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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Author Manuscript
This is a pre-publication author manuscript of the final, published article.

Recommended Citation
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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Abbreviations: ADME, absorption, distribution, metabolism and exctetion; Ar, aryl; Arg, arginine; Bid, twice daily; CY, cylophosphamide; DMEM, Dulbecco’s Modified Eagle Medium; DMF, dimethylformamide; EA, ethyl acetate; EDC, 1-ethyl-3-[3-dimethylaminopropyl]
Abstract

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 cartilage degradation in vitro. 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) 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.\(^10-13\) In order 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.\(^4,5,14-16\)

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.\(^23-26\)

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\textsuperscript{31} and for Kaposi Sarcoma.\textsuperscript{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.\textsuperscript{33} A Phase III study of 3 (Prinomastat/AG3340) in non-small-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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{36} Carboxylic acid 4 also induced musculoskeletal toxicity without clear benefit in patients with knee osteoarthritis in a 12-month, double-blind study.\textsuperscript{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.\textsuperscript{4, 5}

We previously described the synthesis and MMP inhibitory activity of β-sulfone hydroxamates\textsuperscript{38, 39} inspired by the Roche broad-spectrum MMP-inhibitor 5 which was in the clinic for OA.\textsuperscript{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.\textsuperscript{42} Hydroxamates tend to be rapidly metabolized, but we believe that the \( \alpha \)-spiro moiety in combination with the \( \alpha \)-sulfone moiety sterically hinder the metabolism of the otherwise labile hydroxamate moiety \textit{in vivo} leading to the outstanding pk properties of molecules of type 6. Herein we highlight our further efforts in the exploration of \( \alpha \)-sulfone \( \alpha \)-piperidine and \( \alpha \)-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 \( \alpha \)-piperidine 19w (SC-77964) and \( \alpha \)-THP 9i (SC-77774).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{mmp_inhibitors.png}
\caption{MMP Inhibitors}
\end{figure}
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 by hydrolysis of the methyl ester of 6 with potassium trimethylsilanoate followed by EDC coupling with O-(tetrahydro-2H-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. Specifically 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.
Scheme 1. Preparation of \( \alpha \)-tetrahydropyran-\( \alpha \)-sulfone 9a

Scheme 2. Synthesis of \( \alpha \)-tetrahydropyran-\( \alpha \)-sulfones 9b-d, f-h, j-m

The preparation of \( \alpha \)-tetrahydropyranyl sulfone hydroxamate 9i bearing the 4-trifluoromethyl group commenced with diaryl ether 12 (Scheme 3). According to the general method of Samaritoni,\textsuperscript{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 trimethylsilylanoate to afford
coupled carboxylic acid 8i. Coupling with THP-protected hydroxylamine was accomplished with the water-soluble diimide reagent (EDC) to afford the protected hydroxamate 11i, which was deprotected with HCl in 1,4-dioxane to afford hydroxamate 9i.

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

The N-unsubstituted α-piperidines 19j, p, and u were prepared as summarized in Scheme 4. N-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 4. Synthesis of unsubstituted $\alpha$-piperidine hydroxamates 19j,p,u

Scheme 5 outlines the general synthesis of N-substituted $\alpha$-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-2H-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
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.

**Scheme 5.** Synthesis of N-alkylated α-piperidine hydroxamates 19a-z

**Scheme 6.** Alternate synthesis of N-alkylated α-piperidine ethyl esters 20a-bb
Results and Discussion

The synthesized \( \alpha \)-tetrahydropyranyl (THP) and \( \alpha \)-piperidine hydroxamates were tested for inhibitory potency versus MMP-1, -2, -3, -7, -8, -9, -13 and -14 (Tables 1 and 2, respectively). Selected analogs 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 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 \( \alpha \)-spiro, \( \alpha \)-sulfone moiety that was optimized in our earlier work\(^{42}\) was maintained because of its beneficial effect on pharmacokinetic properties of the analogs, apparently through sterically limiting access to the hydroxamate by metabolic enzymes, in addition to improving enzyme potency and selectivity. Intermediate carbylic acid of all hydroxamates were also tested but failed to show any significant inhibitory potency for the MMP isozymes tested.

