molecules bridge across the two sides of the pocket and encapsulate the trifluormethyl tail of the compound.

Metalloproteinase selectivity for **19v** was achieved by exploiting the larger S1′ pocket found in MMP-13 compared to other MMPs such as MMP-1. As was previously reported,[53−55] MMP-1 and MMP-13 S1′ pockets differ in two key ways. First, the length of the loop and thus the depth of the pocket are shorter in MMP-1 because of a two residue deletion in that sequence relative to MMP-13. In addition, MMP-1 has a significantly larger residue, Arg214, in place of Leu218 in MMP-13. This presents a steric blockade for inhibitors of sufficient length from binding to the S1′ site. The relevance of this amino acid difference was evaluated for **19v** by superimposing the structure of MMP-1 (PDB accession code: 1HFC) onto the structure of MMP-13 with **19v**. Overall, the two catalytic domains aligned well, differing by an rmsd of only 0.75 Å over 154 residues aligned. However, at the S1′ subsite, their structures diverged as expected with MMP-1, presenting a significantly smaller cavity within which the compound would have to fit. In the case of **19v**, the diphenyl ether tail of the compound would collide with the Arg side chain in MMP-1 (Figure 2B). While this Arg residue has been observed in alternate conformations in MMP-1 with compounds similar to **19v**,[55] the molecular determinants for when that conformation is accessible and its relevance to full length enzyme remain unclear.

As noted above, the piperidine N-substituents (R_1) extend into solvent and generally had little or no impact on potency at MMP-13, although the larger 2-pyridylmethyl substituent of **19b** did impact selectivity toward several other isozymes. The capacity for the P1′ pocket to accommodate such large moieties as the biphenyloxyphenylsulfone of **9g** is rather remarkable but also demonstrates that the pocket is both flexible and open at the bottom, near Phe252. The size of the pocket is consistent with the ability to substitute only on the 3- and/or 4-positions of the distal phenyl ring in P1′. The substituents at the terminus of the distal phenyl ring in P1′ are surrounded by the hydroxyl of Thr 245, the methyl of Thr247, the edge of the phenyl ring of Phe252, and the hydrophobic chain of Leu218 plus several solvent (water) molecules. Smaller, hydrophobic but polarizable moieties tended to be the best aryl substituents at this position.

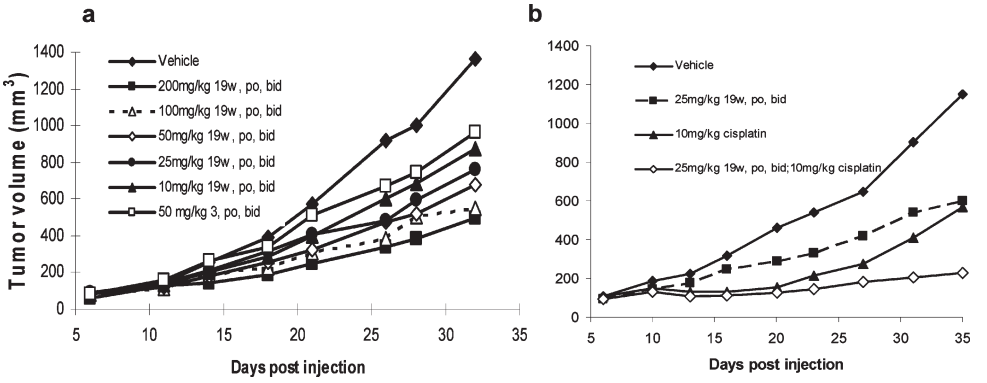


Figure 3. Efficacy of **19w** in the PC3 tumor growth delay model, either as single agent (a) or in combination with cisplatin (b).

The distance of 2.87 Å between F35 and the Thr245 oxygen is more consistent with a simple van der Waals interaction than a potential but very rare[56] OH···F hydrogen bond.

Antitumor Efficacy. Marimastat and prinomastat are effective in preclinical models of cancer but produce a dose-limiting musculoskeletal syndrome characterized as joint fibrosis, pain, and limited mobility in humans. As noted above, one strategy for improving the therapeutic index of MMP inhibitors is to design selective inhibitors of the MMPs that inhibit neoplastic growth while sparing MMP-1, a widely distributed collagenase thought to play a central role in connective tissue homeostasis. Hydroxamate **19w** is a potent inhibitor of several MMPs, with IC_{50}s of 0.1, 22, 1.2, 0.15 and 0.1 nM against MMP-2, -3, -8, -9, and -13, respectively. Although potent against MMPs that are thought to play a significant role in angiogenesis and tumor growth, **19w** is highly sparing of MMP-1 (IC_{50} = 4000 nM). The IC_{50} of **19w** for MMP-1 is 100-fold greater than that of prinomastat.[57] Hydroxamate **19w** has good oral bioavailability and half-life across multiple species, and it is well tolerated in mice dosed twice daily for greater than 90 days. MMPi **19w** is a dose-dependent and potent inhibitor of angiogenesis in the mouse bFGF-induced corneal micropocket model and delays tumor growth in a variety of models of human cancer including the androgen-independent PC3 human prostate tumor, the difficult-to-treat SKMES human lung carcinoma (data not shown), and MX-1 human breast tumors was significantly inhibited by treatment of tumor-bearing mice with **19w**.

The efficacy of **19w** in the PC3 tumor growth delay model, either as single agent or in combination with cisplatin, is shown in parts a and b of Figure 3, respectively. BALB/c nu/nu mice, implanted with PC3 cells, were administered **19w** twice daily beginning on the day of cell injection. Tumor volume was measured over the course of the experiment. MMP inhibitor **19w** inhibited PC3 tumors in a dose responsive manner; animals dosed with 100 and 200 mg/kg **19w** inhibited tumor growth by greater than 65% ($p < 0.001$ vs vehicle -treated mice).

MMPi **19w** in combination with cisplatin therapy was more effective than treatment with either agent alone. Mice implanted with PC3 cells and administered **19w** by gavage twice daily were injected with a single intraperitoneal injection of cisplatin on day 8. Treatment of mice bearing PC3 tumors with 25 mg/kg **19w** or 10 mg/kg cisplatin inhibited tumor growth by 49% and 53%, respectively, whereas PC3 tumor growth was inhibited by 78% in mice treated with **19w** and cisplatin.

MMPi **19w** was shown to significantly delay the growth of MX-1 human breast tumors in nude mice when used as a single agent (data not shown). Inhibitor **19w** was subsequently tested in the MX-1 adjuvant model, a clinically relevant disease model designed to determine the anticancer activity of nontraditional, noncytotoxic agents in a setting of minimal tumor burden. Mice bearing MX-1 tumors were treated with Cytoxan (cyclophosphamide, CY) and beginning approximately two weeks later mice were administered **19w** delivered by gavage twice a day over the remainder of the experiment. Efficacy was measured by survival extension. As shown in Figure 4, adjuvant therapy with **19w**, following initial cytoreduction of MX-1 breast carcinomas in nude mice by CY treatment, greatly increased the survival times of animals compared to treatment with CY monotherapy. CY alone (120 mg/kg) extended survival by three weeks compared to saline controls. High dose **19w** (50 mg/kg) following CY treatment further increased the mean survival time of mice by an additional four weeks compared to CY monotherapy. Significant survival gains over CY monotherapy were shown for all doses of **19w** following CY treatment. The highly effective adjuvant therapy seen with **19w** after CY treatment was obtained with no side effects observed, indicating that the adjuvant efficacy was achieved with a good therapeutic index.

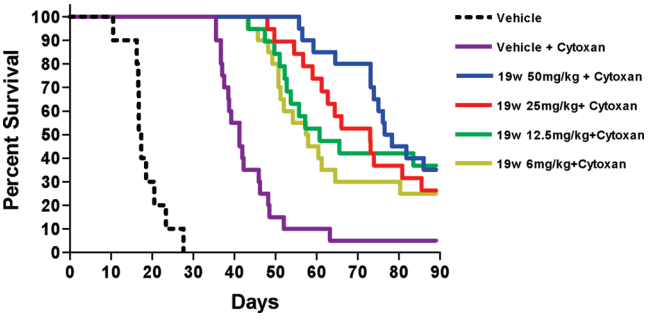


Figure 4. Survival extension provided by **19w** to mice bearing MX-1 tumors.

These results support the potential utility of **19w** in the treatment of patients with malignancies of the lung, prostate, and breast.

Inhibition of Cartilage Degradation. Osteoarthritis (OA) is a degenerative disease of the joints that is characterized by the progressive degeneration and loss of articular cartilage. Current treatments focus on alleviating the pain associated with OA but do not address the underlying disease process. While the precise etiology of OA is not known, it appears to be the result of a complex system of interacting mechanical, biologic, biochemical, and enzymatic feedback loops.

The final common pathway of articular cartilage deterioration results from a failure of chondrocytes to maintain a homeostatic balance between matrix synthesis and degradation. The major matrix components of articular cartilage, aggrecan and collagen, provide the physical properties essential for maintaining joint function, compressibility, and tensile strength, respectively. Accumulating evidence implicates an imbalance between intra-articular synthesis of matrix-degrading enzymes, particularly MMPs, and their endogenous tissue inhibitors of metalloproteinases (TIMPs), as causally associated with cartilage loss in OA.

In that no disease-modifying OA drugs (DMOADs) have yet been approved, animal models capable of predicting efficacy in human disease have not been validated. Furthermore, the translatability of relatively acute in vivo preclinical models to the human disease which develops over decades is not known. However, in an attempt to provide early evidence of the cartilage protective properties of test compounds, a cytokine-induced bovine nasal cartilage degradation (BNCD) assay was developed and has been used to evaluate the importance to cartilage metabolism of numerous targets. Using an adaptation of the assay described by Bottomley et al.,[58] selected compounds were tested for their ability to inhibit cartilage degradation, which is enhanced in osteoarthritic articular cartilage.[59] Importantly, this model system allows for the concentration-dependent characterization of compounds, including end point measurements that reflect both loss of aggrecan and collagen. Additionally, the same collagenase-dependent collagen fragments generated using this in vitro system have also been detected in urine, providing some confidence that this assay may be relevant to what occurs in the whole animal.

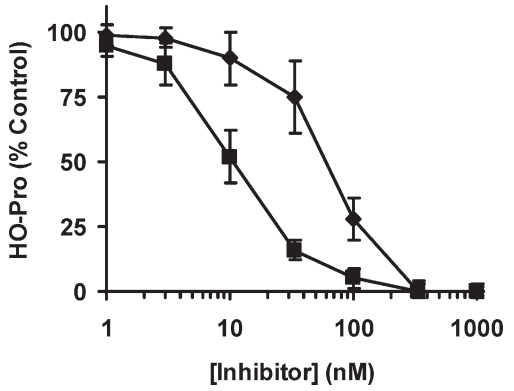


Figure 5. MMP inhibitors protect bovine nasal cartilage from cytokine-induced degradation in the ex vivo cartilage explant assay of Bottomley.[58] Individual uniform cartilage disks were treated with cytokines (IL-1 and oncostatin M) in the presence of **19w** (squares) or **9i** (diamonds). HO-Pro released into the supernatant over 16 days of tissue culture was measured to determine cartilage breakdown, and 0% and 100% degradation were defined as the HO-Pro released from inhibitor-free cartilage without and with cytokine stimulation, respectively. Quantification of HO-Pro release as a function of inhibitor concentration (1 nM to 1 μM) allowed for IC_{50} determinations estimated at 10 nM and 70 nM for **19w** and **9i**, respectively. Each data point represents the average of at least three independent incubations, and error bars indicate the standard deviation of the data for the specific condition.

The α-THP sulfone **9i**, which had an IC_{50} of 0.4 nM when assayed using a purified MMP-13 enzyme preparation and synthetic small molecule as substrate, exhibited an IC_{50} of 70 nM in the BNCD assay (Figure 5). The α-piperidine **19w** was somewhat more potent than α-THP **9i** in both the enzyme (IC_{50} = 0.1 nM) and cartilage explant (IC_{50} = 10 nM) assays. Compound **5**, which was included as a standard in all BNCD assays, had an IC_{50} = 0.6 and 30 nM in the enzyme and explant assays, respectively. A complete understanding of the reduced potency demonstrated by these compounds in the explant system relative to the purified enzyme system is not known. However, this right-shift in potency was a consistent feature of all compounds tested and may represent differences between synthetic and native substrates, ability of inhibitors to reach the target enzyme in the cartilage matrix, or microenvironments in the cartilage that are not represented in the purified system assay.

Further demonstration of the cartilage-protective potential of these compounds was evidenced by a reduction of collagenase-dependent type II collagen fragments excreted in the urine of healthy dogs treated with the α-piperidine sulfone MMP inhibitor **19v** (data not shown). Consistent with the pharmacokinetic properties of this compound in canine, urinary collagen fragment excretion returned to pretreatment levels as inhibitor was cleared.

Inhibition of Postinfarction Left Ventricular Dilation. The effects of α-piperidine **19w** and α-THP **9i** on left ventricular (LV) dilation following myocardial infarction were investigated in a rat model of myocardial infarction (MI). MI was induced by permanent ligation of the left coronary artery as

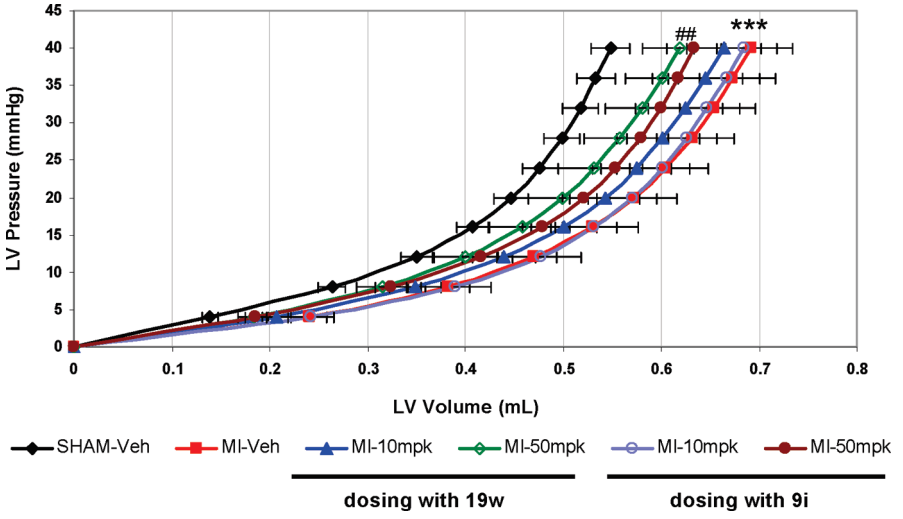


Figure 6. Effect of **19w** and **9i** on LV post-MI. * $p < 0.05$ vs sham-vehicle, # $p < 0.05$ vs MI-vehicle.

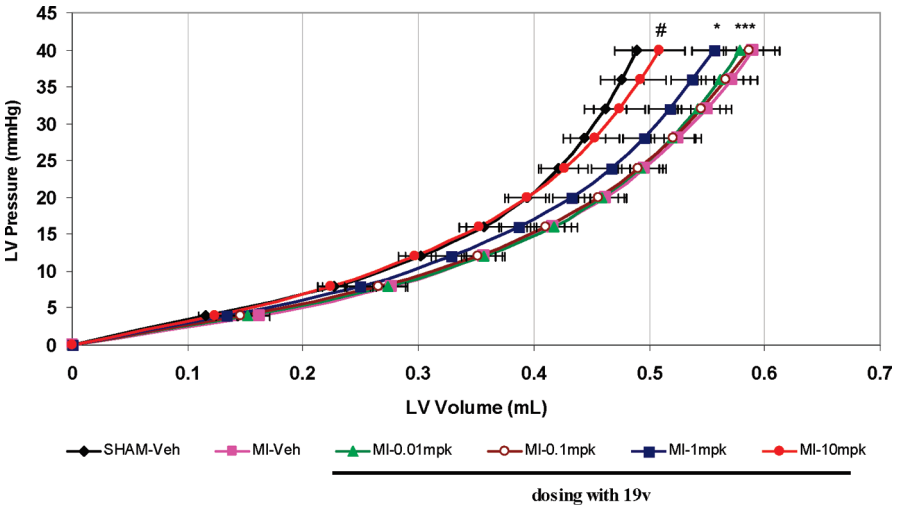


Figure 7. Effect of **19v** on LV post-MI. * $p < 0.05$ vs sham-vehicle, #$p < 0.05$ vs MI-vehicle.

Table 3. Pharmacokinetic Parameters of **19v** After a Single Oral Administration of 20 mg/kg[a]

	T_{max} (hr)	C_{max} (μg/mL)	$AUC_{(0-\infty)}$ (h·μg/mL)	BA (%)
mouse (M)	0.167	26.6	29.3	51.7
mouse (F)	0.167	41.0	36.1	80.8
rat (M)	2.00	42.4	273	66.6
rat (F)	4.00	69.8	668	82.2
dog (M)	0.833 ± 0.167	60.6 ± 5.9	228 ± 41	64.0 ± 6.1
dog (F)	0.500 ± 0.000	68.9 ± 1.2	156 ± 16	69.2 ± 2.1
cyno monkey (M)	1.67 ± 0.33	37.1 ± 2.9	191 ± 35	53.8 ± 0.7

[a] Blood sampled out to 24 h.

previously described.[60] The efficacy of **19w** and **9i** in reducing postinfarction LV dilation was assessed by ex vivo diastolic pressure−volume relationship, a measure of LV size and compliance, as described by Fletcher et al.[61] MMP inhibitors **19w** and **9i** were administered orally at doses of 10 and 50 mg/kg/day (qd) for four weeks. LV dilation was significantly shifted to the right in the MI-vehicle group relative to the sham-vehicle group, indicating significant LV dilation. At an intraventricular pressure of 40 mmHg, the mean LV volume of the MI-vehicle group (0.69 ± 0.02 mL) was significantly greater than the sham-vehicle group (0.55 ± 0.02 mL). Both **19w** and **9i** produced dose-dependent inhibition of postinfarction LV dilation (Figure 6), and 50 mg/kg **19w** and **9i** significantly attenuated LV dilation, with mean LV volumes of 0.62 ± 0.01 mL and 0.63 ± 0.03 mL, respectively ($p < 0.05$ vs MI-vehicle group, 0.69 ± 0.02 mL).

In a separate experiment, the efficacy of **19v** in reducing postinfarction LV dilation was assessed. Compound **19v** was administered orally at doses of 0.01, 0.1, 1, and 10 mg/kg/day (qd) for four weeks following MI. The LV diastolic pressure−volume relationship of the MI-vehicle group was significantly shifted to the right compared to the sham-vehicle group (Figure 7). At an intraventricular pressure of 40 mmHg, the mean LV volume of the MI-vehicle group (0.59 ± 0.02 mL) was significantly greater than that of sham-vehicle group (0.49 ± 0.02 mL). Hydroxamate **19v** produced a dose-dependent inhibition of postinfarction LV dilation. At dose of 10 mg/kg, **19v** significantly attenuated LV dilation, with mean LV volume of 0.51 ± 0.02 mL ($p < 0.05$ vs MI-vehicle group, 0.59 ± 0.02 mL).

Conclusions

Our first-generation MMP-1 sparing hydroxamate development candidate **6** was replaced by *N*-methoxyethyl α-piperidine sulfone **19v**, with *N*-cyclopropylpiperidine hydroxamate **19w** as the backup compound. Compound **6** was ultimately deemed inferior to the compounds described in this manuscript due to its metabolically labile piperidine *N*-propargyl group and diaryl thioether and the presence of vinyl chloride in the final product after final HCl deprotection of the THP-protected hydroxamate. Furthermore, the present diaryl ether compounds were generally superior in potency, selectivity, and pharmaceutical properties.

Compound **19v** is a ca. 100 pM inhibitor of MMP-13 and the gelatinases (MMP-2 and MMP-9), with > 100000-fold selectivity over MMP-1 for MMP-2 and MMP-13 and > 50000-fold selectivity for MMP-9 over MMP-1. We have found that **19v** does not inhibit TNFα release in a cellular assay. The compound has good oral bioavailability (52 to 82%) in the mouse, rat, dog, and cynomolgus monkey (Table 3), including the species used for testing cancer efficacy (tumor bearing mice) and cardiovascular post-MI efficacy (rat). It is rapidly absorbed after oral dosing, with a T_{max} ranging from 10 min (mouse) to 4 h (rat). The elimination half-life ($T_{1/2}$) ranges from 4 to 6 h. Compound **19v** shows dose-dependent inhibition of angiogenesis in the mouse corneal micropocket model with a maximal inhibition of about 60% at 5 mg/kg bid. It also demonstrates dose-dependent inhibition of tumor growth of human prostate PC3 with efficacy that is additive with cisplatin and nearly achieving stasis at the highest dose tested.

Nonetheless, although **19v** caused less joint fibroplasia in rats, the marmoset indicated that MSS would still be an issue clinically, and we realized that an MMP-1 sparing approach was not adequate to provide joint safety. While this side effect is obviously unacceptable for OA, the merits of a short-term regiment post-MI in the prevention of CHF are arguable.

But even for life-threatening cancer, dose limitations and holidays due to MSS have limited the efficacy and effectiveness of MMP inhibitors in the clinic. Specifically, these highly MMP-1-sparing inhibitors were not completely devoid of fibroplasia in either rat or marmoset, consistent with the findings of others.[21] Thus, toward attaining the greatest promise of safety, we turned our attention to even more selective profiles, specifically to a dual-sparing approach, sparing both MMP-1 and MMP-14 (MT-1 MMP), based on the observation that MT-1 MMP knockout mice suffer connective tissue disease due to inadequate collagen turnover[62] and impaired endochondral ossification[63] histologically similar to joint lesions in MSS. We subsequently found that highly selective compounds that spared both MMP-1 and MMP-14 do maintain efficacy in attenuating cardiovascular post-MI hypertrophy as well as maintaining antitumor efficacy, without eliciting a similar joint toxicity, despite the reported potential role for MMP-14 itself in tumor growth, invasion, and neovascularization.[64] Our initial progress toward *dual* MMP-1/14 sparing inhibitors, including modifications in the P′ region incorporating aryl piperidines and isonipecotamide derivatives that are highly selective for MMP-13 and sparing of both MMP-1 and MMP-14, has just been reported,[44,45] and the discovery of joint-safe, dual MMP-1/14-sparing hydroxamate MMPi's with oral antitumor efficacy in mice and the ability to block post-MI LV hypertrophy in rats will be reported in due course.

Experimental Section

General Procedures and Analysis. All solvents and reagents were used without further purification unless otherwise noted. All reactions were performed under an atmosphere of nitrogen or argon. Merck silica gel 60 (230−400 mesh) was used for flash chromatography. Merck Kieselgel 60 F254 DC-Fertigplatten (0.25 mm, Art. 5719) were used for TLC. High performance liquid chromatograms (HPLC) were obtained from YMC AQ C-18 reverse-phase columns. ^{1}H NMR spectra were obtained from either General Electric QE-300 or Bruker-400 MHz Ultrashield spectrometers with tetramethylsilane (TMS) as an internal standard. Noise-decoupled and APT ^{13}C NMR spectra were recorded at 75 MHz on a General Electric QE-300 spectrometer. IR spectra were recorded on a Perkin-Elmer 685 spectrophotometer. High-resolution mass spectra were recorded on a Finnigan MAT8430 instrument. Elemental analyses were conducted on a Control Equipment CEC240-XA instrument. All final products were analyzed for purity by reverse-phase HPLC eluting with a gradient of acetonitrile/water with or without 1% HCl and were determined to be ≥95% pure. All animal procedures were approved the Institutional Animal Care and Use Committee and conform to the NIH Guidelines for the Ethical Care and Treatment of Animals.

Tetrahydro-*N*-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-2*H*-pyran-4-carboxamide (9a). To a stirred solution of α-tetrahydropyranyl 4-fluorophenylsulfone methyl ester **7**, (0.96 g, 3.2 mmol) in DMF-(30 mL) was added phenol (0.3 g, 3.2 mmol), followed by Cs_2CO_3 (3.2 g, 10 mmol). The resulting mixture was heated to 70 °C for 5 h. The solution remained at ambient temperature for 18 h, was diluted with H_2O, and was extracted with EtOAc. The organic layer was washed with half-brine and dried over Na_2SO_4. The solvent was removed by rotary evaporation to yield the desired diaryl ether methyl ester (1.1 g, 92%). Sodium hydroxide (1.0 g, 25 mmol) was added to a solution of the methyl ester (1.1 g, 2.9 mmol) in THF (10 mL) and ethanol (10 mL). The resulting solution was stirred at ambient temperature for 1 h. The solution was then heated to 80 °C for 1 h. The solvent was removed by rotary evaporation, and the resulting sodium salt was acidified with 1 N HCl (50 mL) and extracted with EtOAc. The organic layer was dried over Na_2SO_4. The solvent was removed by rotary evaporation to yield the desired carboxylic acid **8a** (1.1 g, 99%).

To a stirred solution of carboxylic acid **8a** (1.1 g, 3.0 mmol) in DMF (7 mL) was added *N*-hydroxybenzotriazole−H_2O (0.623 g, 4.6 mmol), followed by EDC (0.634 g, 3.3 mmol). After 10 min, a 50% aqueous hydroxylamine solution was added (2 mL, 30 mmol) and the solution was stirred at ambient temperature for 18 h. The solution was diluted with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with water and followed by half-brine and then dried over Na_2SO_4. Reverse phase chromatography (on silica, acetonitrile/H_2O) provided the hydroxamate **9a** as a white solid (0.37 g, 33%). HRMS (ES+) MH^+ for $C_{18}H_{19}NO_6S$, 378.1011; found, 378.0994.

4-[[4-(3-Chlorophenoxy)phenyl]sulfonyl]tetrahydro-*N*-hydroxy-2*H*-pyran-4-carboxamide (9b). Fluorophenylsulfone THP-protected hydroxamate **10** was prepared from methyl ester **7** by hydrolysis with trimethylsilanoate followed by coupling with *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine and EDC as previously described.[42] To a solution of fluorophenylsulfone **10** (5.0 g, 13 mmol) in DMF (20 mL) was added *m*-chlorophenol (5.0 g, 39 mmol), followed by Cs_2CO_3 (17 g, 52 mmol). The resulting solution was heated to 95 °C for 7 h. The solution was maintained at ambient temperature for 7 h, diluted with water, and extracted with EtOAc. The organic layer was washed with half-brine and dried over Na_2SO_4. The solution was concentrated by rotary evaporation. Chromatography (on silica, EtOAc/hexane) provided the *m*-chloro phenoxyphenyl THP-protected hydroxamate compound **11b** (5.2 g, 82%).

To a solution of the *m*-chloro phenoxyphenyl THP-protected hydroxamate **11b** (5.2 g, 10 mmol) in dioxane (5 mL) was added 4N HCl in dioxane (5 mL, 20 mmol), followed by methanol (10 mL). The resulting solution was stirred at ambient temperature for 1 h. The solvent was removed by rotary evaporation to provide the hydroxamate **9b** as a white solid (3.4 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1 H), 9.18 (d, J = 1.56 Hz, 1 H), 7.73 (d, J = 8.99 Hz, 2 H), 7.51 (t, J = 8.20 Hz, 1 H), 7.36 (d, J = 8.99 Hz, 1 H), 7.32 (t, J = 2.15 Hz, 1 H), 7.18 (d, J = 8.99 Hz, 2 H), 7.15 (dd, J = 7.81, 1.95 Hz, 1 H), 3.88 (dd, J = 11.53, 3.71 Hz, 2 H), 3.16 (t, J = 11.33 Hz, 2 H), 2.22 (d, J = 12.50 Hz, 2 H), 1.83−1.98 (m, 2 H). HRMS (ES+) M·NH_4^+ calcd for $C_{18}H_{18}NO_6SCl$, 429.0887; found, 429.0880. HRMS MH^+ calcd for $C_{18}H_{18}NO_6SCl$, 412.0622; found, 412.0615.

4-{[4-(4-Chlorophenoxy)phenyl]sulfonyl}-*N*-hydroxytetrahydro-2*H*-pyran-4-carboxamide (9c). The α-THP *p*-chlorophenyloxyphenylsulfone **9c** was prepared as previously described.[42]

4-[[4-(3,4-Dichlorophenoxy)-phenyl]sulfonyl]-tetrahydro-*N*-hydroxy-2*H*-pyran-4-carboxamide (9d). To a solution of fluorophenylsulfone **10** (3.1 g, 8 mmol) in *N*,*N*-DMAC (20 mL) were added Cs_2CO_3 (8.8 g, 27 mmol) and 3,4-dichlorophenol (2.61 g, 16 mmol). The slurry was stirred at 95 °C for 41 h. The reaction was concentrated in vacuo, and the residue was taken up in EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Chromatography (on silica, EtOAc/hexanes) provided the substituted THP-protected hydroxamate **11d** as a white foam (4.17 g, 98%). MS (ES+) M·NH_4^+ calcd for $C_{23}H_{25}NO_7SCl_2$, 547.11; found, 547.10.

To a slurry of the THP-protected hydroxamate **11d** (3.5 g, 6.6 mmol) in dioxane (20 mL) were added a 4N HCl dioxane solution (20 mL) and methanol (20 mL). After 15 min at ambient temperature, the reaction was diluted with EtOAc and washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydroxamate **9d** as a white solid (2.98 g, 100%). MS (ES+) M·NH_4^+ calcd for $C_{18}H_{17}NO_6SCl_2$, 463.05; found, 463.05.

***N*-Hydroxy-4-{[4-(4-hydroxyphenoxy)phenyl]sulfonyl}tetrahydro-2*H*-pyran-4-carboxamide (9e).** To a solution of fluorophenylsulfone **10**[42] (2.7 g, 7.0 mmol) in DMAC (20 mL) was added

Cs_2CO_3 (6.84 g, 21 mmol) and 4-(benzyloxy)phenol (2.8 g, 14 mmol). The slurry was stirred at 95 °C for 6 h. The reaction was concentrated in vacuo and the residue was taken up in EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated. Chromatography on silica gel eluting with EtOAc/hexanes provided the diaryl ether **11e** as a white foam (3.94 g, 99%). MS (ES+) $M \cdot NH_4^+$ calcd for $C_{30}H_{33}NO_8S$, 585.23; found, 585.23.

To a solution of the THP-protected hydroxamate **11e** (1.5 g, 2.64 mmol) in glacial acetic acid (5 mL) was added concentrated HCl (5 mL) and the reaction was heated to 60 °C for 20 min. The reaction was cooled, diluted with water (100 mL), and extracted with EtOAc. The EtOAc extract was washed successively with water (3×) and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give hydroxamate **9e** as a white solid (810 mg, 78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (1H br s), 9.54 (1H, s), 9.16 (1H, s), 7.59−7.82 (2H, m), 6.95−7.14 (4H, m), 6.77−6.95 (2H, m), 3.86 (2H, dd, J = 11.4 Hz), 3.15 (2H, t, J = 11.6 Hz), 2.20 (2H, d, J = 13.1 Hz), 1.76−1.96 (2H, m). MS (ES+) $M \cdot MH_4^+$ calcd for $C_{18}H_{19}NO_7S$, 468.15; found, 468.15. HRMS MH^+ calcd for $C_{18}H_{19}NO_7S$, 394.0960; found, 394.0962.

***N*-Hydroxy-4-{[4-(4-isopropoxyphenoxy)phenyl]sulfonyl}-tetrahydro-2*H*-pyran-4-carboxamide (9f).** To a solution fluorophenylsulfone **10**[42] (3.1 g, 8.0 mmol) in DMAC (20 mL) was added Cs_2CO_3 (7.28 g, 24 mmol) and 4-isopropoxyphenol (2.4 g, 16 mmol). The slurry was stirred at 95 °C for 21 h. The reaction was concentrated in vacuo. The residue was taken up in EtOAc, washed successively with water (3×) and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc/hexanes provided the diaryl ether **11f** as an off-white foam (3.65 g, 88%). MS (IS+) MH^+ calcd for $C_{26}H_{33}NO_8S$, 520.20; found, 520.20.

To a solution of the THP-protected hydroxamate **11f** (3.5 g, 6.7 mmol) in 1,4-dioxane (17 mL) was added 4N HCl in dioxane (17 mL) and methanol (17 mL). After 15 min at rt, the reaction was diluted with EtOAc and washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give the hydroxamate **9f** as an off-white solid (2.2 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (1H, s), 9.16 (1H, s), 7.58−7.78 (2H, m), 6.93−7.23 (6H, m), 4.60 (1H, dt, J = 11.9 Hz), 3.86 (2H, dd, J = 11.5 Hz), 3.15 (2H, t, J = 11.6 Hz), 2.21 (2H, d, J = 12.9 Hz), 1.87 (2H, td, J = 4.5 Hz), 1.25−1.40 (2H, m). MS (ES+) MH^+ calcd for $C_{21}H_{25}NO_7S$, 436.14; found, 436.14. HRMS calcd for $C_{21}H_{25}NO_7S$, 436.1430, found, 436.1431.

4-[[4-([1,1′-Biphenyl]-4-yloxy]phenyl)sulfonyl]tetrahydro-*N*-hydroxy-2*H*-pyran-4-carboxamide (9g). To a solution of fluorophenylsulfone **9** (2.0 g, 5.2 mmol) in DMAC (8 mL) was added 4-phenylphenol (1.3 g, 7.8 mmol) followed by Cs_2CO_3 (6.8 g, 20.8 mmol). The reaction was heated at 95 °C for 5 h. Stripping the DMAC in vacuo afforded a brown solid (5.3 g, 100%). Preparative reverse-phase chromatography on a C-18 column eluting with acetonitrile/water gave the THP-protected biphenyl product **11g** in solution. To this solution of **11g** in acetonitrile/water (50 mL) was slowly added 10% HCl aq (100 mL). After stirring overnight for 18 h, the acetonitrile was removed in vacuo. The resultant precipitate was collected, giving the hydroxamate **9g** as a white solid (2.0 g, 83%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.75−1.99 (2H, m), 2.21 (2H, d, J = 12.9 Hz), 3.15 (2H, t, J = 11.3 Hz), 7.11−7.31 (2H, m) 3.85 (2H, d), 7.31−7.52 (2H, m), 7.61−7.82 (6H, m), 10.97 (1H, br s). MS (FAB) MH^+ calcd for $C_{24}H_{23}NO_6$, 454; found, 454.

***N*-Hydroxy-4-({4-[3-(trifluoromethyl)phenoxy]phenyl}sulfonyl)-tetrahydro-2*H*-pyran-4-carboxamide (9h).** To a solution of fluorophenylsulfone **10**[42] in DMAc (20 mL) was added $CsCO_2$ (7.28 g, 24 mmol) and *m*-(trifluoromethyl)phenol (1.95 mL, 16 mmol). The slurry was stirred at 95 °C for 20 h. After the reaction mixture was concentrated, the residue was dissolved in EtOAc and washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc/hexane provided the diaryl ether **11h** as a white foam (4.1 g, 97%). HRMS (ES+) MH^+ calcd for $C_{24}H_{26}NO_7SF_3$, 530.15; found, 530.14.

To a solution of the THP-protected hydroxamate **11h** (3.9 g, 7.4 mmol) in 1,4-dioxane (20 mL) was added 4N HCl in dioxane (20 mL) and methanol (20 mL). After 15 min at rt, the reaction was diluted with EtOAc and washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was crystallized from acetone/hexanes to give the hydroxamate **9h** as a white solid (1.9 g, 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (1H, s), 9.18 (1H, s), 7.69−7.82 (3H, m), 7.63−7.69 (1H, m), 7.58 (1H, s), 7.49 (1H, d, J = 8.0 Hz), 7.17−7.25 (2H, m), 3.88 (2H, dd, J = 11.5 Hz), 3.16 (2H, t, J = 11.6 Hz), 2.22 (2H, d, J = 12.9 Hz), 1.90 (2H, td). HRMS (ES+) MH^+ calcd for $C_{19}H_{18}N_3O_6SF_3$, 446.09; found, 446.09. HRMS calcd for $C_{19}H_{18}N_3O_6SF_3$, 446.0885; found, 446.0872.

***N*-Hydroxy-4-({4-[4-(trifluoromethyl)phenoxy]phenyl}sulfonyl)-tetrahydro-2*H*-pyran-4-carboxamide (9i).** According to the general method of Samaritoni[43] in dry equipment under nitrogen, sodium hydride (60% oil dispersion, 11.0 g, 0.275 mol) was added to a solution of 4-[4-(trifluoromethyl)phenoxy]-phenol **12** (50.0 g, 0.197 mol) in dry DMF (150 mL) at 0 °C. After 15 min, a solution of dimethylthiocarbamoyl chloride (32.0 g, 0.259 mol) in dry DMF (100 mL) was added. The reaction was stirred at rt for 16 h. The reaction was poured onto 10% aqueous HCl (1 L). Vacuum filtration of the resulting precipitate provided the thiono compound as a white solid (67.0 g, 100%). The thiono derivative (67 g, 0.20 mol) was heated to 317 °C for 30 min behind a safety shield. The reaction temperature rose to 330 °C. The heat was removed, and the reaction was allowed to cool to rt to yield the thiocarbamate as a brown solid (67 g, 100%). To a solution of the thiocarbamate (65.0 g, 0.19 mol) in methanol (510 mL) with a subsurface nitrogen stream was added 2.5N NaOH solution (160 mL, 0.40 mol). The slurry was stirred at 74 °C for 2 h. The reaction was cooled and the methanol removed in vacuo to yield the crude 4-[4-(trifluoromethoxy)phenoxy]-benzenethiol **13**.

The crude sample of thiol **13** was diluted with water (100 mL) and extracted with diethyl ether (4×). A subsurface stream of nitrogen was added to the aqueous solution, and sodium chloroacetate (22.2 g, 0.19 mol) was added. The reaction was stirred at rt, and after 30 min the nitrogen stream was removed. After 12 h, the solution was cooled and 6N HCl was added until pH = 1. The slurry was extracted with EtOAc (4×), and the combined extracts were washed with 0.1N HCl, water, and brine, and dried over Na_2SO_4 and filtered. Concentration in vacuo gave the arylthioacetic acid as a tan solid (61.0 g, 98%). To a solution of the thioacetic acid (54.45 g, 0.166 mol) in THF (370 mL) was added water (45 mL) and potassium peroxymonosulfate (306 g, 0.498 mol) at rt. An exotherm to 42 °C was noted. After 2 h, the reaction was filtered and the filter cake was washed well with THF and then water (250 mL) was added to the filtrate. The filtrate was concentrated in vacuo. The slurry was extracted with EtOAc (4×). The combined extracts were washed with water three times and then brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the sulfone **14** as a beige solid (60.0 g, 100%).

A solution of the sulfone **14** (119.5 g, 0.332 mol) in methanol (660 mL) and 4N HCl in dioxane (20 mL) was stirred at rt for 12 h. The reaction was heated to reflux and then cooled to rt. The resulting crystals were filtered, washed well with cold methanol, and then dried to give the methyl ester as a white solid (89.4 g, 72%).

To a solution of the methyl ester (64.5 g, 0.180 mol) in DMF (360 mL) was added K_2CO_3 (66.8 g, 0.48 mol), bis(2-bromoethyl)ether (40 mL, 0.305 mol), 4-dimethylaminopyridine (1.1 g, 9 mmol), and tetrabutylammonium bromide (2.9 g, 9 mmol). The reaction was stirred overnight at rt. The reaction was slowly poured into 1N HCl (500 mL). The resulting precipitate was

filtered and then washed with water and then with hexanes. The solid was recrystallized from methanol to give the pyran methyl ester as a white solid (62.8 g, 79%). MS (ES+) $M \cdot MH_4^+$ calcd for $C_{20}H_{19}O_6SF_3$, 462.12; found, 462.12.

In dry equipment under an atmosphere of nitrogen, the pyran (64.0 g, 0.144 mol) was dissolved in dry THF (250 mL) and a solution of potassium trimethylsilanoate (55.9 g, 0.432 mol) in dry THF (40 mL) was added at rt. After 2 h, water (200 mL) was added and the solution was concentrated in vacuo. The slurry was extracted with EtOAc to remove unreacted starting material. The aqueous solution was treated with 6N HCl until pH = 1. The slurry was extracted with EtOAc, and the combined extracts were washed with water and brine and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was heated in diethyl ether, and the resulting solid filtered and dried to give the carboxylic acid **8i** as a white solid (56.3 g, 91%). HRMS (ES+) $M \cdot NH_4^+$ calcd for $C_{19}H_{17}O_6SF_3$, 448.10; found, 448.10.

To a solution of the carboxylic acid **8i** (49.0 g, 0.114 mol) in dry DMF (280 mL) was added HOBt hydrate (18.5 g, 0.137 mol), NMM (37.5 mL, 0.342 mol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (41.3 g, 0.353 mol), and EDC (30.6 g, 0.160 mol). After 4 h at rt, the reaction was concentrated in vacuo. The residue was taken up in EtOAc, washed with water, 5% aqueous $KHSO_4$, saturated $NaHCO_3$, and brine and dried over Na_2SO_4, filtered, and concentrated to give the THP-protected hydroxamate **11i** as a white foam (62.6 g, 100%). MS (ES+) $M \cdot NH_4^+$ calcd for $C_{24}H_{26}NO_7SF_3$, 547.17; found, 547.17.

To a solution of the THP-protected hydroxamate **11i** (58.5 g, 0.11 mol) in 1,4-dioxane (280 mL) was added 4N HCl in dioxane (280 mL) and methanol (280 mL). After 15 min at rt, the reaction was diluted with EtOAc and washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give compound **9i** as a white solid (42.79 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (1H, s), 9.19 (1H, d, J = 1.2 Hz), 7.68−7.94 (4H, m), 7.19−7.44 (4H, m), 3.88 (2H, dd, J = 11.4, 3.2 Hz), 3.16 (2H, t, J = 11.7 Hz), 2.23 (2 H, d, J = 13.3 Hz), 1.84−2.00 (2 H, m). MS (ES+) $M \cdot NH_4^+$ calcd for $C_{19}H_{18}NO_6SF_3$, 463; found, 463. HRMS MH^+ calcd for $C_{19}H_{18}NO_6SF_3$, 446.0885; found, 446.0871.

***N*-Hydroxy-4-({4-[4-(trifluoromethoxy)phenoxy]phenyl}sulfonyl)-tetrahydro-2*H*-pyran-4-carboxamide (9j).** To a solution of fluorophenylsulfone **10** (3.1 g, 8 mmol) in DMAC (20 mL) were added Cs_2CO_3 (8.8 g, 27 mmol) and *p*-(trifluoromethoxy)phenol (2.1 mL, 16 mmol). The slurry was stirred at 95 °C for 19 h. The reaction was concentrated in vacuo. The residue was taken up in EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Chromatography on silica eluting with EtOAc/hexanes provided the THP-protected hydroxamate **11j** as a white foam (4.2 g, 96%). MS (ES+) MH^+ calcd for $C_{24}H_{26}NO_8SF_3$, 546.14; found, 546.14.

To a slurry of the THP-protected hydroxamate **11j** (4.0 g, 7.3 mmol) in 1,4-dioxane (20 mL) were added a 4N HCl dioxane solution (20 mL) and methanol (20 mL). After 15 min at ambient temperature, the reaction was diluted with EtOAc and washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give the hydroxamate **9j** as a white solid (2.2 g, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (1H, br s), 9.19 (1H, br s), 7.73 (2H, d, J = 8.8 Hz), 7.49 (2H, d, J = 8.8 Hz), 7.26−7.43 (2H, m), 7.18 (2H, d, J = 9.0 Hz), 3.87 (2H, dd, J = 3.8 Hz), 3.16 (2H, t, J = 11.6 Hz), 2.22 (2H, d, J = 12.9 Hz), 1.89 (2H, td). MS (ES+) $M \cdot NH_4^+$ calcd for $C_{19}H_{18}NO_7SF_3$, 479.11; found, 479.11. HRMS MH^+ calcd for $C_{19}H_{18}NO_7SF_3$, 462.0834; found, 462.0815.

***N*-Hydroxy-4-({4-[4-(methylthio)phenoxy]phenyl}sulfonyl)-tetrahydro-2*H*-pyran-4-carboxamide (9k).** To a solution of fluorophenylsulfone **10**[42] (3.1 g, 8.0 mmol) in DMAC (20 mL) was added Cs_2CO_3 (7.28 g, 24 mmol) and 4-(methylthio)phenol (2.24 g, 16 mmol). The slurry was stirred at 95 °C for 24 h. The reaction was concentrated in vacuo, and the residue was taken up in EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc/hexanes provided the diaryl ether **11k** as a white foam (4.1 g, 100%). MS (ES+) calcd for $C_{24}H_{29}NO_7S_2$, 208.15; found, 508.15.

To a solution of the THP hydroxamate **11k** (4.0 g, 7.9 mmol) in 1,4-dioxane (20 mL) was added 4N HCl in dioxane (20 mL) and methanol (20 mL). After 15 min at rt, the reaction was diluted with EtOAc and washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was recrystallized (acetone/hexanes) to give the hydroxamate **9k** as a white solid (1.9 g, 57%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (1H, br s), 7.62−7.81 (2H, m) 9.17 (1H, s), 7.32−7.51 (2H, m), 7.03−7.26 (4H, m), 3.87 (2H, dd, J = 3.7 Hz), 3.15 (2H, t, J = 11.6 Hz), 2.50 (3H, s), 2.21 (2H, d, J = 12.9 Hz), 1.74−2.03 (2H, m). HRMS (ES+) MH^+ calcd for $C_{19}H_{21}NO_6S_2$, 424.09; found, 424.09. HRMS MH^+ calcd for $C_{19}H_{21}NO_6S_2$, 424.0889; found, 424.0874.

***N*-Hydroxy-4-[(4-{4-[(trifluoromethyl)thio]phenoxy}phenyl)-sulfonyl]tetrahydro-2*H*-pyran-4-carboxamide (9l).** To a solution of fluorophenylsulfone **10**[42] (2.0 g, 5.2 mmol) in DMAC (6 mL) was added 4-(trifluoromethylthio)thiophenol (1.5 g, 7.8 mmol) followed by Cs_2CO_3 (6.8 g, 20.8 mmol). After adding a catalytic amount of potassium fluoride, the reaction was heated at 95 °C for 12 h. The DMAC was removed in vacuo to afford the diaryl ether **11l** as a brown solid (7.2 g, 100%).