The \( \alpha \)-THP series was generally employed for rapidly screening the \( P_{1} \) (diaryl ether) moieties for enzyme inhibitory potency and selectivity, since synthesis via common intermediate 10 (Scheme 2) enabled rapid analog production. Most analogs in Table 1 were prepared via this method. This strategy of rapidly screening \( \alpha \)-THP analogs, 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 \( \alpha \)-piperidines exhibited greater exposure than the \( \alpha \)-THP analogs.
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 2700X, but we sought an even wider therapeutic window (>10,000X) with respect to MMP-1 to avoid any inhibition of this isozyme at \(C_{\text{max}}\). We had noted previously that the phenyloxyphenyl ethers were more potent than phenylthiophenyl ethers of type \(6\), but turned our attention away from the more metabolically labile thioethers to the oxygen-linked analogs 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 bioavailability of \(~2\)^{46}, which was consistent with our findings in this series. Thus, our strategy in analog 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 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 \(\alpha\)-sulfone analog of \(\beta\)-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 to demonstrate the superiority of \(\alpha\)-sulfones over \(\beta\)-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 nM 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 4-position gave a more selective compound (12,500X for MMP-13 over MMP-1) and modest pk in the rat. Moving the trifluoromethyl group to the para position improved both potency and selectivity (20,000X 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 4-chloro derivative 9c, and rivaling 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 hours, possibly due to oxidation of the pyridine nitrogen as well as its dramatically lower clogP of -2.6.

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. 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 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. 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 \( (R_2 =\text{4-MeOPh}) \) combined with an N-propargyl substituent on the piperidine gave 19a which exhibited good potency and selectivity and a very high \( C_{\text{max}} \), 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 two 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 analog. 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 $C_{\text{max}}$ 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 one hour, 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, giving the higher clogP fo 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 30X relative to some analogs. Interestingly, whereas most analogs did not spare the non-target MT1-MMP (MMP-14) enzyme, 19i was 1200X 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-poropargyl piperidine 19k exhibited a very high exposure when dosed orally as judged by the high Cmax of over 18,000 ng/mL, but the
half life was less than 1 h. N-Methoxyethyl piperidine 19i 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 sub-nanomolar 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 analog was 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, particular 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.\textsuperscript{50} In contrast, the 4-trifluoromethoxyphenyl ether contributed to overall spectacular profiles within the series and was installed in a number of analogs, including all subsequent analogs in Table 2, with varying piperidine N-substituents. Nonetheless, unsubstituted piperidine 19p bearing the 4-trifluoromethyl group in P1’ suffered from limited exposure and low bioavailability of only 6.7%, nearly identical to the rat pk of trifluoromethoxyphenyl ether 19u. 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 six hours after dosing. Thus, N-methoxyethylpiperidine hydroxamate 19v was selected for development as a 50 pM inhibitor of the gelatinases (MMP-2 and MMP-9) with 100,000-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 analogs 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 one hour. 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,\textsuperscript{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
food exposure in the rat, but with only a 14.7% bioavailability (19z) and a 1.39 h half life (19aa), respectively. 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 (active pharmaceutical ingredient) 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 simply not advanced.

Thus, preparation of the α-THP derivatives enabled rapid exploration of SAR, but these compounds had poorer pk profiles than the corresponding α-piperidines. The trifluoromethyl-substituted analogs 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 enhancement 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 the leads and spread the risk among different chemistries.
**Crystallography**

The crystal structure of MMP-13 in complex with 19v was determined at 1.9Å resolution (R\text{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 sidechain of Glu223. For that close interaction (2.8Å), 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.
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.

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, 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 0.75Å 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 sidechain in MMP-1 (Figure 2B). While this Arg residue has been observed in alternate conformations in MMP-1 with compounds similar to 19v 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 (R1) 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 inability 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. 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 OH⁻F hydrogen bond.
**Antitumor Efficacy**

Marimastat and AG-3340 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 promote 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 0.2nM, 56.5nM, 1.0nM, <0.1nM and 0.2nM 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$_{50}$ = 3883 nM). The IC$_{50}$ of 19w for MMP-1 is 100-fold greater than that of AG-3340.$^{57}$ 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 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 Figures 3a and 3b. 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 10 mg/kg 19w or 10mg/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.

Figures 3a and 3b. Efficacy of 19w in the PC3 tumor growth delay model, either as single agent or in combination with 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 non-traditional, non-cytotoxic agents in a setting of minimal tumor burden. Mice bearing MX-1 tumors were treated with 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, 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 intraarticular 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., selected compounds were tested for their ability to inhibit cartilage degradation. Importantly, this model system allows for the concentration-dependent characterization of compounds, including endpoint 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.