To the crude THP-protected diaryl ether **11l** (7.2 g, 5.2 mmol) in acetonitrile/water (50 mL) was slowly added 10% aqueous HCl (100 mL). After stirring for 18 h at rt, the acetonitrile was removed in vacuo. The resultant precipitate was collected by filtration to afford hydroxamate **11l** as a tan solid (0.60 g, 24%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88−11.06 (1H, m), 9.19 (1H, d, J = 2.0 Hz), 7.63−7.94 (4H, m), 7.16−7.36 (4H, m), 3.88 (2H, dd, J = 11.5, 4.3 Hz), 3.05−3.22 (2H, m), 2.23 (2H, d, J = 13.5 Hz), 1.79−1.99 (2H, m). MS (FAB) calcd for $C_{19}H_{18}F_3NO_6S$, 476; found, 476. HRMS MH^+ calcd for $C_{19}H_{18}F_3NO_6S$, 478.0606; found, 478.0615.

4-Pyridyl *N*-hydroxy-4-(4-(pyridin-4-yloxy)phenylsulfonyl)-tetrahydro-2*H*-pyran-4-carboxamide (9m). Pyridyloxyphenyl sulfone hydroxamate **9m** was prepared from fluorophenylsulfone **10** according to the general method of **9l** to afford the desired hydroxamate **9m** as a colorless foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.08 (1H, s), 9.25 (1H, d, J = 1.9 Hz), 8.12 (2H, d, J = 8.2 Hz), 7.78−7.91 (4H, m), 6.29 (2H, d, J = 7.8 Hz), 3.89 (2H, dd, J = 11.9, 3.7 Hz), 3.17 (2H, t, J = 11.7 Hz), 2.24 (2H, d, J = 12.9 Hz), 1.89−2.02 (2H, m). HRMS calcd for $C_{17}H_{18}N_2O_6S$, 378.0886; found, 379.0970.

***N*-Hydroxy-4-(4-(4-methoxyphenoxy)phenylsulfonyl)-1-(prop-2-ynyl)piperidine-4-carboxamide (19a).** To a solution of *N*-propargyl piperidine 4-fluorophenylsulfone ethyl ester **22a**[42] (3.00 g, 5.66 mmol) in DMF (10 mL) was added Cs_2CO_3 (4.7 g, 14.5 mmol) and 4-methoxyphenol (1.80 g, 14.5 mmol) and the solution was heated to 95 C for 24 h. The solution was diluted with EtOAc and washed successively with 1N NaOH and brine and then dried over $MgSO_4$. Concentration and chromatographic purification of the residue afforded the methoxyphenyl ether **20a** as a solid (2.67 g, 100%).

To a solution of the phenoxy ether **20a** (2.40 g, 5.25 mmol) in ethanol (30 mL) and H_2O (6 mL) was added KOH (2.0 g, 31.37 mmol), and the solution was heated to reflux for 4 h. The solution was then cooled and acidified with conc HCl to pH = 3, and the resulting precipitate was collected by vacuum filtration to provide the crude acid **17a** that was carried on without additional purification.

To a solution of the carboxylic acid **17a** (2.25 g, 5.25 mmol) in acetonitrile (30 mL) was added triethylamine (1 mL) and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (1.34 g, 9.0 mmol). After the solution was stirred for 15 min, EDC (1.72 g, 9.0 mmol) was added and the solution was stirred at rt for 18 h. The solution was concentrated in vacuo, and the residue was dissolved in EtOAc and washed successively with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over $MgSO_4$. After concentration the resulting residue was chromatographed on silica

gel eluting with EtOAc/hexane to afford the THP-protected hydroxamate **18a** as a white solid (0.93 g, 33%).

To a solution of the THP-protected hydroxamate **18a** (0.93 g, 1.7 mmol) in methanol (15 mL) was added acetyl chloride (0.36 mL, 5.1 mmol) and the solution was stirred for 3 h. The solution was concentrated in vacuo to provide the hydroxamate **19a** as a white solid (650 mg, 82%). MS MH^+ calcd for $C_{22}H_{24}N_2O_6S$, 445; found, 445. Anal. calcd for $C_{22}H_{24}N_2O_6S \cdot HCl$: C, 54.84; H, 5.24; N, 5.82; S, 6.67; Cl, 6.67. Found: C, 53.10; H, 5.07; 5.59; S, 7.04; Cl, 6.32.

***N*-Hydroxy-4-{[4-(4-methoxyphenoxy)phenyl]sulfonyl}-1-(pyridin-2-ylmethyl)piperidine-4-carboxamide (19b).** To a solution of *N*-BOC 4-fluorophenylsulfone ethyl ester **15**[42] (2.31 g, 4.0 mmol) in 1,4-dioxane (5 mL) was added 4N HCl in 1,4-dioxane (5 mL), and the solution was stirred for 2 h at rt. The solution was then diluted with ethyl ether, and the resulting precipitate was collected by vacuum filtration to provide the deprotected piperidine hydrochloride salt **21** (2.1 g, 100%). The piperidine hydrochloride salt **21** (2.01 g, 5.76 mmol) was combined with K_2CO_3 (2.48 g, 18 mmol), 2-(chloromethyl)pyridine hydrochloride (1.00 g, 6.1 mmol), and DMF(12 mL) and heated at 40 °C for 24 h. The mixture was taken up in water (80 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography, the desired *N*-pyridylmethyl piperidine **22b** (2.30 g, 98%).

The pyridinyl ester **22b** (5.66 mmol, 2.30 g), K_2CO_3 (9.0 mmol, 1.29 g), 4-hydroxyanisole (9 mmol, 1.12 g), and DMF(3 mL) were heated at 75−80 °C for 24 h. The reaction was judged to be incomplete based on TLC, so an additional 350 mg of base and 300 mg of the phenol were added, and stirring was continued at ambient temperature for 2 d. The reaction was then taken up in water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were concentrated. The residue was purified by chromatography, affording the diaryl ether **20b** as an oil (2.85 g, 100%).

The ethyl ester **20b** (5.7 mmol, 2.85 g) was heated at reflux in the presence of KOH (40 mmol, 2.24 g) in ethanol (18 mL) and water (6 mL) for 4.5 h. The mixture was allowed to cool, acidified to ∼pH 3 with HCl, and concentrated and azeotroped to dryness using acetonitrile. This crude acid (∼5.7 mmol) was combined with *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (7 mmol, 0.82 g), HOBt (7 mmol, 0.945 g), NMM (1 mL), and EDC (7 mmol, 1.34 g) in the presence of DMF (21 mL). After 16 h of stirring, the mixture was diluted with 200 mL of EtOAc and was washed with 50% saturated $NaHCO_3$ (100 mL). The aqueous layer was extracted with additional EtOAc (50 mL), and the combined organic layer was dried over $MgSO_4$. Concentration and chromatography afforded the desired THP-protected hydroxamate **18b** as a yellow oil (2.82 g, 85%).

The THP-protected hydroxamate **18b** (2.82 g, 5.0 mmol) was dissolved in dry methanol (20 mL). Acetyl chloride (30 mmol, 2.1 mL) was added over several minutes. The solution was stirred for 4 h at ambient temperature. Concentration afforded 2.59 g of crude product, which was recrystallized from ethanol/water, yielding the first crop of hydroxamate **19b** (525 mg, 18%). MS (EI) MH+ calcd for $C_{25}H_{27}N_3O_6S$, 498; found, 498. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (1H, br s), 10.62 (1H, s), 8.66 (1H, d, J = 4.3 Hz), 7.87−7.97 (1H, m), 7.72 (2H, d, J = 9.0 H), 7.56 (1H, d, J = 7.8 Hz), 7.45−7.52 (1H, m), 7.10−7.19 (2H, m), 7.01−7.10 (4H, m), 4.45 (2H, s), 3.79 (3H, s), 3.50 (2H, d, J = 12.1 Hz), 2.90 (2H, t, J = 12.1 Hz), 2.52−2.56 (2H, m), 2.29 (2H, t, J = 12.9 Hz). Anal. Calcd for $C_{25}H_{27}N_3O_6S \cdot 2HCl \cdot 1.5H_2O$: C, 50.17; H, 5.18; N, 7.02. Found: C, 50.45; H, 5.13; N, 7.02. HRMS MH^+ calcd for $C_{25}H_{27}N_3O_6S$, 498.1699; found, 498.1688.

1-Cyclopropyl-4-{[4-(4-ethoxyphenoxy)phenyl]sulfonyl}-*N*-hydroxypiperidine-4-carboxamide (19c). To a solution of *N*-BOC 4-fluorophenylsulfone ethyl ester **15**[42] (8.0 g, 19.2 mmol) in DMF (30 mL) was added K_2CO_3 (4.00 g, 28.8 mmol) and 4-ethoxyphenol (3.99 g, 28.8 mmol). The solution was stirred at 90 °C for 24 h. The solution was diluted with H_2O (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with 10% EtOAc/hexane provided the desired ester **16c** as an oil (9.62 g, 94%). MS MH^+ calcd for $C_{27}H_{35}NSO_8$, 534.2162; found, 534.2175. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, J = 6 Hz), 7.01 (2H, d, J = 6 Hz), 6.99 (2H, d, J = 6 Hz), 6.94 (2H, d, J = 6 Hz), 4.21 (2H, q, J = 7 Hz), 4.05 (2H, q, J = 7 Hz), 2.62 (2H, br m), 2.32 (2H, br m), 2.02 (4H, m), 1.46 (9H, s), 1.43 (3H, t, J = 7 Hz), 1.26 (3H, t, J = 7 Hz).

To a solution of *N*-BOC ethyl ester **16c** (9.62 g, 18 mmol) in EtOAc (100 mL) cooled to 0 °C was bubbled gaseous HCl for 5 min. The reaction was stirred at this temperature for 0.5 h. The solution was then concentrated in vacuo to give the hydrochloride salt (8.1 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (2H, br s), 7.70 (2H, d, J = 6 Hz), 7.02 (2H, d, J = 6 Hz), 7.00 (2H, d, J = 6 Hz), 6.94 (2H, d, J = 6 Hz), 4.22 (2H, q, J = 7 Hz), 4.04 (2H, q, J = 7 Hz), 3.64 (2H, m), 2.85 (2H, m), 2.55 (4H, m), 1.43 (3H, t, J = 7 Hz), 1.26 (3H, t, J = 7 Hz). HRMS MH^+ calcd for $C_{22}H_{27}NSO$, 434.1637; found, 434.1637.

To a solution of the hydrochloride salt (8.1 g, 17.2 mmol) in methanol (70 mL) was added acetic acid (9.86 mL, 172 mmol), a portion of 4 Å molecular sieves (ca. 2 g), (1-ethoxycyclopropyl)-oxytrimethyl silane (20.7 mL, 103 mmol), and sodium cyanoborohydride (4.86 g, 77.4 mmol), and the solution was refluxed for 8 h. The precipitate was removed by filtration, and the filtrate was concentrated in vacuo. The residue was diluted with H_2O (400 mL) and extracted with EtOAc. The organic layer was washed with 1 N NaOH and brine, and dried over $MgSO_4$, filtered, and concentrated in vacuo. Trituration with diethyl ether provided the desired cyclopropyl amine **20c** as a white solid (6.84 g, 84%). DSC 146.95−150.60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (2H, d, J = 6 Hz), 7.00 (2H, d, J = 6 Hz), 6.98 (2H, d, J = 6 Hz), 6.92 (2H, d, J = 6 Hz), 4.21 (2H, t, J = 7 Hz), 4.04 (2H, t, J = 7 Hz), 3.05 (2H, m), 2.32 (2H, m), 2.09 (4H, m), 1.53 (1H, m), 1.43 (3H, t, J = 7 Hz), 1.27 (3H, t, J = 7 Hz), 0.42 (2H, m), 0.37 (2H, m).

To a solution of cyclopropyl amine **20c** (6.84 g, 14.0 mmol) in ethanol (50 mL) and tetrahydrofuran (50 mL) was added a solution of NaOH (5.60 g, 140 mmol) in water (30 mL), and the solution was heated at 60 °C for 18 h. The solution was concentrated in vacuo, and the aqueous residue was acidified to pH = 3. Filtration gave the carboxylic acid **17c** (6.07 g, 88%). MS MH^+ calcd for $C_{22}H_{27}NSO_6$, 446; found, 446. Anal. Calcd for $C_{23}H_{27}NSO_6 \cdot 0.5HCl$: C, 59.57; H, 5.98; N, 3.02. Found: C, 59.33; H, 5.35; N, 2.98.

To a solution of carboxylic acid **17c** (6.07 g, 12.6 mmol) in DMF (60 mL) was added 1-HOBt (2.04 g, 15.1 mmol), NMM (4.15 mL, 37.8 mmol), and *O*-tetrahydropyranyl hydroxyl amine (2.21 g, 18.9 mmol) followed by EDC (3.38 g, 17.6 mmol). The solution was stirred at ambient temperature for 18 h. The solution was diluted with H_2O (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with 60% EtOAc/hexane provided the desired THP-protected hydroxamate **18c** as a white foam (6.29 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (1H, s), 7.73 (2H, d, J = 6 Hz), 7.02 (2H, d, J = 6 Hz), 6.98 (2H, d, J = 6 Hz), 6.93 (2H, d, J = 6 Hz), 5.01 (1H, t, J = 1 Hz), 4.05 (2H, q, J = 7 Hz), 4.01 (1H, m), 3.70 (1H, m), 3.01 (2H, m), 2.34 (2H, m), 2.14 (4H, m), 1.88 (2H, m), 1.81 (2H, m), 1.60 (2H,), 1.44 (3H, t, J = 7 Hz), 0.42 (2H, m), 0.37 (2H, m). HRMS MH^+ calcd for $C_{28}H_{36}N_2SO_7$, 545.2321; found, 545.2316.

To a solution of the THP-protected hydroxamate **18c** (2.84 g, 5.0 mmol) in 1,4-dioxane (40 mL) was added 4 N HCl/dioxane (30 mL). After stirring at ambient temperature for 2.5 h, the solution was concentrated in vacuo. Trituration of the resulting solid with diethyl ether and filtration gave the hydroxamate **19c** as a white solid (2.33 g, 90%). DSC 223.15−229.94 °C at 442.3 J/g. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (1H, br s), 9.31 (1H, s),

7.70 (2H, d, J = 8.7 Hz), 7.11 (2H, d, J = 7.8 Hz), 7.06 (2H, d, J = 7.8 Hz), 7.06 (2H, d, J = 7.8 Hz), 7.02 (2H, d, J = 8.7 Hz), 4.04 (2H, q, J = 7 Hz), 3.59 (2H, m), 3.28 (2H, m), 2.95 (4H, m), 2.20 (1H, m), 0.97 (2H, m), 0.76 (2H, m). HRMS M^+ calcd for $C_{23}H_{28}N_2SO_6$, 460.1677; found, 460.1678. Anal. Calcd for $C_{23}H_{28}N_2SO_6 \cdot HCl$: C, 55.58; H, 5.88; N, 5.64; Cl, 7.13; S, 6.45. Found: C, 55.22; H, 5.73; N, 5.59; Cl, 7.49; S, 6.64.

***N*-Hydroxy-4-{[4-(4-isopropylphenoxy)phenyl]sulfonyl}-1-prop-2-yn-1-ylpiperidine-4-carboxamide (19d).** To a solution of *N*-propargyl ethyl ester *p*-fluorosulfone **22d**[42] (6.0 g, 15.4 mmol) in DMF (70 mL) was added powdered K_2CO_3 (8.0 g, 38.5 mmol) and 4-isopropyl phenol (5.24 g, 38.5 mmol), and the solution was heated to 90 °C for 32 h. The reaction mixture was then concentrated under high vacuum, and the residue was then partitioned between EtOAc and water. The organic layer was washed successively with 1N aqueous NaOH and water and then concentrated to give a residue that was chromatographed on silica gel eluting with EtOAc/hexane to provide the diaryl ether **20d** as a light-yellow gel (6.89 g, 87%).

To a solution of the diaryl ether ethyl ester **20d** (6.89 g, 14.7 mmol) in ethanol (14 mL) and THF (14 mL) was added a solution of NaOH (5.88 g, 147 mmol) in water (28 mL) via an addition funnel at rt. The solution was then heated to 60 °C. Concentration in vacuo gave a residue which was diluted with water, washed with ether, and then acidified to pH = 2 with concentrated aqueous HCl. The resulting precipitate was collected via filtration to afford the carboxylic acid **17d** as a white solid (6.56 g, 100%).

To a solution of carboxylic acid **17d** (6.56 g, 14.86 mmol), NMM (6.5 mL, 59.4 mmol), HOBt (6.0 g, 44.6 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (3.5 g, 29.7 mmol) in DMF (50 mL) was added EDC (8.5 g, 44.6 mmol), and the solution was stirred at rt for 20 h. The reaction mixture was then concentrated under high vacuum, and the residue was partitioned between water and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and water and dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel eluting with EtOAc/hexane provided the THP-protected hydroxamate **18d** as a white foam (8.03 g, 100%).

To a solution of THP-protected hydroxamate **18d** (8.03 g, 14.9 mmol) in methanol (5 mL) and 1,4-dioxane (15 mL) was added a 4N solution of HCl in 1,4-dioxane (37 mL, 149 mmol), and the solution was stirred at rt for 3 h. Concentration and trituration of the residue with diethyl ether provided the *N*-propargyl piperidine hydroxamate **19d** (5.0 g, 71.1%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (1H, br s), 7.73 (2H, d, J = 9.0 Hz) 9.36 (1H, s), 7.37 (2H, d, J = 8.6 Hz), 7.11 (4H, dd, J = 8.8, 3.3 Hz), 4.01−4.15 (2H, m), 3.79−3.91 (1H, m), 3.49−3.66 (2H, m), 2.88−3.02 (1H, m), 2.71−2.85 (2H, m), 2.60 (2H, s), 2.11−2.28 (2H, m), 1.24 (3H, s), 1.22 (3H, s). Anal. Calcd for $C_{24}H_{28}N_2O_5S \cdot HCl \cdot 0.9H_2O$: C, 56.61; H, 6.10; N, 5.50; S, 6.30. Found: C, 56.97; H, 6.05; N, 5.41; S, 5.98. HRMS MH^+ calcd for $C_{24}H_{28}N_2O_5S$, 457.1797; found, 457.1816.

***N*-Hydroxy-4-{[4-(4-isopropylphenoxy)phenyl]sulfonyl}-1-(2-methoxyethyl)piperidine-4-carboxamide (19e).** Hydroxamate **19e** was prepared according to the general method illustrated for **19d** to afford *N*-methoxyethyl 4-isopropylphenyloxyphenylsulfone -hydroxamate **19e**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (1H, br s), 9.32 (1H, br s), 7.74 (2H, d, J = 9.0 Hz), 7.37 (2H, d, J = 8.6 Hz), 7.11 (4H, dd, J = 8.8, 6.8 Hz), 3.54−3.64 (4H, m), 3.22−3.30 (5H, m), 2.89−2.99 (m), 2.71−2.83 (2H, m), 2.52−2.58 (2H, m), 2.17−2.30 (2H, m), 1.24 (3H, s), 1.22 (3H, s). HRMS MH^+ calcd for $C_{24}H_{32}N_2O_6S$, 477.2059; found, 477.2073.

***N*-Hydroxy-1-isopropyl-4-{[4-(4-isopropylphenoxy)phenyl]-sulfonyl}piperidine-4-carboxamide (19f).** To a solution of *N*-BOC 4-fluorophenylsulfone ethyl ester **15**[42] (30 g, 161 mmol) in dichloromethane (40 mL) cooled to 0 °C was added trifluoroacetic acid (30 mL), and the solution was stirred at rt for 1 h. Concentration in vacuo provided the trifluoroacetate salt as a light-yellow oil. To the solution of the trifluoroacetate salt and triethylamine (28 mL, 201 mmol) in dichloromethane (250 mL) cooled to 0 °C were added acetone (24 mL, 320 mmol) and sodium triacetoxyborohydride (68 g, 201 mmol) in small portions followed by addition of acetic acid (18.5 mL, 320 mmol), and the solution was stirred at rt for 48 h. The reaction mixture was concentrated and the residue diluted with diethyl ether and washed with 1N aqueous NaOH and water and dried over $MgSO_4$. Concentration in vacuo provided the *N*-isopropyl amine **22f** as a light-yellow oil.

To a solution of *N*-isopropyl piperidine **22f** (4.0 g, 11.2 mmol) and powdered K_2CO_3 (3.909 g, 22.4 mmol) in DMF (30 mL) was added 4-isopropylphenol (3.05 g, 22 mmol), and the solution was heated to 90 °C for 25 h. Concentration under high vacuum afforded a residue which was dissolved in EtOAc. This organic phase was washed with 1N aqueous NaOH and water and dried over $MgSO_4$. Chromatography on silica gel eluting with EtOAc/hexane provided the desired diaryl ether **20f** as a light-yellow gel (5.10 g, 96.2%).

To a solution of diaryl ether ethyl ester **20f** (5.10 g, 10.77 mmol) in ethanol (10 mL) and THF (10 mL) was added a solution of NaOH (4.3 g, 108 mmol) in water (20 mL), and the solution was heated to 60 °C for 24 H. Concentration afforded a residue which was dissolved in water. This aqueous phase was washed with diethyl ether and then acidified with concentrated HCl to pH = 2. Vacuum filtration of the resulting precipitate provided carboxylic acid **17f** (4.80 g, 100%) as a white solid.

To a solution of carboxylic acid **17f** (4.80 g, 10.8 mmol), NMM (3.6 mL, 32.4 mmol), HOBt (4.4 g, 32.4 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (2.6 g, 21.6 mmol) in DMF (100 mL) was added EDC (6.17 g, 32.4 mmol), and the solution was stirred at rt for 7 d. The mixture was filtered to remove unreacted starting material, and the filtrate was concentrated under high vacuum. The residue was dissolved in EtOAc, and this organic phase was washed with saturated aqueous $NaHCO_3$, water and dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel eluting with EtOAc/hexane provided the THP-protected hydroxamate **18f** (2.45 g, 41.7%) as a white foam.

To a solution of THP-protected hydroxamate **18f** in methanol (4 mL) and 1,4-dioxane (8 mL) was added a 4N solution of HCl in 1,4-dioxane (11.2 mL, 45 mmol), and the solution was stirred at rt for 3 h. Concentration in vacuo gave a residue which was triturated with diethyl ether to provide *N*-isopropyl piperidine hydroxamate **19f** (2.01 g, 89.7%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (1H, br s), 9.29 (1H, s), 7.73 (2H, d, J = 8.6 Hz), 7.36 (2H, d, J = 8.6 Hz), 7.12 (4H, t, J = 9.0 Hz), 3.49−3.62 (2H, m), 3.36−3.48 (3H, m), 2.87−3.00 (1H, m), 2.52−2.70 (2H, m), 2.17−2.31 (2H, m), 1.24 (3H, s), 1.22 (3H, s), 1.21 (3H, s), 1.19 (3H, s). HRMS calcd for $C_{24}H_{32}N_2O_5S$, 461.2110; found, 461.2108. Anal. Calcd for $C_{24}H_{32}N_2O_5S \cdot HCl \cdot 0.5H_2O$: C, 56.96; H, 6.77; N, 5.54; S, 6.34. Found: C, 56.58; H, 6.71; N, 5.44; S, 6.25.

***N*-Hydroxy-4-{[4-(4-isopropoxyphenoxy)phenyl]sulfonyl}-1-(2-methoxyethyl)piperidine-4-carboxamide (19g).** To a solution of *N*-methoxyethyl-piperidine ethyl ester *p*-flourosulfone **22g** (2.0 g, 5.4 mmol) in DMF (20 mL) were added 4-isopropoxyphenol[65] (1.63 g, 10.7 mmol) and Cs_2CO_3 (7 g, 21.5 mmol), and the resulting suspension was heated to 60 °C for 16 h. The reaction mixture was then concentrated in vacuo. The residue was dissolved in EtOAc and washed with 1N NaOH, water, and brine and dried over $MgSO_4$. Concentration of the organic phase gave a residue that was purified by chromatography on silica gel eluting with EtOAc/hexane to afford the desired diaryl ether **20g** (1.37 g, 50%).

To a solution of ethyl ester diaryl ether **20g** (1.37 g, 2.7 mmol) in ethanol (30 mL) and water (30 mL) was added NaOH (1.08 g, 27 mmol), and the mixture was heated to 65 °C for 16 h. The solvents were removed in vacuo. Water (50 mL) was added, and the mixture was again concentrated in vacuo and the resulting mixture was acidified with 2N HCl to pH = 4−5. The resulting precipitate was collected by filtration and rinsed with diethyl ether to afford carboxylic acid **17g** (1.25 g, 100%).

To a suspension of carboxylic acid **17g** (1.25 g, 2.7 mmol) in DMF (15 mL) were added NMM (0.82 g, 8.1 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.61 g, 4.1 mmol), followed by bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP, 1.51 g, 3.3 mmol). After stirring for 16 h at rt, the reaction was concentrated to a residue that was dissolved in EtOAc and washed with water and brine. Concentration and purification by chromatography on silica gel eluting with EtOAc/hexane afforded the THP-protected hydroxamate **18g** (1.0 g, 63%) as a white solid.

Through a solution of the THP-protected hydroxamate **18g** (1.0 g, 1.7 mmol) in EtOAc (20 mL) was bubbled HCl gas for 5 min. After stirring at rt for an additional 5 h, the solvent was removed in vacuo. EtOAc (30 mL) was added and then removed in vacuo. EtOAc (30 mL) was again added, and the resulting solid was collected by filtration to afford the *N*-methoxyethyl piperidine hydroxamate hydrochloride salt **19g** (0.50 g, 56%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (1H, br s), 9.32 (1H, br s), 7.72 (2H, d, J = 9.0 Hz), 7.06−7.16 (4H, m), 6.98−7.06 (2H, m), 4.51−4.67 (1H, m), 3.51−3.67 (4H, m), 3.20−3.32 (5H m), 2.69−2.84 (2H, m), 2.50−2.59 (2H, m), 2.15−2.30 (2H, m), 1.29 (3H, s), 1.28 (3H, s). Anal. Calcd for $C_{24}H_{32}N_2O_7S \cdot HCl \cdot 1.5H_2O$: C, 51.84; H, 6.53; N, 5.04; Cl, 6.38; S, 5.77. Found: C, 51.87; H, 6.12; N, 4.92; Cl, 6.38; S, 5.84. MS MH^+ calcd for $C_{24}H_{32}N_2O_7S$, 493; found, 493. HRMS calcd for $C_{24}H_{32}N_2O_7S$, 493.2008; found, 493.1992.

1-Cyclopropyl-*N*-hydroxy-4-{[4-(4-isopropoxyphenoxy)phenyl]-sulfonyl}piperidine-4-carboxamide (19h). To a solution of *N*-cyclopropyl 4-fluorosulfone ethyl ester **22h** (2.49 g, 7.0 mmol) in DMAC (30 mL) were added 4-isopropoxyphenol[65] (1.28 g, 8.4 mmol) and Cs_2CO_3 (5.48 g, 16.8 mmol), and the resulting suspension was heated at 60 °C for 16 h. The reaction mixture was then concentrated in vacuo. The residue was dissolve in EtOAc and washed with 1 N NaOH, water, and brine. Concentration of the organic phase gave a residue which was purified by chromatography on silica gel eluting with EtOAc/hexane to afford aryl ether **20h** (2.8 g, 82%).

To a solution of the ethyl ester **20h** (2.8 g, 5.7 mmol) in ethanol (50 mL) and water (50 mL) was added NaOH (2.3 g, 57 mmol), and the mixture was heated to 60 °C for 16 h. The solvents were removed in vacuo. Water (50 mL) was added, and the mixture was acidified with 2N HC1 to pH = 4. The resulting precipitate was collected by filtration to afford carboxylic acid **17h** (1.4 g, 53%).

To a solution of carboxylic acid **17h** (1.4 g, 3.1 mmol) in DMF(15 mL) were added NMM (0.92 g, 9.1 mmol), HOBt (0.49 g, 3.66 mmol), and EDC (0.82 g, 4.26 mmol), followed by *O*-(tetrahydro-2*H*-pyran-2-yl) hydroxylamine (0.68 g, 4.5 mmol). After stirring for 16 h at ambient temperature, the reaction mixture was concentrated to a residue that was dissolved in EtOAc and washed with water and brine. Concentration and purification by chromatography on silica gel, eluting with EtOAc/hexane, afforded THP-protected hydroxamate **18h**.

To a solution of protected hydroxamate **18h** in methanol/1,4-dioxane (1:3, 20 mL) was added 4 N HC1/1,4-dioxane (10 mL), and the solution was stirred at ambient temperature for 3 h. The solvent was then removed in vacuo. An additional portion of EtOAc was added and then removed in vacuo. Diethyl ether was added, and the resulting solid was collected by filtration to afford hydroxamate **19h** (0.3 g, 19%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (1H, br s), 9.34 (1H, br s), 7.70 (2H, d, J = 8.6 Hz), 7.09 (4H, d), 6.99−7.04 (2H, m), 4.57−4.65 (1H, m), 2.87−3.06 (3H, m), 2.52−2.60 (2H, m), 2.09−2.25 (3H, m), 1.29 (3H, s), 1.28 (3H, s), 0.91−0.98 (2H, m), 0.74−0.79 (2H, m). Anal. Calcd for $C_{24}H_{30}N_2O_6S \cdot HC1$: C, 56.41; H, 6.11; N, 5.48. Found: C, 56.04; H, 5.82; N, 5.44. MS (CI) MH^+ calcd for $C_{24}H_{30}N_2O_6S$, 475; found, 475. HRMS MH^+ calcd for $C_{24}H_{30}N_2O_6S$, 475.1903; found, 475.1893.

***N*-Hydroxy-4-(4-(4-(methylsulfonyl)phenoxy)phenylsulfonyl)-1-(prop-2-ynyl)piperidine-4-carboxamide (19i).** To a solution of *N*-propargyl ethyl ester *p*-fluorosulfone **22i**[42] (2.5 g, 6.4 mmol) in DMF (15 mL) were added 4-methylsulfonylphenol (3.5 g, 20.3 mmol) and Cs_2CO_3 (8.7 g, 27 mmol), and the resulting suspension was heated to 90 °C for 16 h. The reaction mixture was then concentrated in vacuo. The residue was dissolved in EtOAc (500 mL) and washed with 1N NaOH, water, and brine. Concentration of the organic phase gave a residue which was purified by chromatography on silica gel eluting with EtOAc/hexane (1;1) to afford diaryl ether **20i** (2.5 g, 77%).

To a solution of the diaryl ether ethyl ester **20i** (2.5 g, 4.9 mmol) in ethanol (50 mL) and water (30 mL) was added NaOH (2.0 g, 49 mmol), and the mixture was heated to 65 °C for 8 h. The solvents were removed in vacuo. Water (50 mL) was added, the mixture was again concentrated in vacuo, and the resulting mixture was acidified with 2N HCl to pH = 4−5. The resulting precipitate was collected by filtration to afford carboxylic acid **17i** (1.57 g, 67%).

To a solution of carboxylic acid **17i** (1.57 g, 3.3 mmol) in DMF (15 mL) were added NMM (0.5 g, 4.9 mmol), HOBt (0.53 g, 3.9 mmol), and EDC (0.88 g, 4.6 mmol), followed by *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.74 g, 4.9 mmol). After stirring for 16 h at rt, the reaction mixture was concentrated to a residue that was dissolved in EtOAc (200 mL) and washed with water and brine. Concentration and purification by chromatography on silica gel eluting with EtOAc/hexane afforded THP-protected hydroxamate **18i** (1.5 g, 79%), which was used directly.

To a solution of THP-protected hydroxamate **18i** (1.5 g, 2.60 mmol) in methanol/1,4-dioxane (1:3, 40 mL) was added 4N HCl/1,4-dioxane (10 mL), and the solution was stirred at rt for 3 h. The solvent was then removed in vacuo. Methanol (30 mL) was added and then removed in vacuo. Diethyl ether (100 mL) was added, and the resulting solid was collected by filtration to afford hydroxamate **19i** (1.35 g, 98%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (1H, br s), 9.41 (1H br s), 8.01 (2H, d, J = 9.0 Hz), 7.82 (d, J = 9.0 Hz), 7.40 (2H, d, J = 8.6 Hz, 2 H), 7.33 (2H, d, J = 8.6 Hz), 3.98−4.14 (2H, m), 3.76−3.89 (1H, m), 3.51−3.64 (2H, m), 3.45 (3H, br s), 2.72−2.86 (2H, m), 2.53−2.64 (2H, m), 2.19−2.31 (2H, m). Anal. Calcd for $C_{22}H_{24}N_2O_7S_2 \cdot HCl$: C, 49.95; H, 4.76; N, 5.30; Cl, 6.70; S, 12.12. Found: C, 49.78; H, 4.56; N, 5.25; Cl, 6.98; S, 11.98. HRMS (ESI) MH^+ calcd for $C_{22}H_{24}N_2O_7S_2$, 493.1103; found, 493.1106.

4-(4-(Benzo[d][1,3]dioxol-5-yloxy)phenylsulfonyl)-*N*-hydroxypiperidine-4-carboxamide (19j). To a solution of *N*-BOC 4-fluorophenylsulfone ethyl ester **15**[42] (25.0 g, 67.3 mmol) and powdered K_2CO_3 (23.3 g, 16.9 mmol) in DMF was added sesamol (23.24 g, 16.8 mmol) at rt, and the solution was heated to 90 °C for 24 h. The solution was concentrated and then dissolved in EtOAc. The organic layer was washed successively with 1N NaOH and water and then dried over $MgSO_4$. Concentration gave a residue which was chromatographed on silica gel eluting with EtOAc/hexane to provide *N*-BOC diaryl ether **16j** as a white foam (33.6 g, 93.6%).

To a solution of ethyl ester **16j** (29.31 g, 54.93 mmol) in ethanol (60 mL) and THF (60 mL) was added NaOH (21.97 g, 544 mmol) over 20 min at rt. The solution was then heated to 60 °C for 9 h. The reaction mixture was then concentrated and diluted with water and extracted with diethyl ether and then acidified to pH = 2. The mixture was then extracted with EtOAc. The combined organic layers were washed with water and dried over $MgSO_4$. Concentration gave carboxylic acid **17j** as a white solid (25.3 g, 91.0%).

To a solution of *N*-BOC-piperidine carboxylic acid **17j** (1.25 g, 2.47 mmol), NMM (1.00 g, 9.89 mmol), and HOBt (0.40 g, 2.96 mmol) in DMF (6 mL) was added solid EDC (0.616 g, 3.21 mmol) followed by a solution of *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine in DMF (2 mL). After stirring for 2 d at rt the pale-yellow solution was concentrated in vacuo, then dissolved in EA and washed successively with water (3 × 40 mL) and brine (30 mL). The solution was dried over Na_2SO_4 and concentrated to give THP-protected hydroxamate **18j** as a

nearly colorless foam (1.54 g, 100%): DSC 221.01 °C. MIR ν 32 85, 1693, 1478 cm^{-1}.

To a solution of THP-protected hydroxamate **18j** (1.49 g, 2.46 mmol) in 1,4-dioxane (9 mL) and methanol (3 mL) was added 4N HCl in dioxane (10 mL, 40 mmol). After 1.5 h at rt, the suspension was treated with diethyl ether (15 mL) and filtered to afford hydroxamic acid **19j** (1.00 g, 89%) as a colorless powder. DSC 255.96C; IR ν 3213, 3107, 1653, 1144 cm^{-1}. MS MH^+ calcd for $C_{19}H_{20}N_2O_7S$, 421; found, 421; $C_{19}H_{20}N_2O_7S$, 49.95; H, 4.73; N, 6.13; Cl, 7.76; S, 7.02. Found: C, 49.82; H, 4.60; N, 5.98; Cl, 17.38; S, 7.10.

4-{[4-(1,3-Benzodioxol-5-yloxy)phenyl]sulfonyl}-*N*-hydroxy-1-prop-2-yn-1-ylpiperidine-4-carboxamide (19k). To 4-(4-fluorobenzenesulfonyl)-1-prop-2-ynyl-piperidine-4-carboxylic acid ethyl ester **22k** (19.8 mmol, 7.00 g) was added 1,3-benzodioxol-5-ol (40 mmol, 5.52 g), K_2CO_3 (40 mmol, 5.52 g), and DMF (30 mL). The mixture was heated at 80 °C for 48 h. The mixture was then partitioned between EtOAc (200 mL) and water (150 mL). The aqueous phase was extracted with additional EtOAc (2 × 100 mL). The combined organic phases were dried over $MgSO_4$, then filtered through silica and concentrated. Chromatography afforded diaryl ether **20k** as an oil (9.38 g, 100%). Elem. Anal. Calcd for $C_{24}H_{25}NO_7S$: C, 61.13; H, 5.34; N, 2.97. Obsd: C, 61.02; H, 5.44; N, 2.72.

Ethyl ester **20k** (2.72 g, 5.92 mmol) was combined with ethanol (30 mL), water, (5 mL), and potassium hydroxide (2.0 g, 36 mmol) and stirred for 1 h at ambient. Reaction was incomplete, so the mixture was heated at reflux for 4 h. The mixture was allowed to cool and was acidified to ~pH 3 using conc HCl. Concentration following by azeotropic drying with acetonitrile afforded crude carboxylic acid **17k**, which was used without purification.

To carboxylic acid **17k** was added *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (9 mmol, 1.053 g) and acetonitrile (30 mL). Triethylamine (1 mL) was added, followed by EDC (9 mmol, 1.72 g). The mixture was stirred for 16 h and worked up using half-saturated $NaHCO_3$ (20 mL) and EtOAc (2 × 50 mL). The combined organic phase was dried over $MgSO_4$, concentrated, and chromatographed, affording THP-protected hydroxamate **18k** (2.86 g, 89%).

The THP-protected hydroxamate **18k** (5.27 mmol, 2.86 g) was diluted with methanol (40 mL) and lowered into a water bath. Acetyl chloride (1.14 mL, 15.8 mmol) was added over 1 min. After stirring at ambient temperature for 3 h, the mixture was concentrated and azeotroped 5 times with chloroform to afford 2.42 g white solid was obtained, of which 1 g (41%) was purified by reverse-phase chromatography on a C-18 column eluting with 15% acetonitrile, 85% 0.1N HCl. Concentration of the eluent gave hydroxamate **19k** (1.0 g, 97%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (1H, br s), 9.36 (1H, s), 7.72 (2H, d, J = 9.0 Hz), 7.11 (2H, d, J = 9.0 Hz), 7.00 (1H, d, J = 8.6 Hz), 6.88 (1H, d, J = 2.3 Hz), 6.65 (1H, dd, J = 8.6, 2.3 Hz), 3.98−4.18 (2H, m) 6.10 (2H, s), 3.79−3.90 (1H, m), 3.50−3.68 (2H, m), 2.69−2.87 (2H, m), 2.52−2.62 (2H, m), 2.11−2.28 (2H, m). MS (CI) MH^+ calcd for $C_{22}H_{22}N_2O_7S$, 459; found, 459. HRMS calcd for $C_{22}H_{22}N_2O_7S$, 459.1226; found, 459.1222. Anal. Calcd for $C_{22}H_{22}N_2O_7S \cdot HCl \cdot 1.5H_2O$: C, 51.56; H, 5.07; N, 5.47. Found: C, 51.54; H, 4.55; N, 5.64.

4-{[4-(1,3-Benzodioxol-5-yloxy)phenyl]sulfonyl}-*N*-hydroxy-1-(2-methoxyethyl)piperidine-4-carboxamide (19l). To a solution of *N*-BOC ethyl ester diaryl ether **16l** (4.0 g, 7.4 mmol) in dichloromethane (7 mL) at 0 °C was added trifluoroacetic acid (7 mL), and the solution was stirred a rt for 2 h. Concentration in vacuo provided the piperidine trifluoroacetate salt as a light-yellow gel. To a solution of the trifluoroacetate salt in DMF (50 mL) was added K_2CO_3 (3.6 g, 26 mmol) and 2-bromoethyl methyl ether (1.8 mL, 18.7 mmol), and the solution was stirred at rt for 36 h. The DMF was evaporated under high vacuum and the residue was diluted with EtOAc. This organic phase was then washed with water and brine and dried over $MgSO_4$. Concentration in vacuo provided the *N*-methoxyethyl-piperidine **20l** as a light-yellow oil (3.7 g, 100%).

To a solution of the ethyl ester **20l** in ethanol (7 mL) and THF (7 mL) was added a solution of NaOH (3.0 g, 75 mmol) in water (15 mL), and the solution was heated to 60 °C for 19 h. The solution was then concentrated in vacuo and diluted with water. This aqueous phase was washed with ether and then acidified to pH = 2. Vacuum filtration of the white precipitate provided carboxylic acid **17l** as a white solid (4.0 g, 100%).

To a solution of carboxylic acid **17l** (4.0 g, 7.5 mmol), NMM (3.3 mL, 30 mmol), HOBt (3.0 g, 22.5 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (1.8 g, 15 mmol) in DMF (100 mL) was added EDC (4.3 g, 22.5 mmol), and the solution was stirred at rt for 4 d. The reaction mixture was then concentrated under high vacuum, and the residue was dissolved in EtOAc. This organic phase was washed with saturated aqueous $NaHCO_3$ and water and dried over $MgSO_4$. Concentration in vacuo and chromatography of the residue on silica gel eluting with EtOAc/hexane provided the THP-protected hydroxamate **18l** as a white foam (2.40 g, 57.1%).

To a solution of THP-protected hydroxamate **18l** (2.4 g, 4.3 mmol) in methanol (2 mL) and 1,4-dioxane (6 mL) was added a 4N solution of HCl in 1,4-dioxane (11 mL, 43 mmol). The solution was stirred at rt for 3 h. Concentration in vacuo and trituration of the residue with ether provided the *N*-methoxyethyl piperidine hydroxamate **19l** (1.88 g, 85.8%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (1H, br s), 9.33 (1H, br s), 7.72 (2H, d, J = 9.0 Hz), 7.11 (2H, d, J = 9.0 Hz), 7.01 (1H, d, J = 8.6 Hz), 6.87 (1H, d, J = 2.7 Hz), 6.64 (1H, dd, J = 8.6, 2.3 Hz), 6.10 (2H, s), 3.52−3.67 (2H, m), 3.34−3.43 (2H, m), 3.19−3.31 (5H, m), 2.71−2.85 (2H, m), 2.53−2.59 (2H, m), 2.13−2.28 (2H, m). Anal. Calcd for $C_{22}H_{26}N_2O_8S \cdot HCl \cdot H_2O$: C, 49.58; H, 5.48; N, 5.26; S, 6.02. Found: C, 49.59; H, 5.53; N, 5.06; S, 5.71. HRMS MH^+ calcd for $C_{22}H_{26}N_2O_8S$, 479.1488; found, 479.1497.

4-(4-(Benzo[d][1,3]dioxol-5-yloxy)phenylsulfonyl)-1-cyclopropyl-*N*-hydroxypiperidine-4-carboxamide (19m). To a solution of *N*-BOC 4-fluorophenylsulfone ethyl ester **15**[42] (9.0 g, 22.0 mmol) in DMF (30 mL) was added K_2CO_3 (4.55 g, 33 mmol) and sesamol (4.55 g, 33 mmol). The solution was stirred at 90 °C for 24 h. The mixture was diluted with H_2O (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc/hexane (10/90) provided diaryl ether **16m** as an oil (9.3 g, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (2H, d, J = 7 Hz), 7.01 (2H, d, J = 7 Hz), 6.60 (1H, s), 6.55 (1H, d, J = 7 Hz), 6.02 (2H, s), 4.20 (2H, q, J = 7 Hz), 4.19 (4 h, br m), 2.72 (2H, br m), 2.32 (2H, br m), 1.45 (9H, s), 1.26 3H, t, J = 7 Hz). HRMS MH^+ calcd for $C_{26}H_{31}NSO_9$, 534.1798; found, 534.1796.

Through a solution of ethyl ester **16m** (9.3 g, 17 mmol) in EtOAc (100 mL) cooled to 0 °C was bubbled HCl gas for 10 min. The reaction was stirred for an additional 0.5 h at 0 °C. Concentration afforded the piperidine hydrochloride salt (7.34 g, 92%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (2H, br s), 7.71 (2H, d, J = 6 Hz), 7.04 (2H, d, J = 6 Hz), 6.82 (1H, d, J = 6 Hz), 6.62 (1H, s), 6.57 (1H, d, J = 6 Hz), 6.03 (2H, s), 4.22 (2H, q, J = 7 Hz), 3.63 (2H, m), 2.83 (2H, br m), 2.53, 4H, br m), 1.26 (3H, t, J = 7 Hz). HRMS MH^+ calcd for $C_{21}H_{23}NSO_7$, 434.1273; found, 434.1285. To a solution of this hydrochloride salt (7.34 g, 15.6 mmol) in methanol (60 mL) was added acetic acid (8.94 mL, 156 mmol), a portion of 4Å molecular sieves (2 g), (1-ethoxycyclopropyl)-oxytrimethylsilane (18.8 mL, 93.6 mmol), and sodium cyanoborohydride (4.41 g, 70.2 mmol). The reaction was heated under reflux for 8 h. Upon cooling, the precipitate was removed by filtration and the filtrate was concentrated in vacuo. The residue was partitioned between water and EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc

provided *N*-cyclopropyl amine **20m** (7.9 g, 100%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (2H, d, J = 7 Hz), 7.00 (2H, d, J = 7 Hz), 6.82 (1H, d, J = 7 Hz), 6.60 (1H, d, J = 7 Hz), 6.55 (1H, d, J = 7 Hz), 6.02 (2H, s), 4.21 (2H, q, J = 7 Hz), 3.10 (2H, m), 2.31 (2H, m), 2.09 (4H, m), 0.94 (1H, m), 0.40 (4H, m). HRMS MH^+ calcd for $C_{24}H_{27}NSO_7$, 474.1586; found, 474.1599.

To a solution of the *N*-cyclopropyl piperidine ethyl ester **20m** (7.9 g, 16.7 mmol) in ethanol (50 mL) and THF (50 mL) was added a solution of NaOH (6.68 g, 166.8 mmol) in water (30 mL), and the solution was heated to 60 °C for 18 h. The solution was then concentrated in vacuo, and the aqueous remnant was acidified to pH = 3 with concentrated aqueous HCl. The resulting precipitate was filtered to give carboxylic acid **17m** (6.14 g, 76%) as a colorless solid. HRMS MH^+ calcd for $C_{22}H_{25}NSO_7$, 446.1273; found, 446.1331.

To a solution of carboxylic acid **17m** (6.14 g, 12.7 mmol) in DMF (60 mL) was added HOBt (2.06 g, 15.2 mmol), NMM (4.2 mL, 38.0 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (2.23 g, 19.0 mmol) followed by EDC (3.41 g, 17.8 mmol). The solution was stirred at rt for 18 h. The solution was then cooled and diluted with water (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc/hexane (40/60) provided the THP-protected hydroxamate **18m** (6.67 g, 96%) as a colorless solid.