The α-THP sulfone 9i, which had an IC\textsubscript{50} of 0.4 nM when assayed using a purified MMP-13 enzyme preparation and synthetic small molecule as substrate, exhibited an IC\textsubscript{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\textsubscript{50} = 0.1 nM) and cartilage explant (IC\textsubscript{50} = 10 nM) assays. Compound 5,
which was included as a standard in all BNCD assays, had an IC$_{50}$ = 0.6 nM 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 alpha-piperidine sulfone MMP inhibitor 19v (data not shown). Consistent with the pharmacokinetic properties of this compound in canine, urinary collagen fragment excretion returned to pre-treatment levels as inhibitor was cleared.
Figure 5. MMP inhibitors protect bovine nasal cartilage from cytokine-induced degradation in the *ex vivo* cartilage explant assay of Billinghurst. 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, 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 uM) allowed for IC$_{50}$ determinations estimated at 10 nM and 75 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.

**Inhibition of post-infarction 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 previously described. The efficacy of 19w and 9i in reducing post-infarction LV dilation was assessed by ex vivo diastolic pressure-volume relationship a measure of LV size and compliance, as described by Fletcher et al. 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 post-infarction LV dilation (Figure 6). 50 mg/kg 19w and 9i significantly attenuated LV dilation, with mean LV volumes of $0.62 \pm 0.01 \text{ mL}$ and $0.63 \pm 0.03 \text{ mL}$, respectively (p<0.05 vs. MI-vehicle group, $0.69 \pm 0.02 \text{ mL}$).

**Figure 6.** Effect of 19w and 9i on LV post-MI. * p<0.05 vs. Sham-vehicle, #p<0.05 vs. MI-vehicle
In a separate experiment, the efficacy of 19v in reducing post-infarction 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 post-infarction 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).

**Figure 7.** Effect of 19v on LV post-MI. * p<0.05 vs. Sham-vehicle, #p<0.05 vs. MI-vehicle
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 >100,000-fold selectivity over MMP-1 for MMP-2 and MMP-13, and >50,000-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 hours (rat). The elimination half life (T_{1/2}) ranges from 4 to 6 hr. 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, b.i.d. 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.\textsuperscript{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\textsuperscript{62} and impaired endochondral ossification\textsuperscript{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.\textsuperscript{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,\textsuperscript{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. DSC refers to differential scanning calorimetry. MIR refers to multiple internal reflectance infrared spectroscopy. DMAC refers to N,N-dimethylacetamide. EDC refers to 1,3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride. NMM refers to N-methylmorpholine. 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 and were determined to be $\geq$95% pure. All animal work was carried out in accordance with institutional guidelines. All animal procedures were approved the Institutional Animal Care and Use Committee and conform to the NIH Guidelines for the Ethical Care and Treatment of Animals.
Tetrahydro-N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]-2H-pyran-4-carboxamide (9a). To a stirred solution of α-tetrahydropyranyl 4-fluorophenylsulfone methyl ester 7, (0.96 g, 3.2 mmol) in DMF (30 mL) was added phenol (0.3 g, 3.2 mmol), followed by Cs$_2$CO$_3$ (3.2 g, 10 mmol). The resulting mixture was heated to 70°C for 5 hours. The solution remained at ambient temperature for 18 hours, was diluted with H$_2$O and extracted with EtOAc. The organic layer was washed with half-brine and dried over Na$_2$SO$_4$. 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 hour. The solution was then heated to 80°C for 1 hour. 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$_2$SO$_4$. 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$_2$O (0.623 g, 4.6 mmol), followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.634 g, 3.3 mmol). After 10 minutes, a 50% aqueous hydroxylamine solution was added (2 mL, 30 mmol) and the solution was stirred at ambient temperature for 18 hours. 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$_2$SO$_4$. Reverse phase chromatography (on silica, acetonitrile/H$_2$O) provided the hydroxamate 9a as a white solid (0.37 g, 33%). HRMS (ES+) MH$^+$ for C$_{18}$H$_{19}$NO$_6$S, 378.1011, found: 378.0994.
4-[[4-(3-chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-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-2H-pyran-2-yl)hydroxylamine and EDC as previously described. To a solution of fluorophenylsulfone 10 (5.0 g, 13 mmol) in DMF (20 mL) was added p-chloro-phenol (5.0 g, 39 mmol), followed by Cs₂CO₃ (17 g, 52 mmol). The resulting solution was heated to 95°C for 7 hours. The solution was maintained at ambient temperature for 7 hours, diluted with water and extracted with EtOAc. The organic layer was washed with half-brine and dried over Na₂SO₄. 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 hour. The solvent was removed by rotary evaporation to provide the hydroxamate 9b as a white solid (3.4 g, 79%).