To a solution of THP-protected hydroxamate **18m** (6.67 g, 12.0 mmol) in 1,4-dioxane (70 mL) was added 4N HCl in 1,4-dioxane (6.6 mL). After stirring at rt for 3 h, the solution was concentrated in vacuo. Chromatography on a C18 reverse-phase column eluting with acetonitrile/(HCl)water provided the desired hydroxamate **19m** (4.21 g, 69%) as a white solid. DSC 188.76−198.88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (1H, s), 10.18 (1H, br s), 9.31 (1H, s), 7.71 (2H, d, J = 7 Hz), 7.10 (2H, d, J = 7 Hz), 6.99 (1H, d, J = 7 Hz), 6.88 (1H, s), 6.66 (1H, d, J = 7 Hz), 6.09 (2H, s), 3.55 (2H, br m), 3.00−2.83 (4H, br m), 2.26 (2H, br m), 1.02 (2H, m), 0.74 (2H, m). HRMS MH^+ calcd for $C_{22}H_{24}N_2SO_7$, 461.1382; found, 461.1386. Anal. Calcd for $C_{22}H_{24}N_2SO_7 \cdot HCl$ C, 53.17; H, 5.07; N, 5.64; Cl, 7.14; S, 6.45. Found: C, 52.97; H, 5.03; N, 5.63, Cl, 6.99; S, 6.78.

1-Cyclopropyl-4-{[4-(2,3-dihydro-1,4-benzodioxin-6-yloxy)-phenyl]sulfonyl}-*N*-hydroxypiperidine-4-carboxamide (19n). To a solution of 4-fluorophenyl sulfone piperidine hydrochloride **21**[42] (14.36 g, 40 mmol) in methanol (50 mL) was added acetic acid (24.5 g, 400 mmol), a portion of 4Å molecular sieves (2 g), (1-ethoxycyclopropyl)-oxytrimethylsilane (25.8 mL, 148 mmol), and sodium cyanoborohydride (7.l05 g, 112 mmol). The solution was heated under reflux for 8 h. The reaction was allowed to cool, and the precipitated solids were removed by filtration and the filtrate was concentrated in vacuo. The residue was diluted with water (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated in vacuo to give the *N*-cyclopropyl piperidine **22n** as a colorless solid (11.83 g, 81.5%). MS MH^+ calcd for $C_{17}H_{22}NO_4SF_3$, 356; found, 356.

To a solution of the *N*-cyclopropyl amine ethyl ester *p*-fluoro sulfone **22n** (1.36 g, 3.47 mmol) in DMF (8 mL) was added 6-hydroxybenzo-1,4-dioxane (792 mg, 5.21 mmol) followed by Cs_2CO_3 (2.83 g, 8.69 mmol), and the solution was heated to 100 °C for 20 h. The solution was then cooled and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with water and brine and dried over Na_2SO_4. Filtration through a pad of silica gel eluting with EtOAc/hexane provided the diaryl ether ethyl **20n** an orange oil (1.81 g, 100%). MS(CI) MH^+ calcd for $C_{25}H_{29}NO_7S$, 488; found, 488.

To a solution of the ethyl ester **20n** (1.81 g) in THF (10 mL) and ethanol (10 mL) was added sodium hydroxide (1.39 g, 34.7 mmol) in water (5 mL). The solution was heated to 60 °C for 20 h. The solution was then concentrated in vacuo and the aqueous residue acidified to pH = 2 with 10% aqueous HCl. The resulting solid was collected by vacuum filtration to provide carboxylic acid **17n** as a yellow solid (1.23 g, 72%). HRMS(CI) MH^+ calcd for $C_{23}H_{25}NO_7S$, 460.1430; found, 460.1445.

To a suspension of carboxylic acid **17n** (1.21 g, 2.46 mmol) in DMF (20 mL) was added HOBt (399 mg, 2.95 mmol), NMM (0.81 mL, 7.38 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (432 mg, 3.69 mmol). After stirring for 1 h, EDC (660 mg, 3.44 mmol) was added and the solution was stirred for 20 h at rt. The mixture was then partitioned between EtOAc and water. The organic layer was washed with brine and dried over Na_2SO_4. Chromatography on silica gel eluting with EtOAc/hexane provided the THP-protected hydroxamate **18n** as a yellow oil (940 mg, 70%). MS (CI) MH^+ calcd for $C_{28}H_{34}N_2O_2S$, 559; found, 559.

To a solution of THP-protected hydroxamate **18n** (920 mg, 1.68 mmol) in 1,4-dioxane (15 mL) was added 4N HCl in 1,4-dioxane (10 mL). After stirring at rt for 2 h, the resulting precipitate was collected by vacuum filtration and washed with diethyl ether to provide the *N*-cyclopropylpiperidine hydroxamate **19n** as a white solid (510 mg, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (1H, br s), 9.34 (1H, br s), 7.70 (2H, d, J = 9.0 Hz), 7.09 (2H, d, J = 9.0 Hz), 6.96 (1H, d, J = 8.6 Hz), 6.74 (1H, d, J = 2.7 Hz), 6.66 (1H, dd, J = 8.8, 2.9 Hz), 4.27 (4H, s), 3.60 (2H, d, J = 11.7 Hz), 2.85−3.04 (3H, m), 2.53−2.59 (2H, m), 2.06−2.28 (2H, m), 0.91−1.03 (2H, m), 0.64−0.81 (2H, m). MS (CI) MH^+ calcd for $C_{23}H_{26}N_2O_7S$, 475; found, 475. HRMS calcd for $C_{23}H_{26}N_2O_7S$, 475.1539; found, 475.1553. Anal. Calcd for $C_{23}H_{26}N_2O_7S \cdot 1.15HC \cdot 1.05H_2O$: C, 52.57; H, 5.40; N, 5.33; Cl, 7.76. Found: C, 52.62; H, 5.42; N, 5.79; Cl, 7.71.

1-Cyclopropyl-*N*-hydroxy-4-(4-(4-(trifluoromethyl)phenoxy)-phenylsulfonyl)piperidine-4-carboxamide (19o). To a solution of the *N*-cyclopropyl piperidine ethyl ester *p*-fluoro sulfone **21o** (5.96 g, 15.0 mmol) in DMF (100 mL) was added K_2CO_3 (12.34 g, 38.0 mmol) and α,α,α-trifluoromethylphenol (3.65 g, 22.5 mmol). The solution was stirred at 90 °C for 28 h. The solution was the cooled and diluted with H_2O (400 mL) and extracted with EtOAc. This organic phase was washed with water and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the desired aryl ether **20o** (7.54 g, 100%) as an oil.

To the ethyl ester **20o** (7.54 g, 15.0 mmol) in ethanol (40 mL) and THF (40 mL) was added a solution of NaOH (6.06 g, 15.1 mmol) in water (20 mL), and the solution was heated at 60 °C for 18 h. The reaction mixture was then concentrated in vacuo, and the aqueous residue was acidified to pH = 2. The resulting precipitate was filtered to give carboxylic acid piperidine hydrochloride salt **17o** (7.98 g, 100%) as a white solid: HRMS MH^+ calcd for $C_{22}H_{22}NSO_5F_3$, 470.1171; found, 470.1253

To a solution of the carboxylic acid **17o** (7.60 g, 15.0 mmol) in DMF (100 mL) were added HOBt (2.44 g, 18.0 mmol), NMM (3.4 mL, 30.9 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine hydrochloride (2.63 g, 22.5 mmol), followed by EDC (4.02 g, 21.0 mmol). The solution was stirred at rt for 96 h. The reaction was then diluted with H_2O (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc/hexane (30/70) provided the THP-protected hydroxamate **18o** (5.93 g, 69%) as a white solid.

To a solution of the THP-protected hydroxamate **18o** (3.8 g, 6.7 mmol) in 1,4-dioxane (100 mL) was added 4N HCl in 1,4-dioxane (30 mL). The reaction was stirred at rt for 2 h, then the solution was concentrated in vacuo. Trituration of the residue with diethyl ether afforded the *N*-cyclopropyl piperidine hydroxamate hydrochloride salt **19o** (3.33 g, 96%) as a white solid: DSC 207.29−211.84 °C at 373.8 J/g. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (1H, br s), 9.32 (1H, s), 7.75 (2H, d, J = 8 Hz), 7.49 (2H, d, J = 8 Hz), 7.32 (2H, d, J = 8 Hz), 7.19 (2H, d, J = 8 Hz), 3.60 (2H, m), 3.31 (2H, m), 2.95 (4H, m), 2.22 (1H, m), 0.99 (2H, m), 0.77 (2H, m). MS MH^+ calcd for $C_{22}H_{23}N_2SO_5F_3$, 485; found, 485.

***N*-Hydroxy-4-({4-[4-(trifluoromethyl)phenoxy]phenyl}sulfonyl)-piperidine-4-carboxamide (19p).** To a solution of *N*-BOC 4-fluorophenylsulfone ethyl ester **15**[42] (1.5 g, 3.61 mmol) in DMF (10 mL) was added Cs_2CO_3 (2.95 g, 9.03 mmol) and α,α,α-trifluoro-*p*-cresol (877 mg, 5.41 mmol). The solution was heated to 90 °C for 20 h. The solution was then cooled and partitioned between EtOAc and water, and the organic layer was washed with brine and dried over Na_2SO_4. Filtration through a pad of silica gel eluting with EtOAc provided diaryl ether **16p** as a yellow oil (2.30 g, 100%). MS(CI) MH^+ calcd for $C_{26}H_{30}NO_7SF_3$, 558; found, 558.

To a solution of ethyl ester **16p** (2.30 g, 3.61 mmol) in THF (10 mL) and ethanol (10 mL) was added NaOH (1.44 g, 36.1 mmol) in water (5 mL), and the solution was heated to 60 °C for 18 h. The solution was concentrated and the aqueous residue was acidified to pH = 2 with 10% aqueous HCl and then extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration in vacuo provided the carboxylic acid **17p** as a solid (2.11 g, 100%). MS (CI) MH^+ calcd for $C_{24}H_{26}NO_7SF_3$, 530; found, 530.

To a solution of carboxylic acid **17p** (2.11 g, 3.61 mmol) in DMF (10 mL) was added HOBt (586 mg, 4.33 mmol), NMM (1.19 mL, 10.8 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (634 mg, 5.41 mmol). After stirring for 1 h at rt, EDC (969 mg, 5.05 mmol) was added, and the solution was stirred for 18 h. The mixture was then partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water and brine and dried over $MgSO_4$. Chromatography on silica gel eluting with EtOAc/hexane provided the THP-protected hydroxamate **18p** as a clear, colorless oil (1.40 g, 62%). MS (CI) MH^+ calcd for $C_{29}H_{35}N_2O_8SF_3$, 629; found, 629.

To a solution of the THP-protected hydroxamate **18p** (1.40 g, 2.23 mmol) in 1,4-dioxane (10 nM) was added 4N HCl in 1,4-dioxane (15 mL), and the solution was stirred for 2 h. The solution was then diluted with diethyl ether, and the resulting precipitate was collected by vacuum filtration to provide compound **19p** as a white solid (747 mg, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (1H, br s), 9.32 (1H, s), 8.78 (1H, d, J = 8.99 Hz), 7.86 (2H, d, J = 8.6 Hz), 7.78 (2H, d, J = 8.99 Hz), 7.36 (2H, d, J = 8.6 Hz), 7.29 (2H, d, J = 8.99 Hz), 3.40 (2H, d, J = 12.5 Hz), 2.58−2.70 (2H, m), 2.42−2.58 (2H, m), 2.04−2.20 (2H, m). MS (CI) MH+ calcd for $C_{19}H_{19}N_2O_5SF_3$, 445; found, 445. HRMS calcd for $C_{19}H_{19}N_2O_5SF_3$, 445.1045; found, 445.1052. Anal. Calcd for $C_{19}H_{19}N_2O_5SF_3 \cdot 0.5H_2O \cdot 1.0HCl$: C, 46.58; H, 4.32; N, 5.72; S, 6.55; Cl, 7.24. Found: C, 46.58; H, 3.82; N, 5.61; S, 6.96; Cl, 7.37.

***N*-Hydroxy-1-(2-morpholin-4-ylethyl)-4-({4-[4-(trifluoromethyl)-phenoxy]phenyl}sulfonyl)piperidine-4-carboxamide (19q).** According to the general procedure specified for hydroxamate **19m**, *N*-morpholinylethyl piperidine hydroxamate **19q** was prepared as a colorless foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (1H, br s), 7.73−7.90 (4H, m), 7.40 (2H, d, J = 8.5 Hz), 7.30 (2H, d, J = 8.9 Hz), 3.22−4.08 (8H, m), 2.94−3.23 (2H, m), 2.45−2.89 (6H, m), 2.32 (2H, d, J = 12.3 Hz), 1.67−2.05 (2H, m). HRMS MH^+ calcd for $C_{25}H_{30}F_3N_3O_6S$, 558.1886; found, 558.1894.

***N*-Hydroxy-4-{[4-(4-isopropoxyphenoxy)phenyl]sulfonyl}-tetrahydro-2H-pyran-4-carboxamide (19r).** To a solution of *N*-BOC piperidine **15**[42] (30.0 g, 80.8 mmol) in methylene chloride (100 mL) was added trifluoroacetic acid (30 mL) in methylene chloride (40 mL). The solution was stirred at rt for 2 h and then concentrated in vacuo. To the residue redissolved in methylene chloride (150 mL) at 0 °C were added triethylamine (28.0 mL, 277 mmol), acetone (24.0 mL, 413 mmol), sodium cyanoborohydride (68 g, 323.1 mmol), and acetic acid (18.5 mL, 308 mmol). The reaction mixture was stirred at rt for 18 h, then diluted with 1N NaOH and extracted with ethyl ether. The organic layer was washed with 1N NaOH, water, and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo to provide the desired *N*-isopropyl piperidine **22r** (21.03 g, 72%).

To a solution of the *N*-isopropyl piperidine **22r** (4.04 g, 11.0 mmol) in DMF (50 mL) was added Cs_2CO_3 (10.75 g, 33.3 mmol) and α,α,α-trifluoro-*p*-cresol (2.67 g, 16.5 mmol). The solution was stirred at 90 °C for 40 h. The mixture was then diluted with H_2O (400 mL) and extracted with EtOAc. The organic layer was washed with water and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc/hexane (30/70) provided diaryl ether **20r** as an oil (5.35 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, J = 8 Hz), 7.68 (2H, d, J = 8 Hz), 7.17 (2H, d, J = 8 Hz), 7.10 (2H, d, J = 8 Hz), 4.23 (2H, q, J = 7 Hz), 2.92 (2H, m), 2.68 (1H, m), 2.37 (2H, m), 2.14 (2H, m), 2.06 (2H, m), 1.28 (3H, t, J = 7 Hz), 0.99 (6H, d, J = 7 Hz). HRMS MH^+ calcd for $C_{24}H_{28}NSO_5F_3$, 500.1640; found, 500.1678.

To a solution of the ethyl ester **20r** (5.3 g, 10.6 mmol) in ethanol (50 mL) and THF (50 mL) was added a solution of NaOH (4.2 g, 106 mmol) in H_2O (25 mL), and the solution was heated at 60 °C for 18 h. The mixture was then concentrated in vacuo, and the aqueous residue was acidified to pH = 3.0 with concentrated aqueous HCl. The resulting precipitate was filtered to give the carboxylic acid as the piperidine hydrochloride salt **17r** (5.38 g, 100%) as a white solid: DSC 189.24−205.07 °C at 115.7 J/g. HRMS MH^+ calcd for $C_{22}H_{24}NSO_5F_3$, 472.1406; found, 472.1407.

To a solution of the carboxylic acid **17r** (5.4 g, 10.6 mmol) in DMF (90 mL) were added HOBt (1.72 g, 12.3 mmol), NMM (3.5 mL, 32.0 mmol), and *O*-tetrahydropyranyl hydroxylamine hydrochloride (1.87 g, 15.9 mmol) followed by EDC (2.8 g, 15.0 mmol). The reaction was stirred at rt for 144 h. The solution was then diluted with H_2O (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with methanol/EtOAc (2/98) provided the THP-protected hydroxamate **18r** (2.75 g, 45%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (1H, br s), 7.83 (2H, d, J = 8 Hz), 7.67 (2H, d, J = 8 Hz), 7.18 (2H, d, J = 8 Hz), 7.09 (2H, d, J = 8 Hz), 5.00 (1H, t, J = 1 Hz), 4.00 (1H, td, J = 7, 1 Hz), 4.69 (1H, dt, J = 7, 1 Hz), 3.88 (2H, m), 2.69 (1H, m), 2.28 (2H, m), 2.20 (4H, m), 1.87 (2H, m), 1.80 (2H, m), 1.61 (2H, m), 0.99 (6H, d). HRMS MH^+ calcd for $C_{27}H_{33}N_2SO_5F_3$, 571.2090; found, 571.2103.

To a solution of the THP-protected hydroxamate **18r** (2.7 g, 4.7 mmol) in 1,4-dioxane (50 mL) was added 4N HCl in 1,4-dioxane (20 mL). The reaction was stirred at rt for 2 h. Filtration afforded the hydroxamate as the piperidine hydrochloride salt **19r** (2.08 g, 84%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (1H, br s), 9.29 (1H, s), 7.84 (2H, d, J = 8 Hz), 7.78 (2H, d, J = 8 Hz), 7.37 (2H, d, J = 8 Hz), 7.29 (2H, d, J = 8 Hz), 3.57 (1H, m), 3.41 (1H, m), 2.60 (4H, m), 2.26 (1H, m), 1.21 (6H, d, J = 7 Hz). MS MH^+ calcd for $C_{22}H_{25}SN_2O_5F_3$, 487; found, 487.

1-Ethyl-*N*-hydroxy-4-({4-[4-(trifluoromethyl)phenoxy]phenyl}-sulfonyl)piperidine-4-carboxamide (19s). Through a solution of *N*-BOC 4-fluorophenylsulfone ethyl ester **15**[42] (48 g, 115 mmol) in EtOAc (750 mL) at 0 °C was bubbled HCl gas for 45 min and then stirred at 0 °C for 7 h. The solution was concentrated in vacuo to afford a residue that was triturated with diethyl ether to afford piperidine hydrochloride salt **21** (32.76 g, 81%) as a white solid.

To a solution of the piperidine hydrochloride salt **21** (15.8 g, 45.0 mmol) in DMF (75 mL) was added K_2CO_3 (12.4 g, 90.0 mmol) and bromoethane (3.4 mL, 45.0 mmol). The solution was stirred at rt for 18 h and then diluted with H_2O (200 mL) and extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo to provide the desired *N*-ethyl piperidine **22s** (15.4 g, 100%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, m), 7.22 (2H, m), 4.19 (2H, t, J = 7 Hz), 2.98 (2H, m), 2.33 (5H, m), 2.17 (1H, td, J = 11, 1 Hz), 1.82 (1H, td, J = 11, 1 Hz), 1.24 (3H, t, J = 7 Hz), 1.03 (3H, t, J = 7 Hz). HRMS calcd for $C_{16}H_{22}NSO_4F$, 343.1254; found, 343.1292.

To a solution of the *N*-ethyl piperidine *p*-fluoro sulfone **22s** (5.2 g, 15.0 mmol) in DMF (50 mL) was added Cs_2CO_3 (12.2 g, 37.5 mmol) and α,α,α,-trifluoro-*p*-cresol (3.65 g, 23.0 mmol). The solution was stirred at 90 °C for 25 h. The reaction mixture was then diluted with H_2O (400 mL) and extracted with EtOAc. The organic layer was washed with water and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc/hexane (20/80) provided the diaryl ether **20s** (7.3 g, 100%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, J = 8 Hz), 7.68 (2H, d, J = 8 Hz), 7.17 (2H, d, J = 8 Hz), 7.10 (2H, d, J = 8 Hz), 4.21 (2H, t J = 7 Hz), 2.99 (2H, m), 2.34 (6H, m), 2.17 (2H, td, J = 11, 5 Hz), 1.83 (2H, td, J = 11, 1 Hz), 1.27 (3H, t, J = 7 Hz), 1.05 (3H, t, J = 7 Hz). MS MH^+ calcd for $C_{23}H_{26}NSO_5F_3$, 486; found, 486.

To a solution of the ethyl ester **20s** (7.3 g, 15.0 mmol) in ethanol (40 mL) and THF (40 mL) was added a solution of NaOH (6.0 g, 150 mmol) in water (30 mL), and the solution was heated at 60 °C for 16 h. The solution was then concentrated in vacuo, and the aqueous residue was acidified to pH = 4. The resulting precipitate was filtered to give carboxylic acid piperidine hydrochloride salt **17s** (5.96 g, 80%) as a white solid: DSC 177.57−189.45 °C at 117.2 J/g. HRMS MH^+ calcd for $C_{21}H_{22}NSO_5F_3$, 458.1249; found, 458.1260.

To a solution of the hydrochloride salt **17s** (5.96 g, 12.0 mmol) in DMF (80 mL) were added HOBt (1.96 g, 14.0 mmol), NMM (3.9 mL, 36.0 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (2.11 g, 18.0 mmol), followed by EDC (3.24 g, 17.0 mmol). The reaction was stirred at rt for 18 h. The insoluble material was removed by filtration, and the filtrate was diluted with H_2O (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc/hexane (70/30) provided the THP-protected hydroxamate **18s** (2.80 g, 41%) as a white solid. MS MH^+ calcd for $C_{28}H_{39}N_2SO_6$, 531; found, 531.

To a solution of the THP-protected hydroxamate **18s** (2.8 g, 5.0 mmol) in 1,4-dioxane (80 mL) was added 4N HCl in 1,4-dioxane (20 mL). The reaction was stirred at rt for 5 h and then concentrated in vacuo. Trituration with diethyl ether afforded the hydroxamate piperidine hydrochloride salt (2.08 g, 84%) as a white solid: DSC 229.31−235.74 °C at 187.8 J/g. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (1H, s), 7.83 (2H, d, J = 8 Hz), 7.78 (2H, d, J = 8 Hz), 7.37 (2H, d, J = 8 Hz), 7.29 (2H, d, J = 8 Hz), 3.57 (2H, m), 3.05 (2H, m), 2.60 (2H, m), 2.54 (2H, m), 2.23 (2H, m), 1.18 (3H, t, J = 7 Hz). HRMS MH^+ calcd for $C_{21}H_{23}N_2SO_5F_3$, 473.1358; found, 473.1361. Anal. Calcd for $C_{21}H_{23}N_2SO_5F_3 \cdot HCl$: C, 49.56; H, 4.75; N, 5.50; Cl, 6.70; S, 6.30. Found: C, 49.18; H, 4.61; N, 5.51; Cl, 6.95; S, 6.14.

***N*-Hydroxy-1-(2-methoxyethyl)-4-[(4-{4-[(trifluoromethyl)thio]phenoxy}phenyl)sulfonyl]piperidine-4-carboxamide (19t).** To a solution of *N*-methoxyethyl-piperidine *p*-flourosulfone **22t** (5.0 g, 13.4 mmol) and powdered K_2CO_3 (3.7 g, 27 mmol) in DMF (20 mL) was added 4-(trifluoromethylthio)phenol (3.9 g, 20 mmol), and the mixture was heated to 90 °C for 24 h. The solution was concentrated under high vacuum, and the residue was dissolved in EtOAc. The organic phase was washed with 1N aqueous NaOH and water and dried over $MgSO_4$. Chromatography on silica gel eluting with EtOAc/hexane provided diaryl ether **20t** as a light-yellow gel (5.94 g, 81.0%).

To a solution of the ethyl ester **20t** (5.94 g, 210 mmol) in ethanol (10 mL) and THF (10 mL) was added a solution of NaOH (4.34 g, 108 mmol) in water (20 mL). The solution was then heated to 60 °C for 24 h. After cooling, the solution was concentrated in vacuo and diluted with water. This aqueous phase was washed with diethyl ether and then acidified to pH = 2. Vacuum filtration of the resulting precipitate provided the carboxylic acid **17t** (5.5 g, 100%) as a white solid.

To a solution of the carboxylic acid **17t** (5.5 g, 10.8 mmol), NMM (3.6 mL, 32.4 mmol), HOBt (4.4 g, 32.4 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (2.6 g, 21.8 mmol) in DMF (200 mL) was added EDC (6.2 g, 32.4 mmol), and the solution was stirred at rt for 24 h. The reaction mixture was then concentrated under high vacuum and the residue dissolved in EtOAc. This organic phase was washed with saturated aqueous $NaHCO_3$ and water and dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel eluting with EtOAc/hexane provided the THP-protected hydroxamate **18t** (4.66 g, 69.8%) as a white foam.

To a solution of the THP-protected hydroxamate **18t** (4.65 g, 7.9 mmol) in methanol (2.5 mL) and 1,4-dioxane (8 mL) was added a 4N solution of HCl in 1,4-dioxane (20 mL, 79 mmol), and the solution was stirred at rt for 3 h. Concentration in vacuo gave a residue which was triturated with diethyl ether to afford the *N*-methoxyethyl piperidine hydroxamate **19t** (3.95 g, 92.1%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (1H, s), 10.50 (1H, br s), 9.37 (1H, br s), 7.81 (4H, d, J = 8.5 Hz), 7.32 (4H, dd, J = 16.9, 8.7 Hz), 3.53−3.74 (4H, m), 3.20−3.30 (5H, m), 2.70−2.87 (2H, m), 2.46−2.59 (2H, m), 2.30 (2H, t, J = 12.1 Hz). HRMS calcd for $C_{22}H_{25}F_3N_2O_6S_2$, 535.1184; found, 535.1179. Anal. Calcd for $C_{22}H_{25}F_3N_2O_6S_2 \cdot HCl$: C, 46.27; H, 4.59; N, 4.91; S, 11.23. Found: C, 46.02; H, 4.68; N, 4.57; S, 11.11.

***N*-Hydroxy-4-({4-[4-(trifluoromethoxy)phenoxy]phenyl}sulfonyl)-piperidine-4-carboxamide (19u).** To a solution of *N*-BOC 4-fluorophenylsulfone ethyl ester **15**[42] (1.5 g, 3.61 mmol) in DMF (10 mL) was added Cs_2CO_3 (2.94 g, 9.03 mmol) and 4-(trifluoromethoxy)-phenol (0.70 mL, 5.41 mmol). The solution was heated to 90 °C for 20 h. The solution was then cooled and partitioned between EtOAc and water, and the organic layer was washed with brine and dried over Na_2SO_4. Filtration through a pad of silica gel eluting with EtOAc provided the diaryl ether **16u** as a yellow oil (2.11 g, 100%). MS(CI) MNa^+ calcd for $C_{26}H_{30}F_3NO_8S$, 596; found, 596.

To a solution of the ethyl ester **16u** (2.11 g, 3.61 mmol) in THF (10 mL) and ethanol (10 mL) was added a solution of sodium hydroxide (1.44 g, 36.1 mmol) in water (5 mL), and the solution was heated to 60 °C for 18 h. The solution was concentrated, and the aqueous residue was then acidified to pH = 2 with 10% aqueous HCl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration in vacuo provided the carboxylic acid **17u** as a solid (2.2 g, 100%). MS(CI) MH^+ calcd for $C_{24}H_{26}NO_8SF_3$, 546; found, 546.

To a solution of the carboxylic acid **17u** (2.2 g, 3.6 mmol) in DMF (10 mL) was added HOBt (586 mg, 4.33 mmol), NMM (1.19 mL, 10.8 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (634 mg, 5.41 mmol). After stirring at rt for 30 min, EDC (969 mg, 5.05 mmol) was added and the solution was stirred for 96 h. The solution was then partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water and brine and dried over $MgSO_4$. Chromatography on silica gel eluting with EtOAc/hexane provided the THP-protected hydroxamate **18u** as a clear, colorless oil (1.26 g, 53%).

To a solution of the THP-protected hydroxamate **18u** (1.26 g, 1.96 mmol) in 1,4-dioxane (10 mL) was added 4N HCl in 1,4-dioxane (10 mL), and the solution was stirred for 2 h. The solution was then diluted with ethyl ether, and the resulting precipitate was collected by vacuum filtration to provide **19u** as a white solid (455 mg, 47%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (1H br s), 9.31 (1H, s), 8.79 (1H, d, J = 8.99 Hz), 7.75 (2H, d, J = 8.6 Hz), 7.51 (2H, d, J = 8.6 Hz), 7.31 (2H, d, J = 8.99 Hz), 7.20 (2H, d, J = 8.99 Hz), 3.34−3.45 (2H, m), 2.57−2.70 (2H, m), 2.45 (2H, d, J = 13.6 Hz), 2.10 (2H, t, J = 12.5 Hz). MS(CI) MH^+ calcd for $C_{19}H_{19}N_2O_6SF_3$, 461; found, 461. HRMS calcd for $C_{19}H_{19}N_2O_6SF_3$, 461.0994; found, 461.0997. Anal. Calcd for $C_{19}H_{19}N_2O_6SF_3 \cdot HCl$: C, 45.93; H, 4.06; N, 5.64; S, 6.45; Cl, 6.45. Found: C, 46.23; H, 4.07; N, 5.66; S, 6.59; Cl, 7.03.

***N*-Hydroxy-1-(2-methoxyethyl)-4-({4-[4-(trifluoromethoxy)-phenoxy]phenyl}sulfonyl)piperidine-4-carboxamide (19v).** To a solution of *N*-BOC 4-fluorophenylsulfone ethyl ester **15**[42] (30.0 g, 161 mmol) in dichloromethane (50 mL) cooled to 0 °C

was added trifluoroacetic acid (25 mL), and the solution was stirred at rt for 1 h. Concentration in vacuo provided the piperidine trifluoroacetate salt as a light yellow gel. To the solution of the trifluoroacetate salt in DMF (50 ML) at 0 °C was added K_2CO_3 (3.6 g, 26 mmol) and 2-bromoethyl methyl ether (19 mL, 201 mmol), and the reaction was stirred at rt for 36 h. The DMF was then removed under high vacuum, and the residue was diluted with EtOAc. This organic phase was washed with water and brine and dried over $MgSO_4$. Concentration in vacuo provided the *N*-methoxyethyl-piperidine **22v** as a light-yellow gel (26.03 g, 86.8%).

To a solution of the *N*-methoxyethyl piperidine 4-fluorosulfone **22v** (6.0 g, 16.0 mmol) and powdered K_2CO_3 (4.44 g, 32 mmol) in DMF (30 mL) was added 4-(trifluoromethoxy)phenol (5.72 g, 32 mmol), and the mixture was then heated to 90 °C for 25 h. The solution was concentrated under high vacuum, and the residue was dissolved in EtOAc. This organic phase was washed with 1N aqueous NaOH, water, and brine and dried over $MgSO_4$. Chromatography on silica gel eluting with EtOAc/hexane provided the trifluoromethoxy phenoxyphenyl sulfone **20v** as a light-yellow gel (7.81 g, 91.5%).

To a solution of the ethyl ester **20v** (7.81 g, 14.7 mmol) in ethanol (14 mL) and THF (14 mL) was added a solution of NaOH (5.88 g, 147 mmol) in H_2O (28 mL). The solution was then heated to 60 °C for 18 h. The mixture was then concentrated in vacuo and diluted with water. This aqueous phase was washed with ether and then acidified to pH = 2 with concentrated aqueous HCl. Vacuum filtration of the resulting precipitate provided carboxylic acid **17v** (5.64 g, 73.3%) as a white solid.

To a solution of carboxylic acid **17v** (5.64 g, 10.8 mmol), NMM (4.8 mL, 43.1 mmol), HOBt (4.38 g, 32.4 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (2.5 g, 21.6 mmol) in DMF (50 mL) was added EDC (6.2 g, 32.4 mmol), and the solution was stirred at rt for 24 h. The reaction mixture was then concentrated under high vacuum, and the residue was dissolved in EtOAc. This organic phase was washed with saturated aqueous $NaHCO_3$ and water and dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel eluting with EtOAc/hexane provided the THP-protected hydroxamate **18v** as a white foam (6.65 g, 100%).

To a solution of the THP-protected hydroxamate **18v** (6.65 g, 11.03 mmol) in methanol (3 mL) and 1,4-dioxane (9 mL) was added a 4N solution of HCl in 1,4-dioxane (28 mL, 110 mmol), and the solution was stirred at rt for 3 h. Concentration in vacuo and trituration with ether provided the *N*-methoxyethyl piperidine hydroxamate hydrochloride salt **19v** (4.79 g, 78.2%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (1H, br s), 9.33 (1H, br s), 7.77 (2H, d, J = 8.6 Hz), 7.51 (2H, d, J = 8.99 Hz), 7.32 (2H, d, J = 9.4 Hz), 7.21 (2H, d, J = 8.99 Hz), 3.55−3.66 (4H, m), 3.23−3.31 (5H, m), 2.71−2.85 (2H, m), 2.52−2.59 (2H, m), 2.18−2.30 (2H, m). HRMS MH^+ calcd for $C_{22}H_{25}F_{3N2}O_7S$, 519.1413; found, 519.1399. Anal. Calcd for $C_{22}H_{25}F_{3N2}O_7S \cdot HCl \cdot 0.5H_2O$: C, 46.85; H, 4.83; N, 4.97; S, 5.69. Found: C, 46.73; H, 4.57; N, 4.82; S, 5.77.

1-Cyclopropyl-*N*-hydroxy-4-(4-(4-(trifluoromethoxy)phenoxy)-phenylsulfonyl)piperidine-4-carboxamide (19w). To a solution of the *N*-cyclopropyl amine *p*-fluoro sulfone **22w** (6.97 g, 19.6 mmol) in DMF (500 mL) was added K_2CO_3 (3.42 g, 18.0 mmol) and 4-(trifluoromethoxy)-phenol (3.7 g, 24.8 mmol). The solution was stirred at 90 °C for 40 h. The mixture was then diluted with H_2O (600 mL) and extracted with EtOAc. The organic layer was washed with water and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the desired diaryl ether **20w** as an oil (8.5 g, 100%). HRMS MH^+ calcd for $C_{24}H_{26}NSO_6F_3$, 514.1511; found, 514.1524.

To a solution of the ethyl ester **20w** (8.4 g, 16.4 mmol) in ethanol (50 mL) and THF (50 mL) was added a solution of NaOH (6.54 g, 164 mmol) in H_2O (20 mL), and the solution was heated to 60 °C for 18 h. The solution was concentrated in vacuo to remove most of the organic solvents, and the aqueous residue was acidified to pH = 4.0. The resulting precipitate was filtered to give carboxylic acid piperidine hydrochloride salt **17w** (5.01 g, 63%) as a white solid. HRMS MH^+ calcd for $C_{22}H_{22}NSO_6F_3$, 486.1198; found, 486.1200.

To a solution of the carboxylic acid **17w** (5.0 g, 10.3 mmol) in DMF (80 mL) were added HOBt (3.4 mL, 30.9 mmol) and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (1.8 g, 15.4 mmol), followed by EDC (1.60 g, 12.3 mmol). The solution was stirred at rt for 42 h. The reaction mixture was then diluted with H_2O (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc/hexane (30/70) provided the desired THP-protected hydroxamate **18w** (5.41 g, 89%) as a white solid. HPLC purity 98.38%.

To a solution of the THP-protected hydroxamate **18w** (5.4 g, 9.2 mmol) in 1,4-dioxane (80 mL) and methanol (20 mL) was added 4N HCl in 1,4-dioxane (50 mL). The reaction was stirred at rt for 2.5 h, and then the solution was concentrated in vacuo. Trituration with diethyl ether afforded the *N*-cyclopropyl-piperidine hydroxamate **19w** (4.02 g, 81%) as a white solid: DSC 224.98−231.59 °C at 392.0 J/g. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (1H, br s), 9.34 (1H, s), 7.84 (2H, d, J = 8.0 Hz), 7.77 (2H, d, J = 7.1 Hz), 7.37 (2H, d, J = 7.1 Hz), 7.28 (2H, d, J = 8.0 Hz), 3.60 (2H, m), 3.27 (2H, m), 2.95 (4H, m), 2.22 (1H, m), 0.97 (2H, m), 0.77 (2H, m). HRMS MH^+ calcd for $C_{22}H_{23}N_2SO_6F_3$, 501.1307; found, 501.1324. Anal. Calcd for $C_{22}H_{23}N_2SO_6F_3 \cdot$ HCl: C, 49.30; H, 4.33; N, 5.23; Cl, 6.62; S, 5.98. Found: C, 49.13; H, 4.56; N, 5.17; Cl, 6.98; S, 6.24.

***N*-Hydroxy-1-(2−5-pyridinylmethyl)-4-[4-(4-trifluoro-methoxy-phenoxy)phenyl]sulfonyl]-4-piperidinecarboxamide, Dihydrochloride (19x).** To a solution of 4-fluorophenylsulfone **15**[42] (6.22 g, 15 mmol) in DMF (7 mL) was added powdered K_2CO_3 (3.04 g, 22 mmol) and 4-(trifluoromethoxy)phenol (3.92 g, 322 mmol), and the mixture was stirred at 90 °C for 16 h. Additional 4-(trifluoromethoxy)-phenol (1 g) and K_2CO_3 (800 mg) were added, and the reaction was continued at 115 °C for 20 additional hours. The mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL, then 2 × 25 mL). The combined organic layers were dried using $MgSO_4$, concentrated, and chromatographed, affording the desired diaryl ether **16x** as an oil (9.6 g, 100%).

The *N*-BOC piperidine **16x** (9.6 g, 15 mmol) was dissolved in EtOAc (45 mL). A solution of 4N HCl in dioxane (12 mL, 48 mmol) was added, and the mixture was stirred at rt for 3 h. Concentrated aqueous HCl (4 mL) was added, and the reaction was heated to reflux with a heat gun several times. The solution was concentrated and was then azeotroped with acetonitrile to afford the piperidine hydrochloride salt as a foam (9.6 g). The piperidine hydrochloride salt (6.0 g) was dissolved in EtOAc (125 mL) and washed with aqueous sodium hydroxide (2 g NaOH in 50 mL water). The organic layer was dried with $MgSO_4$ and filtered through a pad of silica gel. The 4-(trifluoromethoxy)phenol contaminant was eluted, and then the desired piperidine was freed from the filter cake by elution with methanol containing 1% aqueous ammonium hydroxide (100 mL). The filtrate was concentrated and azeotroped with acetonitrile to yield the salt (3.3 g 7.3 mmol). This piperidine (1.24 g, 2.7 mmol) was combined with powdered K_2CO_3 (828 mg, 6.0 mmol), 2-picolyl hydrochloride (492 mg, 3.0 mmol), and DMF (3 mL), and the mixture was stirred at ambient temperature for 2 h and then heated at 50 °C for an additional 2 h. The mixture was diluted with water (40 mL) and extracted with EtOAc (150 mL, then 50 mL). The combined organic layers were dried using $MgSO_4$, concentrated, and chromatographed to afford the *N*-picolyl piperidine **20x** as an oil (1.13 g, 74%).

To the ethyl ester **20x** (1.1 g, 2.0 mmol) in ethanol (6 mL) and water (2 mL) was added KOH (0.90 g, 16 mmol). The mixture was brought to reflux and heated for 4.5 h. The solution was then cooled to 0 °C and acidified using concentrated aqueous HCl. The solvent was removed, and the resulting solids were dried by azeotroping with acetonitrile to afford carboxylic acid piperidine hydrochloride **17x**.

Carboxylic acid **17x** was stirred with NMM (about 0.5 mL), 1-hydroxybenzotriazole (0.405 g, 3 mmol), *O*-tetrahydropyranyl hydroxylamine (0.35 g, 3.0 mmol), and DMF (9 mL). After 10 min, EDC (0.57 g, 3.0 mmol) was added, and the mixture was stirred overnight. The reaction was then diluted with half-saturated aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (100 mL, then 25 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed (9:1 EtOAc: methanol) to afford the desired THP-protected hydroxamate **18x** as a yellow oil (1.20 g, 95%).

The THP-protected hydroxamate **18x** (1.20 g, 1.90 mmol) was dissolved in methanol (9 mL). Acetyl chloride (0.78 mL, 11 mmol) was added over 2 min. The reaction was stirred for 2 h at ambient temperature and then concentrated to afford the hydroxamate as the dihydrochloride salt **19x** (1.20 g, 100%) as a white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (1H, br s), 8.67 (1H, d, J = 3.91 Hz), 7.92 (1H, td, J = 7.6, 1.6 Hz), 7.77 (2H, d, J = 8.99 Hz), 7.43−7.56 (4H, m), 7.31 (2H, d, J = 8.99 Hz), 7.20 (2H, d, J = 8.99 Hz), 4.46 (2H, br s), 3.51 (2H, d, J = 11.7 Hz), 2.83−2.98 (2H, m), 2.52−2.60 (2H, m), 2.30 (2H, d, J = 16.4 Hz). HRMS calcd for $C_{25}H_{24}F_3N_3O_6$, 552.1416; found, 522.1428. Anal. Calcd for $C_{25}H_{24}F_3N_3O_6S\cdot 2HCl\cdot 1/3H_2O$: C, 47.58; H, 4.07; N, 6.66. Found: C, 47.31; H, 4.14; N, 6.80.

***N*-Hydroxy-1-(pyridin-3-ylmethyl)-4-({4-[4-(trifluoromethoxy)-phenoxy]phenyl}sulfonyl)piperidine-4-carboxamide (19y).** To a solution of *N*-BOC ethyl ester trifluorophenoxy ether **16p** (2.64 g, 4.6 mmol) in 1,4-dioxane (5 mL) was added 4N HCl in 1,4-dioxane (5 mL), and the solution was stirred for 2 h at rt. The solution was then diluted with ethyl ether, and the resulting precipitate was collected by vacuum filtration to provide the deprotected piperidine as the hydrochloride salt (2.4 g, 100%). To a solution of this hydrochloride salt (2.4 g, 4.6 mmol) in DMF (12 mL) was added 3-picolyl chloride (1.5 g, 8.8 mmol) and K_2CO_3 (4.3 g, 31 mmol), and the mixture was heated to 50 °C for 24 h under an atmosphere of nitrogen. The reaction mixture was then concentrated in vacuo, dissolved in water, and extracted with EtOAc (3×). The combined organic layers were washed with water and brine and dried over $MgSO_4$ and then concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with EtOAc/hexane (50:50) to afford the 3-picolyl piperidine **20y** as an amber oil (1.6 g, 60%). MS MH$^+$ calcd for $C_{27}H_{27}N_2O_6SF_3$, 565; found, 565. Anal. Calcd for $C_{27}H_{27}N_2O_6SF_3$: C, 57.44; H, 4.82; N, 4.96; S, 5.68. Found: C, 57.49; H, 5.10; N, 4.69; S, 5.67.

To a solution of the 3-picolyl piperidine ethyl ester **20y** (1.5 g, 2.6 mmol) in THF (22 mL), ethanol (22 mL), and water (11 mL) was added a 50% aqueous NaOH solution (2.1 g, 26 mmol), and the solution was heated to 65 °C for 24 h. The mixture was concentrated in vacuo and triturated with ether to afford a tan solid which was dissolved in water and acidified to pH = 1 with concentrated hydrochloric acid. The mixture was then concentrated in vacuo and dried at 45 °C under vacuum to afford carboxylic acid **17y** (2.5 g). MS MH+ calcd for $C_{25}H_{23}N_2O_6SF_3$, 537; found, 537.

To a solution of carboxylic acid **17y** (2.5 g) in DMF (40 mL) was added HOBt (1.0 g, 7.7 mmol), NMM (0.64 g, 7.7 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.60 g, 5.1 mmol), and EDC (1.5 g, 7.7 mmol), and the reaction was stirred at rt for 5 d. The mixture was then concentrated in vacuo, dissolved in EtOAc, washed with water and brine, and dried over $MgSO_4$. Concentration in vacuo gave a residue which was purified by chromatography on silica gel eluting with methanol/chloroform (5/95) to afford the THP-protected hydroxamate **18y** as a colorless foam (1.1 g, 66%). MS MH$^+$ calcd for $C_{30}H_{32}N_3O_7SF_3$, 636; found, 636.

To a solution of the THP-protected hydroxamate **18y** (1.0 g, 1.6 mmol) in methanol (11 mL) was added acetyl chloride (0.34 mL, 4.7 mmol), and the solution was stirred at rt for 2.5 h and then poured into diethyl ether. The resulting precipitate was then isolated by filtration and dried at 46 °C in a vacuum oven to afford the *N*-picolyl hydroxamate **19y** as a white solid (0.85 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14−11.33 (2H, br s), 8.88 (1H, s), 8.77 (1H, d, J = 6.2 Hz), 8.32 (1H, d, J = 8.2 Hz), 7.76 (2H, d, J = 8.99 Hz), 7.69−7.74 (1H, m), 7.48 (2H, d, J = 8.20 Hz), 7.33 (2H, d, J = 8.99 Hz), 7.20 (2H, d, J = 8.99 Hz), 4.39 (2H, br s), 3.43 (2H, d, J = 12.1 Hz), 2.71−2.91 (2H, m), 2.51−2.58 (2H, m), 2.23−2.36 (2H, m). HRMS MH$^+$ calcd for $C_{25}H_{24}N_3O_6SF_3$, 552.1416; found, 552.1417. Anal. Calcd for $C_{25}H_{24}N_3O_6SF_3\cdot 2.2HCl$: C, 47.53; H, 4.18; N, 6.65; S, 5.08. Found: C, 47.27; H, 4.34; N, 6.60; S, 5.29.

1-(2-Ethoxyethyl)-*N*-hydroxy-4-({4-[4-(trifluoromethoxy)-phenoxy]phenyl}sulfonyl)piperidine-4-carboxamide (19z). To a solution of *N*-BOC piperidine **15** (1.0 g, 2.4 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (10 mL), and the solution was stirred at ambient temperature for 1 h. Concentration in vacuo provided the amine trifluoroacetate salt **21** as a light-yellow gel. To the solution of the amine trifluoroacetate salt in DMF (5 mL) was added K_2CO_3 (0.99 g, 7.2 mmol) and 2-bromoethyl ethyl ether (0.33 mL, 2.87 mmol), and the solution was stirred at ambient temperature for 36 h. Then DMF was evaporated under high vacuum, and the residue was diluted with EtOAc. The organic layer was washed with water and dried over $MgSO_4$. Concentration in vacuo provided the ethoxyl ethyl piperidine **22z** as a light- yellow gel (0.68 g, 65.4%).

To a solution of 4-fluorophenylsulfone **22z** (0.68 g, 1.56 mmol) and powdered K_2CO_3 (0.43 g, 3.1 mmol) in DMF (5 mL) was added 4-(trifluoromethoxy)phenol (0.4 mL, 3.08 mmol), and the solution was heated to 90 °C for 25 h. The solution was concentrated under high vacuum, and the residue was dissolved in EtOAc. The organic layer was washed with 1N NaOH and water and dried over $MgSO_4$. Chromatography on silica eluting with EtOAc/hexane provided the desired diaryl sulfone **20z** as a light-yellow gel (1.0 g, quantitative).

To a solution of ethyl ester **20z** (1.0 g, 1.72 mmol) in ethanol (2 mL) and tetrahydrofuran (2 mL) was added NaOH (0.688 g, 17.2 mmol) in water (4 mL). The solution was then heated to 60 °C for 18 h. The solution was concentrated in vacuo and diluted with water. The aqueous layer was extracted with ether and acidified to pH = 2. Vacuum filtration of the white precipitate provided the carboxylic acid **17z** as a white solid (0.94 g, 100%).

To a solution of carboxylic acid **17z** (0.94 g, 1.86 mmol), NMM (0.61 mL, 5.55 mmol), HOBt (0.76 g, 5.59 mmol), and *O*-tetrahydropyranyl hydroxyl amine (0.33 g, 2.7 mmol) in DMF (40 mL) was added EDC (1.06 g, 5.59 mmol), and the solution was stirred at rt for 24 h. The solution was concentrated under high vacuum, and the residue was dissolved in EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and water and dried over $MgSO_4$. Concentration in vacuo and chromatography on silica eluting with EtOAc/hexane provided the THP-protected hydroxamate **18z** as a white foam (0.74 g, 66.1%).

To a solution of 4N hydrochloric acid (3 mL, 12 mmol)) in dioxane was added a solution of THP-protected hydroxamate **18z** (0.74 g, 1.2 mmol) in methanol (0.4 mL) and dioxane (1.2 mL) and was stirred at rt for 3 h. Filtration of precipitation gave the title compound as white solid (0.217 g, 32.9%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (1H, s), 9.33 (1H, br s), 7.77 (2H, d, J = 8.59 Hz), 7.50 (2H, d, J = 8.2 Hz), 7.33 (2H, d, J = 8.99 Hz), 7.21 (2H, d, J = 8.99 Hz), 3.64−3.70 (2H, m), 3.59 (2H, d, J = 12.1 Hz), 3.45 (2H, q, J = 7.0 Hz), 3.19−3.28 (2H, m), 2.71−2.86 (2H, m), 2.52−2.57 (2H, m), 2.28 (2H, t, J = 13.5 Hz), 1.12 (2H, t, J = 7.0 Hz). HRMS MH$^+$ calcd for $C_{23}H_{27}N_2O_7SF_3$, 533.1459; found, 533.1566. Anal. Calcd for $C_{23}H_{27}N_2O_7SF_3\cdot HCl\cdot H_2O$: C, 47.06; H, 5.15; N, 4.77; S, 5.46. Found: C, 46.73; H, 4.57; N, 4.82; S, 5.77.

***N*-Hydroxy-1-(2-hydroxyethyl)-4-({4-[4-(trifluoromethoxy)-phenoxy]phenyl}sulfonyl)piperidine-4-carboxamide (19aa).** To a solution of piperidine hydrochloride **21** (3.95 g, 11.3 mmol) in

DMF (11 mL) was added K_2CO_3 (3.45 g, 25 mmol) and 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (1.85 mL, 12 mmol), and the mixture was stirred for 48 h at rt. The reaction was diluted with water (100 mL) and extracted with EtOAc (100 mL, then 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed to afford the desired tetrahydropyranyl ether **22aa** as an oil (4.44 g, 88%)

A solution of tetrahydropyranyl ether **22aa** in DMF (5 mL) was stirred at 110 °C for 20 h in the presence of powdered K_2CO_3 (2.07 g, 15 mmol) and 4-(trifluoromethoxy)phenol (2.67 mL, 15 mmol). The mixture was diluted with saturated $NaHCO_3$ (50 mL) and was extracted with EtOAc (150, then 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and chromatographed to afford diaryl ether **20aa** as an oil (5.72 g, 100%).

Ethyl ester **20aa** (1.28 g, 2.1 mmol) was refluxed in the presence of KOH (954 mg, 16.8 mmol), ethanol (9 mL), and water (3 mL). After 2 h, the reaction was cooled to 0 °C. Concentrated hydrochloric acid was added dropwise to adjust the pH to 4.0. The acidified reaction was concentrated, azeotroped with acetonitrile, and dried in vacuo, affording carboxylic acid **16aa**.

Carboxylic acid **17aa** was converted to the *O*-THP hydroxamate using *O*-tetrahydropyranyl hydroxylamine (351 mg, 3 mmol), NMM (0.5 mL), HOBt (405 mg, 3 mmol), and EDC (573 mg, 3 mmol) in DMF (9 mL) at rt for 16 h. After an aqueous workup, the THP-protected hydroxamate **18aa** (855 mg, 60%) was obtained as an oil.

The tetrahydropyranyl hydroxamate **18aa** (855 mg, 1.26 mmol) was dissolved in methanol (10 mL). Acetyl chloride (0.78 mL, 11 mmol) was added over 2−3 min. After 4 h, both THP groups had been cleaved. The reaction was concentrated, azeotroped with chloroform/acetonitrile, and dried in vacuo, affording hydroxamate **19aa** as a white foam (676 mg, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (1H, br s), 9.33 (1H, br s), 7.77 (2H, d, J = 8.99 Hz), 7.50 (2H, d, J = 8.2 Hz), 7.33 (2H, d, J = 8.99 Hz), 7.21 (2H, d, J = 8.99 Hz), 5.29 (1H, br s), 3.69 (2H, br s), 3.60 (2H, d, J = 13.3 Hz), 3.13 (2H, br s), 2.78 (2H, d, J = 11.7 Hz), 2.48−2.58 (2H, m), 2.21−2.39 (2H, m). HRMS MH$^+$ calcd for $C_{21}H_{23}F_3N_2O_7S$, 505.1256; found, 505.1250.

1-Acetyl-*N*-hydroxy-4-({4-[4-(trifluoromethoxy)phenoxy]-phenyl}sulfonyl)piperidine-4-carboxamide (19bb). To a solution of 4-fluorophenylsulfone **15** (33.2 g, 80.0 mmol) in DMF (150 mL) was added Cs_2CO_3 (65.2 g, 200 mmol) and 4-(trifluoromethoxy)phenol (21.4 g, 120 mmol). The solution was mechanically stirred at 60 °C for 24 h. The solution was then diluted with water (1 L) and extracted with EtOAc. The organic layer was washed with water and brine and dried over $MgSO_4$ and then filtered and concentrated in vacuo. Chromatography on silica gel eluting with 20% EtOAc/hexane provided the desired diaryl ether **16bb** as a white solid (45.0 g, 100%).

To a solution of ethyl ester **16bb** (24.0 g, 42.8 mmol) in ethanol (80 mL) and THF (80 mL) was added a solution of NaOH (14.8 g, 370 mmol) in water (100 mL), and the solution was heated at 60 °C for 18 h. The solution was concentrated in vacuo, and the aqueous residue was acidified to pH = 5 and extracted with EtOAc. The organic extract was washed with brine and dried over $MgSO_4$ and then filtered and concentrated in vacuo to give the desired carboxylic acid **17bb** as a white foam (23.0 g, 100%).

Through a solution of carboxylic acid **17bb** (22.8 g, 43.0 mmol) in EtOAc (400 mL) cooled to 0 °C was bubbled gaseous HCl for 20 min. The reaction was stirred at this temperature for 2.5 h. The solution was then concentrated in vacuo to afford the piperidine hydrochloride salt as a white foam (21.0 g, 100%).

To a solution of hydrochloride salt (**17**, R = H) (17.0 g, 35.0 mmol) in acetone (125 mL) and water (125 mL) was added triethyl amine (24 mL, 175 mmol). The reaction was cooled to 0 °C, and acetyl chloride (3.73 mL, 53.0 mmol) was added. The solution was then stirred at ambient temperature for 18 h. Concentration in vacuo gave a residue which was acidified with aqueous hydrochloric acid to pH 1.0 and then extracted with EtOAc. The organic layer was washed with water and saturated aqueous sodium chloride and dried over $MgSO_4$, then filtered and concentrated in vacuo to give the desired acetamide **17bb** as a white solid (17.0 g, quantitative yield).

To a solution of the acetamide **17bb** (14.4 g, 29.6 mmol) in DMF (250 mL) was added HOBt (4.8 g, 35.5 mmol), NMM (12.3 mL, 88.8 mmol), and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (5.2 g, 44.4 mmol), followed by EDC (7.99 g, 41.4 mmol). The solution was stirred at ambient temperature for 18 h. The solution was diluted with water (500 mL) and extracted with EtOAc. The organic layer was washed with saturated aqueous sodium chloride and dried over $MgSO_4$ and then filtered and concentrated in vacuo. Chromatography on a C-18 reverse-phase column eluting with acetonitrile/water provided the desired THP-protected hydroxamate **18bb** as a white solid (12.0 g, 71%).

To a solution of THP-protected hydroxamate **18bb** (12.0 g, 20.5 mmol) in 1,4-dioxane (250 mL) and methanol (50 mL) was added 4 N HCl/dioxane (51 mL). After stirring at rt for 3.5 h, the solution was concentrated in vacuo. Trituration with diethyl ether and filtration provided piperidine acetamide hydroxamate **19bb** as a white solid (8.84 g, 85%). HRMS MH$^+$ calcd for $C_{21}H_{21}N_2SO_7F_3$, 502.1021; found, 502.0979. Anal. Calcd for $C_{21}H_{21}N_2SO_7F_3$: C, 50.20; H, 4.21; N, 5.58; S, 6.38. Found: C, 49.93; H, 4.14; N, 5.60; S, 6.56.

***N*-Hydroxy-1-prop-2-yn-1-yl-4-({4-[4-(trifluoromethoxy)-phenoxy]phenyl}sulfonyl)piperidine-4-carboxamide (19cc).** *N*-Propargyl piperidine hydroxamate **19cc** was prepared according to the procedure outlined for **19v**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (1H, br s), 9.37 (1H, br s), 7.77 (2H, d, J = 8.99 Hz), 7.50 (2H, d, J = 8.2 Hz), 7.33 (2H, d, J = 8.99 Hz), 7.20 (2H, d, J = 8.99 Hz), 4.08 (2H, br s), 3.82 (1H, br s), 3.48−3.70 (2H, m), 2.79−2.80 (2H, m), 2.52−2.63 (2H, m), 2.14−2.32 (2H, m). HRMS MH$^+$ calcd for $C_{22}H_{21}F_3N_2O_6S$, 499.1151; found, 499.1145.

***N*-Hydroxy-1-methyl-4-({4-[4-(trifluoromethoxy)phenoxy]-phenyl}sulfonyl)piperidine-4-carboxamide (19dd).** *N*-Methyl piperidine hydroxamate **19dd** was prepared according to the procedure outlined for **19v**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (1H, s), 9.33 (1H, s), 7.77 (2H, d, J = 8.99 Hz), 7.50 (2H, d, J = 8.6 Hz), 7.33 (2H, d, J = 9.4 Hz), 7.20 (2H, d, J = 8.99 Hz), 3.48 (2H, d, J = 13.7 Hz), 2.72−2.83 (2H, m), 2.70 (3H, br s), 2.51−2.58 (2H, m), 2.17−2.29 (2H, m). HRMS MH$^+$ calcd for $C_{20}H_{21}F_3N_2O_6S$, 475.1151; found, 475.1142.

***N*-Hydroxy-1-isopropyl-4-({4-[4-(trifluoromethoxy)phenoxy]-phenyl}sulfonyl)piperidine-4-carboxamide (19ee).** *N*-Isopropyl piperidine hydroxamate **19ee** was prepared according to the procedure outlined for **19v**. HRMS MH+ calcd for $C_{22}H_{25}F_3N_2O_6S$, 503.1464; found, 503.1461. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (1H, s) 11.22 (1H, s), 7.77 (2H, d, J = 8.99 Hz), 7.49 (2H, d, J = 8.2 Hz), 7.34 (2H, d, J = 8.99 Hz), 7.22 (2H, d, J = 8.99 Hz), 3.65−3.75 (1H, m), 3.54 (2H, d, J = 10.9 Hz), 3.37−3.46 (2H, m), 2.52−2.66 (2H, m), 2.20−2.35 (2H, m), 1.21 (3H, s), 1.20 (3H, s).

Crystallography. Crystals of the MMP13:tetrahydro-*N*-hydroxy-4-[[4-(phenylmethyl)-1-piperazinyl]sulfonyl]-2*H*-pyran-4-carboxamide hydrochloride[66] complex were grown at 4 °C by sitting drop vapor diffusion using 5 mg/mL protein and a reservoir solution of 1.4 M lithium sulfate, 0.1 M Hepes, pH 7.7. The crystallization drop consisted of 5 μL of protein plus 1 μL of reservoir solution. Rod-like crystals appeared within four to six weeks. Crystals were pre-equilibrated in a soaking solution containing 1.5 M lithium sulfate, 0.1 M Hepes, pH 7.7 without inhibitor at room temperature for more than 2 h. These crystals were then transferred to a second solution containing 1.5 M lithium sulfate, 0.1 M Hepes, pH 7.7, and 2.5 mM of replacement inhibitor (**19v**) and were left to incubate at room temperature for five to seven days. The cryo solution consisted of 20% sucrose, 1.5 M lithium sulfate, and 0.1 M Hepes, pH 7.7. Data were collected using a Rigaku Micromax 007 X-ray generator on a Mar Research MarCCD 165 detector. The diffraction data were

Table 4. Crystallographic Data and Refinement Statistics[a]

PDB accession code	3KRY
Data Collection Statistics	
radiation source	rotating anode
radiation detector	MAR CCD 165
space group	*P*1
resolution (Å)	20.0−1.9 (1.97−1.90)
observed reflections	84869
unique reflections	48703
completeness (%)	95.3, 91.6
mean I/σ_I	6.9, 1.4
R_{sym}%[b]	7.7, 28.0
Refinement Statistics	
resolution (Å)	20−1.9
no. protein + ligand atoms	5358
no. solvent atoms	528
R (%), R_{free} (%)	20.6, 25.6
Wilson B (Å^2), refined $\langle B\rangle$ (Å^2)	14.2, 18.4
rmsd ideal bond lengths (Å)	0.008
bond angles (deg)	1.10
Ramachandran plot statistics	
most favored regions (no., %)	484, 88.8
disallowed regions (no., %)	3, 0.6

[a]Highest resolution bin. [b]$R_{sym} = \sum(|I_i - \langle I\rangle|)/\sum I_i$. All reflections with $I/\sigma_I < -1.0$ eliminated from scaling.

integrated and scaled with HKL-2000,[67] and the structures were determined by molecular replacement using a prior internal structure of MMP-13 as the initial model. The model adjustment occurred as in Kjeldgaard[68] and Coot,[69] and the structures were refined (Table 4) initially with X-PLOR[70] and were further optimized in Refmac.[71]

Enzyme Assays. Inhibitors were assayed against purified hMMP-1, hMMP-2, hMMP-8, hMMP-9, hMMP-13, and MMP-14 using an enzyme assay based on cleavage of the fluorogenic peptide MCA-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2. Human MMP-3 activity was measured using a fluorogenic substrate containing glutamic acid and (*S*)-2-aminopentanoic acid as reported by Nagase.[72] Assay conditions were similar to those described in G. Knight et al.[73] All basic compounds were tested as their hydrochloride salts unless otherwise indicated.

MMP-1 was obtained from MMP-1 expressing transfected HT-1080 cells provided by Dr. Harold Welgus of Washington University in St. Louis, MO. The MMP-1 was activated using 4-aminophenylmercuric acetate (APMA) and then purified over a hydroxamic acid column. MMP-2 was obtained from MMP-2 expressing transfected cells provided by Dr. Gregory Goldberg of Washington University. MMP-9 was obtained from MMP-9 expressing transfected cells provided by Dr. Gregory Goldberg. The MMP-13 was obtained as a proenzyme from a full-length cDNA clone using baculovirus, as described by V. A. Luckow.[74] The expressed proenzyme was first purified over a heparin agarose column and then over a chelating zinc chloride column. The proenzyme was then activated by APMA for use in the assay. Further details on baculovirus expression systems have been described by Luckow.[75]

The enzyme substrate was a methoxycoumarin-containing polypeptide having the following sequence: MCA-ProLeuGly-LeuDpaAlaArgNH_2, where "MCA" is methoxycoumarin and "Dpa" is 3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl alanine as purchased from Baychem (Redwood City, CA) as product M-1895. Compounds were dissolved at various concentrations using 1% dimethyl sulfoxide (DMSO) in a buffer containing 100 mM Tris-HCl, 100 mM NaCl, 10 mM $CaCl_2$, and 0.05% polyethylene glycol lauryl ether at a pH of 7.5. These solutions were then compared to a control (which contained equal amount of DMSO/buffer solution, but no hydroxamate compound) using Microfluor White Plates (Dynatech, Chantilly, VA). Specifically, The MMPs were activated with APMA or trypsin. Then the various hydroxamate/DMSO/buffer solutions were incubated in separate plates at room temperature with the activated MMP and 4 μm of the MMP substrate. The control likewise was incubated at room temperature in separate plates with the MMP and 4 μM of the MMP substrate. In the absence of inhibitor activity, a fluorogenic peptide was cleaved at the Gly−Leu peptide bond of the substrate, separating the highly fluorogenic peptide from a 2,4-dinitrophenyl quencher, resulting in an increase of fluorescent intensity (excitation at 328 nm/emission at 415). Inhibition was measured as a reduction in fluorescent intensity as a function of inhibitor concentration using a Perkin-Elmer (Norwalk, CT) L550 plate reader. The IC_{50} values were calculated from these measurements.

Pharmacokinetic (pk) Evaluation of MMP Inhibitors in Rats. Under metofane anesthesia, the femoral artery (all eight rats) and femoral vein (only four of eight rats) were isolated and canulated with PESO tubing and secured with 3.0 silk suture. The following determinations required two catheters, with the venous line being used for infusion of compound (in the group of rats that receives compound via the intravenous (IV) route) and the arterial line being used for collection of blood samples. The rats were then placed in restraining cages that permitted minimal movement and allowed to recover from anesthesia for approximately 30 min. At time 0 (prior to dosing), blood samples (400 μL) were collected from arterial cannula.

One group of rats (four rats per group) received compound via the oral route at a dosing volume of 2 mL/kg (10 mg/mL, dissolved in 0.5% methylcellulose, 0.1% Tween 20), while the other group of rats received compound via the intravenous cannula, at a dosing volume of 2 mL/kg (10 mg/mL, dissolved in 10% EtOH, 50% PEG 400, 40% saline). The blood samples were collected from the arterial cannula at 15, 30, 60, 120, 240, and 360 min from the oral group, with an additional 3 min sample being collected from IV group. After each sample, the cannulas were flushed with PBS containing 10 units/mL of heparin. The animals were subjected to euthanasia with an excess of anesthesia or carbon monoxide asphyxiation when the study was terminated at 6 h. Blood samples from each time point were assayed for MMP-13 enzyme inhibitory activity, and the circulating concentration of compound plus active metabolites was estimated based on the standard curve. Pharmacokinetic (pk) parameters were calculated by the VAX computer program CSTRIP.

MX1 Tumor Model Method. Mice were implanted subcutaneously with 1 mm^3 MX-1 human breast carcinoma fragments in the flank. Tumors were monitored reached the desired size, approximately 100 mg, and then pair-matched and assigned to treatment groups. The chemotherapy drug cyclophosphamide (CY) was obtained as the formulated pharmaceutical drug (Neosar; Pharmacia). Compound **19w** was formulated in MC/TW 80 vehicle (0.5% methyl cellulose:0.1% polysorbate 80).

CY was administered to mice ip on the day of pair-match (day 1) on a qd × 1 schedule at a dose of 120 mg/kg. Tumors were monitored until they reached an approximate nadir in size, at which time they were administered oral treatment bid to end with vehicle or compound **19w** at doses of 50, 25, 12.5, and 6 mg/kg (bid to end). The test was terminated on day 90.

The tumor growth delay (TGD) method was used in this study; treatment-effected mean increases in survival of various groups were compared to each other and to the mean survival time of breast tumor-bearing mice receiving only vehicle. In the TGD method, each animal was euthanized as a cancer death when its MX-1 carcinoma reached a size of 1.5 g.

PC3 Tumor Model Method. PC3 tumor cells were grown in F12/MEM (Gibco) and 7% FBS (Gibco). The cells were mechanically harvested, washed twice with cold media, and resuspended in cold media with 30% matrigel (Collaborative Research) and stored on ice. Balb/c nu/nu at 7−9 weeks of age were injected with $3-5 \times 10^6$ cells in the flank of the mouse. Cells were injected in the morning, and dosing started that same evening. The animals were gavaged bid from evening of day 0 to day 25−30, when the animals were euthanized and tumors weighed. Vehicle and compound **19w** was formulated in vehicle

(MC/TW 80 vehicle; 0.5% methyl cellulose:0.1% polysorbate 80). Tumor measurements began on day 7 and continue every third to fourth day until the mice were sacrificed.

In some experiments, mice were treated as described above with **19w** and treated with a single dose of cisplatin (10 mg/kg ip diluted in PBS) on day 8 post cell injection.

Bovine Nasal Cartilage Degradation Assay. On the basis of the method described by Bottomley et al.,[58] fresh bovine nasal cartilage disks (1 mm thick × 8 mm in diameter) were sterilely prepared and incubated for 72 h in DMEM containing 5% heat-inactivated FBS containing penicillin (100 IU/mL), streptomycin (100 μg/mL), and amphotericin B (0.25 μg/mL). Disks were weighed to ensure uniformity, divided into eighths, plated one piece per well in a 96-well plate, and incubated overnight in the DMEM plus penicillin/streptomycin/amphotericin B media. Degradation of cartilage explants was induced by replacing media with fresh media containing cytokine stimulation (DMEM plus recombinant human IL-1 (10 ng/mL) and oncostatin M (50 ng/mL)) and various concentrations of test compound. Cultures were incubated at 37 °C/5% CO_2 for up to 16 days, collecting supernatants every 3−4 days and replacing with media containing fresh cytokines and test compound. Minimally, triplicate incubations were conducted for each condition. Inhibition of cartilage degradation was measured by quantification of hydroxyproline in the supernatants collected from explant cultures after hydrolysis with 6N HCl at 110 °C for 24 h. The presence and amount of hydroxyproline in hydrolysates was measured by mass spectrometry. Cartilage degradation was calculated as a percentage of the hydroxproline released into the supernatant collected over the 16 days in the presence of test compound relative to cultures without added inhibitor.

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References

(1) Nagase, H.; Woessner, J. F., Jr. Matrix metalloproteinases. *J. Biol. Chem.* **1999**, *274*, 21491–21494.

(2) Brinckerhoff, C. E.; Matrisian, L. M. Matrix metalloproteinases: a tail of a frog that became a prince. *Nat. Rev. Mol. Cell Biol.* **2002**, *3*, 207–214.

(3) Gross, J.; Lapiere, C. M. Collagenolytic activity in amphibian tissues: a tissue-culture assay. *Pr0c. Natl. Acad. Sci. U.S.A.* **1962**, *48*, 1014–1022.

(4) Fisher, J. F.; Mobashery, S. Recent advances in MMP inhibitor design. *Cancer Metastasis Rev.* **2006**, *25*, 115–136.

(5) Corbitt, C. A.; Lin, J.; Lindsey, M. L. Mechanisms to inhibit matrix metalloproteinase activity: where are we in the development of clinically relevant inhibitors? *Recent Pat. Anti-Cancer Drug Discovery* **2007**, *2*, 135–142.

(6) John, A.; Tuszynski, G. The role of matrix metalloproteinases in tumor angiogenesis and tumor metastasis. *Pathol. Oncol. Res.* **2001**, *7*, 14–23.

(7) Murphy, G.; Nagase, H. Reappraising metalloproteinases in rheumatoid arthritis and osteoarthritis: destruction or repair? *Nat. Clin. Pract. Rheumatol.* **2008**, *4*, 128–135.

(8) Ishikawa, T.; Nishigaki, F.; Miyata, S.; Hirayama, Y.; Minoura, K.; Imanishi, J.; Neya, M.; Mizutani, T.; Imamura, Y.; Ohkubo, Y.; Mutoh, S. Prevention of progressive joint destruction in adjuvant induced arthritis in rats by a novel matrix metalloproteinase inhibitor, FR217840. *Eur. J. Pharmacol.* **2005**, *508*, 239–247.

(9) Martel-Pelletier, J.; Welsch, D. J.; Pelletier, J. P. Metalloproteases and inhibitors in arthritic diseases. *Best Pract. Res., Clin. Rheumatol.* **2001**, *15*, 805–829.

(10) MacFadyen, R. J. Can matrix metalloproteinase inhibitors provide a realistic therapy in cardiovascular medicine? *Curr. Opin. Pharmacol.* **2007**, *7*, 171–178.

(11) Lindsey, M. L. MMP Induction and Inhibition in Myocardial Infarction. *Heart Failure Rev.* **2004**, *9*, 7–19.

(12) Peterson, J. T. Matrix Metalloproteinase Inhibitor Development and the Remodeling of Drug Discovery. *Heart Failure Rev.* **2004**, *9*, 63–79.

(13) Ikejiri, M.; Bernardo, M. M.; Bonfil, R. D.; Toth, M.; Chang, M.; Fridman, R.; Mobashery, S. Potent mechanism-based inhibitors for matrix metalloproteinases. *J. Biol. Chem.* **2005**, *280*, 33992–34002.

(14) Jacobsen, J. A.; Major Jourden, J. L.; Miller, M. T.; Cohen, S. M. To bind zinc or not to bind zinc: an examination of innovative approaches to improved metalloproteinase inhibition. *Biochim. Biophys. Acta, Mol. Cell Res.* **2010**, *1803*, 72–94.

(15) Verma, R. P.; Hansch, C. Matrix metalloproteinases (MMPs): chemical−biological functions and QSARs. *Bioorg. Med. Chem.* **2007**, *15*, 2223–2268.

(16) Skiles, J. W.; Gonnella, N. C.; Jeng, A. Y. The design, structure, and clinical update of small molecular weight matrix metalloproteinase inhibitors. *Curr. Med. Chem.* **2004**, *11*, 2911–2977.

(17) Renkiewicz, R.; Qiu, L.; Lesch, C.; Sun, X.; Devalaraja, R.; Cody, T.; Kaldjian, E.; Welgus, H.; Baragi, V. Broad-spectrum matrix metalloproteinase inhibitor marimastat-induced musculoskeletal side effects in rats. *Arthritis Rheum.* **2003**, *48*, 1742–1749.

(18) Freskos, J. N.; McDonald, J. J.; Mischke, B. V.; Mullins, P. B.; Shieh, H.; Stegeman, R. A.; Stevens, A. M. Synthesis and identification of conformationally constrained selective MMP inhibitors. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1757–1760.

(19) Barta, T. E.; Becker, D. P.; Bedell, L. J.; DeCrescenzo, G. A.; McDonald, J. J.; Munie, G. E.; Rao, S.; Shieh, H.-S.; Stegeman, R.; Stevens, A. M.; Villamil, C. I. Synthesis and activity of selective MMP inhibitors with an aryl backbone. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2815–2817.

(20) Chollet, A.-M.; Le Diguarher, T.; Murray, L.; Bertrand, M.; Tucker, G. C.; Sabatini, M.; Pierre, A.; Atassi, G.; Bonnet, J.; Casara, P. General synthesis of α-substituted 3-bis(aryloxy)propionic acid derivatives as specific MMP inhibitors. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 295–299.

(21) Reiter, L. A.; Robinson, R. P.; McClure, K. F.; Jones, C. S.; Reese, M. R.; Mitchell, P. G.; Otterness, I. G.; Bliven, M. L.; Liras, J.; Cortina, S. R.; Donahue, K. M.; Eskra, J. D.; Griffiths, R. J.; Lame, M. E.; Lopez-Anaya, A.; Martinelli, G. J.; McGahee, S. M.; Yocum, S. A.; Lopresti-Morrow, L. L.; Tobiassen, L. M.; Vaughn-Bowser, M. L. Pyran-containing sulfonamide hydroxamic acids: potent MMP inhibitors that spare MMP-1. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3389–3395.

(22) Li, J.; Rush, T. S.; Li, W.; DeVincentis, D.; Du, X.; Hu, Y.; Thomason, J. R.; Xiang, J. S.; Skotnicki, J. S.; Tam, S.; Cunningham, K. M.; Chockalingam, P. S.; Morris, E. A.; Levin, J. I. Synthesis and SAR of highly selective MMP-13 inhibitors. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4961–4966.

(23) Schnute, M. E.; O'Brien, P. M.; Nahra, J.; Morris, M.; Howard Roark, W.; Hanau, C. E.; Ruminski, P. G.; Scholten, J. A.; Fletcher, T. R.; Hamper, B. C.; Carroll, J. N.; Patt, W. C.; Shieh, H. S.; Collins, B.; Pavlovsky, A. G.; Palmquist, K. E.; Aston, K. W.; Hitchcock, J.; Rogers, M. D.; McDonald, J.; Johnson, A. R.; Munie, G. E.; Wittwer, A. J.; Man, C.; Settle, S. L.; Nemirovskiy, O.; Vickery, L. E.; Agawal, A.; Dyer, R. D.; Sunyer, T. Discovery of (pyridin-4-yl)-2*H*-tetrazole as a novel scaffold to identify highly selective matrix metalloproteinase-13 inhibitors for the treatment of osteoarthritis. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 576–580.

(24) Whitlock, G. A.; Dack, K. N.; Dickinson, R. P.; Lewis, M. L. A novel series of highly selective inhibitors of MMP-3. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6750–6753.

(25) Freeman-Cook, K. D.; Reiter, L. A.; Noe, M. C.; Antipas, A. S.; Danley, D. E.; Datta, K.; Downs, J. T.; Eisenbeis, S.; Eskra, J. D.; Garmene, D. J.; Greer, E. M.; Griffiths, R. J.; Guzman, R.; Hardink, J. R.; Janat, F.; Jones, C. S.; Martinelli, G. J.; Mitchell, P. G.; Laird, E. R.; Liras, J. L.; Lopresti-Morrow, L. L.; Pandit, J.; Reilly, U. D.; Robertson, D.; Vaughn-Bowser, M. L.; Wolf-Gouviea, L. A.; Yocum, S. A. Potent, selective spiropyrrolidine pyrimidinetrione inhibitors of MMP-13. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6529–6534.

(26) Pirard, B. Insight into the structural determinants for selective inhibition of matrix metalloproteinases. *Drug Discovery Today* **2007**, *12*, 640–646.

(27) Bramhall, S. R.; Hallissey, M. T.; Whiting, J.; Scholefield, J.; Tierney, G.; Stuart, R. C.; Hawkins, R. E.; McCulloch, P.; Maughan, T.; Brown, P. D.; Baillet, M.; Fielding, J. W. L. Marimastat as maintenance therapy for patients with advanced gastric cancer: a randomised trial. *Br. J. Cancer* **2002**, *86*, 1864–1870.

(28) Bramhall, S. R.; Rosemurgy, A.; Brown, P. D.; Bowry, C.; Buckels, J. A. Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. *J. Clin. Oncol.* **2001**, *19*, 3447–3455.

(29) Groves, M. D.; Puduvalli, V. K.; Hess, K. R.; Jaeckle, K. A.; Peterson, P.; Yung, W. K. A.; Levin, V. A. Phase II trial of Temozolomide plus the matrix metalloproteinase inhibitor, marimastat, in recurrent and progressive glioblastoma multiforme. *J. Clin. Oncol.* **2002**, *20*, 1383–1388.

(30) Sparano, J. A.; Bernardo, P.; Stephenson, P.; Gradishar, W. J.; Ingle, J. N.; Zucker, S.; Davidson, N. E. Randomized phase III trial of marimastat versus placebo in patients with metastatic breast cancer who have responding or stable disease after first-line chemotherapy: Eastern Cooperative Oncology Group Trial E2196. *J. Clin. Oncol.* **2004**, *22*, 4683–4690.
(31) Lara, P. N., Jr.; Stadler, W. M.; Longmate, J.; Quinn, D. I.; Wexler, J.; Van Loan, M.; Twardowski, P.; Gumerlock, P. H.; Vogelzang, N. J.; Vokes, E. E.; Lenz, H. J.; Doroshow, J. H.; Gandara, D. R. A randomized phase II Trial of the matrix metalloproteinase inhibitor BMS-275291 in hormone-refractory prostate cancer patients with bone metastases. *Clin. Cancer Res.* **2006**, *12*, 1556–1563.
(32) Brinker, B. T.; Krown, S. E.; Lee, J. Y.; Cesarman, E.; Chadburn, A.; Kaplan, L. D.; Henry, D. H.; Von Roenn, J. H. Phase 1/2 trial of BMS-275291 in patients with human immunodeficiency virus-related Kaposi sarcoma: a multicenter trial of the AIDS malignancy consortium. *Cancer* (*Hoboken, NJ, U.S.*) **2008**, *112*, 1083–1088.
(33) Miller, K. D.; Saphner, T. J.; Waterhouse, D. M.; Chen, T.-T.; Rush-Taylor, A.; Sparano, J. A.; Wolff, A. C.; Cobleigh, M. A.; Galbraith, S.; Sledge, G. W. A randomized phase II feasibility trial of BMS-275291 in patients with early stage breast cancer. *Clin. Cancer Res.* **2004**, *10*, 1971–1975.
(34) Bissett, D.; O'Byrne, K. J.; von Pawel, J.; Gatzemeier, U.; Price, A.; Nicolson, M.; Mercier, R.; Mazabel, E.; Penning, C.; Zhang, M. H.; Collier, M. A.; Shepherd, F. A. Phase III study of matrix metalloproteinase inhibitor prinomastat in non-small-cell lung cancer. *J. Clin. Oncol.* **2005**, *23*, 842–849.
(35) Hudson, M. P.; Armstrong, P. W.; Ruzyllo, W.; Brum, J.; Cusmano, L.; Krzeski, P.; Lyon, R.; Quinones, M.; Theroux, P.; Sydlowski, D.; Kim, H. E.; Garcia, M. J.; Jaber, W. A.; Weaver, W. D. Effects of Selective Matrix Metalloproteinase Inhibitor (PG-116800) to Prevent Ventricular Remodeling After Myocardial Infarction. *J. Am. Coll. Cardiol.* **2006**, *48*, 15–20.
(36) Yarbrough, W. M.; Mukherjee, R.; Escobar, G. P.; Mingoia, J. T.; Sample, J. A.; Hendrick, J. W.; Dowdy, K. B.; McLean, J. E.; Lowry, A. S.; O'Neill, T. P.; Spinale, F. G. Selective Targeting and Timing of Matrix Metalloproteinase Inhibition in Post-Myocardial Infarction Remodeling. *Circulation* **2003**, *108*, 1753–1759.
(37) Krzeski, P.; Buckland-Wright, C.; Balint, G.; Cline, G. A.; Stoner, K.; Lyon, R.; Beary, J.; Aronstein, W. S.; Spector, T. D. Development of musculoskeletal toxicity without clear benefit after administration of PG-116800, a matrix metalloproteinase inhibitor, to patients with knee osteoarthritis: a randomized, 12-month, double-blind, placebo-controlled study. *Arthritis Res. Ther.* **2007**, *9*, R109.
(38) Becker, D. P.; Barta, T. E.; Bedell, L.; DeCrescenzo, G.; Freskos, J.; Getman, D. P.; Hockerman, S. L.; Li, M.; Mehta, P.; Mischke, B.; Munie, G. E.; Swearingen, C.; Villamil, C. I. R-Amino-α-sulphone hydroxamates as potent MMP-13 inhibitors that spare MMP-1 *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2719−2722.
(39) Becker, D. P.; DeCrescenzo, G.; Freskos, J.; Getman, D. P.; Hockerman, S. L.; Li, M.; Mehta, P.; Munie, G. E.; Swearingen, C. R-Alkyl-R-amino-α-sulphone hydroxamates as potent MMP inhibitors that spare MMP-1. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2723−2725.
(40) Lollini, L.; Haller, J.; Eugui, E. M.; Womble, S. W.; Martin, R.; Campbell, J. Disease modification by RS-130830, a collagenase-3 selective inhibitor, in experimental osteoarthritis (OA). *Arthritis Rheum.* **1997**, *40* (Suppl S87), 341.
(41) Close, D. R. Matrix metalloproteinase inhibitors in rheumatic diseases. *Ann. Rheum. Dis.* **2001**, *60*, iii62–iii67.
(42) Becker, D. P.; Villamil, C. I.; Barta, T. E.; Bedell, L. J.; Boehm, T. L.; DeCrescenzo, G. A.; Freskos, J. N.; Getman, D. P.; Hockerman, S.; Heintz, R.; Howard, S. C.; Li, M. H.; McDonald, J. J.; Carron, C. P.; Funckes-Shippy, C. L.; Mehta, P. P.; Munie, G. E.; Swearingen, C. A. Synthesis and structure−activity relationships of β- and α-piperidine sulfone hydroxamic acid matrix metalloproteinase inhibitors with oral antitumor efficacy. *J. Med. Chem.* **2005**, *48*, 6713–6730.
(43) Samaritoni, J. G.; Babbitt, G. E. Synthesis of 2-(4-quinazolinyl)ethyl sulfides via addition of thiols to 4-vinylquinazolines. *J. Heterocycl. Chem.* **1997**, *34*, 1263–1266.
(44) Kolodziej, S. A.; Hockerman, S. L.; Boehm, T. L.; Carroll, J. N.; DeCrescenzo, G. A.; McDonald, J. J.; Mischke, D. A.; Munie, G. E.; Fletcher, T. R.; Rico, J. G.; Stehle, N. W.; Swearingen, C.; Becker, D. P. Orally bioavailable dual MMP-1/MMP-14 sparing, MMP-13 selective α-sulfone hydroxamates. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3557–3560.
(45) Kolodziej, S. A.; Hockerman, S. L.; DeCrescenzo, G. A.; McDonald, J. J.; Mischke, D. A.; Munie, G. E.; Fletcher, T. R.; Stehle, N.; Swearingen, C.; Becker, D. P. MMP-13 selective isonipecotamide α-sulfone hydroxamates. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3561–3564.
(46) van de Waterbeemd, H.; Testa, B. In *Drug Bioavailability: Estimation of Solubility, Permeability, Absorption and Bioavailability*; Strauss GmbH: Mörlenbach, Germany, 2009; pp 458.
(47) Silverman, R. B. Lead Modification: Drug Design and Development. In *The Organic Chemistry of Drug Design and Drug Action*; Elsevier Academic Press: New York, 2004; pp 62−65.
(48) Mistryukov, E. A.; Aronova, N. I. Basicity of amines of the piperidine series and dependence of basicity on steric and polar factors. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 789–793.
(49) Gillaspy, M.; Lefker, B. A.; Hada, W. A.; Hoover, D. J. A simple method for the formation of cyclopropylamines: the first synthesis of tricyclopropylamine. *Tetrahedron Lett.* **1995**, *36*, 7399–7402.
(50) Wishart, D. S.; Knox, C.; Guo, A. C.; Cheng, D.; Shrivastava, S.; Tzur, D.; Gautam, B.; Hassanali, M. DrugBank: a knowledgebase for drugs, drug actions and drug targets. *Nucleic Acids Res.* **2008**, *36*, D901–D906.
(51) Kageyama, S.; Anderson, B. D.; Hoesterey, B. L.; Hayashi, H.; Kiso, Y.; Flora, K. P.; Mitsuya, H. Protein binding of human immunodeficiency virus protease inhibitor KNI-272 and alteration of its in vitro antiretroviral activity in the presence of high concentrations of proteins. *Antimicrob. Agents Chemother.* **1994**, *38*, 1107–1111.
(52) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359–4369.
(53) Lovejoy, B.; Cleasby, A.; Hassell, A. M.; Luther, M. A.; Weigl, D.; McGeehan, G.; Lambert, M. H.; Jordan, S. R. Structural analysis of the catalytic domain of human fibroblast collagenase. *Ann. N.Y. Acad. Sci.* **1994**, *732*, 375–378.
(54) Borkakoti, N.; Winkler, F. K.; Williams, D. H.; D'Arcy, A.; Broadhurst, M. J.; Brown, P. A.; Johnson, W. H.; Murray, E. J. Structure of the catalytic domain of human fibroblast collagenase complexed with an inhibitor. *Nat. Struct. Biol.* **1994**, *1*, 106–110.
(55) Lovejoy, B.; Welch, A. R.; Carr, S.; Luong, C.; Broka, C.; Hendricks, R. T.; Campbell, J. A.; Walker, K. A. M.; Martin, R.; Van Wart, H.; Browner, M. F. Crystal structures of MMP-1 and -13 reveal the structural basis for selectivity of collagenase inhibitors. *Nature Struct. Biol.* **1999**, *6*, 217–221.
(56) Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith, G. T. How good is fluorine as a hydrogen bond acceptor? *Tetrahedron* **1996**, *52*, 12613–12622.
(57) Shalinsky, D. R.; Brekken, J.; Zou, H.; McDermott, C. D.; Forsyth, P.; Edwards, D.; Margosiak, S.; Bender, S.; Truitt, G.; Wood, A.; Varki, N. M.; Appelt, K. Broad antitumor and anti-angiogenic activities of AG3340, a potent and selective MMP inhibitor undergoing advanced oncology clinical trials. *Ann. N.Y. Acad. Sci.* **1999**, *878*, 236–270.
(58) Bottomley, K. M.; Borkakoti, N.; Bradshaw, D.; Brown, P. A.; Broadhurst, M. J.; Budd, J. M.; Elliott, L.; Eyers, P.; Hallam, T. J.; Handa, B. K.; Hill, C. H.; James, M.; Lahm, H.; Lawton, G.; Merritt, J. E.; Nixon, J. S.; Rothlisberger, U.; Whittle, A.; Johnson, W. H. Inhibition of bovine nasal cartilage degradation by selective matrix metalloproteinase inhibitors. *Biochem. J.* **1997**, *323*, 483–488.
(59) Billinghurst, R. C.; Dahlberg, L.; Ionescu, M.; Reiner, A.; Bourne, R.; Rorabeck, C.; Mitchell, P.; Hambor, J.; Diekmann, O.; Tschesche, H.; Chen, J.; Van Wart, H.; Poole, A. R. Enhanced cleavage of type II collagen by collagenases in osteoarthritic articular cartilage. *J. Clin. Invest.* **1997**, *99*, 1534–1545.
(60) Pfeffer, M. A.; Pfeffer, J. M.; Fishbein, M. C.; Fletcher, P. J.; Spadaro, J.; Kloner, R. A.; Braunwald, E. Myocardial infarct size and ventricular function in rats. *Circ. Res.* **1979**, *44*, 503–512.
(61) Fletcher, P. J.; Pfeffer, J. M.; Pfeffer, M. A.; Braunwald, E. Left ventricular diastolic pressure−volume relations in rats with healed myocardial infarction. Effects on systolic function. *Circ. Res.* **1981**, *49*, 618–626.
(62) Holmbeck, K.; Bianco, P.; Caterina, J.; Yamada, S.; Kromer, M.; Kuznetsov, S. A.; Mankani, M.; Robey, P. G.; Poole, A. R.; Pidoux, I.; Ward, J. M.; Birkedal-Hansen, H. MT1-MMP-deficient mice develop dwarfism, osteopenia, arthritis, and connective tissue disease due to inadequate collagen turnover. *Cell* (*Cambridge, MA, U. S.*) **1999**, *99*, 81–92.
(63) Zhou, Z.; Apte, S. S.; Soininen, R.; Cao, R.; Baaklini, G. Y.; Rauser, R. W.; Wang, J.; Cao, Y.; Tryggvason, K. Impaired endochondral ossification and angiogenesis in mice deficient in membrane-type matrix metalloproteinase I. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 4052–4057.
(64) Devy, L.; Huang, L.; Naa, L.; Yanamandra, N.; Pieters, H.; Frans, N.; Chang, E.; Tao, Q.; Vanhove, M.; Lejeune, A.; van Gool, R.;

Sexton, D. J.; Kuang, G.; Rank, D.; Hogan, S.; Pazmany, C.; Ma, Y. L.; Schoonbroodt, S.; Nixon, A. E.; Ladner, R. C.; Hoet, R.; Henderikx, P.; TenHoor, C.; Rabbani, S. A.; Valentino, M. L.; Wood, C. R.; Dransfield, D. T. Selective Inhibition of Matrix Metalloproteinase-14 Blocks Tumor Growth, Invasion, and Angiogenesis. *Cancer Res*. **2009**, *69*, 1517–1526.

(65) Vora, R. A.; Vyas, P. R. Mesogenic homologous series: 4-isopropoxyphenyl 4′-*n*-alkoxycinnamates and binary systems comprising the homologs of this series. *J. Indian Chem. Soc*. **1996**, *73*, 507–511.

(66) DeCrescenzo, G. A.; Rico, J. G.; Boehm, T. L.; Carroll, J. N.; Kassab, D. J.; Mischke, D. A.Rao, S. Sulfamato hydroxamic acid metalloprotease inhibitor. U.S. Patent 6,448,250, 2000.

(67) Otwinowski, Z.; Minor, W. Processing of X-ray diffraction data collected in oscillation mode. *Methods Enzymol*. **1997**, *276*, 307–326.

(68) Jones, T. A.; Zou, J. Y.; Cowan, S. W.; Kjeldgaard, M. Improved methods for building protein models in electron density maps and the location of errors in these models. *Acta Crystallogr., Sect. A: Found. Crystallogr*. **1991**, *47*, 110–119.

(69) Emsley, P.; Cowtan, K. Coot: model-building tools for molecular graphics. *Acta Crystallogr., Sect. D: Biol. Crystallogr*. **2004**, *60*, 2126–2132.

(70) Brunger, A. T.; Free, R Free *R* value: a novel statistical quantity for assessing the accuracy of crystal structures. *Nature* **1992**, *355*, 472–475.

(71) Murshudov, G. N.; Vagin, A. A.; Dodson, E. J. Refinement of macromolecular structures by the maximum-likelihood method. *Acta Crystallogr., Sect. D: Biol. Crystallogr*. **1997**, *53*, 240–255.

(72) Nagase, H.; Fields, C. G.; Fields, G. B. Design and characterization of a fluorogenic substrate selectively hydrolyzed by stromelysin 1 (matrix metalloproteinase-3). *J. Biol. Chem*. **1994**, *269*, 20952–20957.

(73) Knight, C. G.; Willenbrock, F.; Murphy, G. A novel coumarin-labeled peptide for sensitive continuous assays of the matrix metalloproteinases. *FEBS Lett*. **1992**, *296*, 263–266.

(74) Luckow, V. A. Insect Cell Expression Technology. In *Protein Engineering: Principles and Practice*; John Wiley & Sons: New York, **1996**; pp 183−218.

(75) Luckow, V. A.; Lee, S. C.; Barry, G. F.; Olins, P. O. Efficient generation of infectious recombinant baculoviruses by site-specific transposon-mediated insertion of foreign genes into a baculovirus genome propagated in *Escherichia coli*. *J. Virol*. **1993**, *67*, 4566–4579.