\[ ^1H \text{NMR (400 MHz, DMSO-d}_6) \delta 10.98 (s, 1 H), 9.18 (d, J=1.56 Hz, 1 H), 7.73 (d, J=8.99 Hz, 2 H), 7.51 (t, J=8.20 Hz, 1 H), 7.36 (d, J=8.99 Hz, 1 H), 7.32 (t, J=2.15 Hz, 1 H), 7.18 (d, J=8.99 Hz, 2 H), 7.15 (dd, J=7.81, 1.95 Hz, 1 H), 3.88 (dd, J=11.53, 3.71 Hz, 2 H), 3.16 (t, J=11.33 Hz, 2 H), 2.22 (d, J=12.50 Hz, 2 H), 1.83 - 1.98 (m, 2 H). \]

HRMS (ES+) M·NH₄⁺ calcd for C₁₈H₁₈NO₆SCl 429.0887; found: 429.0880. HRMS MH⁺ calcd for C₁₈H₁₈NO₆SCl, 412.0622; found, 412.0615.

4-[[4-(4-Chlorophenoxy)phenyl]sulfonyl]-N-hydroxytetrahydro-2H-pyran-4-carboxamide (9c). The α-THP p-chlorophenoxyphenylsulfone 9c was prepared as previously described.42
4-[[4-(3,4-dichlorophenoxy)-phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide (9d). To a solution of fluorophenylsulfone 10 (3.1 g, 8 mmol) in N,N-DMAC (20 mL) were added Cs$_2$CO$_3$ (8.8 g, 27 mmol) and 3,4-dichlorophenol (2.61 g, 16 mmol). The slurry was stirred at 95°C for 41 hours. The reaction was concentrated in vacuo, and the residue was taken up in EtOAc, washed with brine, dried over Na$_2$SO$_4$, 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$^+\text{NH}_4$ calcd for C$_{23}$H$_{25}$NO$_7$SCl$_2$, 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 fifteen minutes at ambient temperature the reaction was diluted with EtOAc and washed with water, dried over Na$_2$SO$_4$, 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$^+\text{NH}_4$ calcd for C$_{18}$H$_{17}$NO$_6$SCl$_2$, 463.05; found, 463.05.

N-hydroxy-4-[[4-(4-hydroxyphenoxy)phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxamide (9e). To a solution of fluorophenylsulfone 10$^{42}$ (2.7 g, 7.0 mmol) in DMAC (20 mL) was added Cs$_2$CO$_3$ (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$_2$SO$_4$, 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$^+\text{NH}_4$ calcd for C$_{30}$H$_{33}$NO$_8$S, 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 (3X) and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give hydroxamate 9e as a white solid (810 mg, 78%). ¹H NMR (400 MHz, DMSO-d₆) 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•MH₄⁺ calcd for C₁₈H₁₉NO₇S, 468.15; found, 468.15. HRMS MH⁺ calcd for C₁₈H₁₉NO₇S 394.0960; found 394.0962.

N-hydroxy-4-{[4-(4-isopropoxyphenoxy)phenyl]sulfonyl}tetrahydro-2H-pyran-4-carboxamide (9f). To a solution fluorophenylsulfone 10 (3.1 g, 8.0 mmol) in DMAC (20 mL) was added Cs₂CO₃ (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 (3X) and brine, dried over Na₂SO₄, 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 C₂₆H₃₃NO₈S, 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 Na₂SO₄, filtered, and concentrated in
The product was recrystallized (acetone/hexanes) to give the hydroxamate 9f as an off-white solid (2.2 g, 80%). \( ^1H \) NMR (400 MHz, DMSO-\( d_6 \)) \( \delta \) 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-2H-pyran-4-carboxamide (9g). To a solution fluorophenylsulfone 9 (2.0 g, 5.2 mmol) in DMAC (8 mL) was added 4-phenylphenol (Aldrich, 1.3 g, 7.8 mmol) followed by Cs\(_2\)CO\(_3\) (6.8 g, 20.8 mmol). The reaction was heated at 95°C for five hours. 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 hours) the acetonitrile was removed in vacuo. The resultant precipitate was collected, giving the hydroxamate 9g as a white solid (2.0 g, 83%). \( ^1H \) NMR (300 MHz, DMSO-\( d_6 \)) \( \delta \) 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-2H-pyran-4-carboxamide (9h). To a solution of fluorophenylsulfone 10 in DMAc (20 mL) was added CsCO2 (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 Na₂SO₄, filtered, and concentrated in vacuo.

Chromatography on silica gel eluting with EtOAc/hexane provided the diaryl ether 10h as a white foam (4.1 g, 97%). HRMS (ES+) MH⁺ calcd for C₂₄H₂₆NO₇SF₃, 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 Na₂SO₄, 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%). ¹H NMR (400 MHz, DMSO-d₆) 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 C₁₉H₁₈N₃O₆SF₃, 446.09, found 446.09. HRMS calcd for C₁₉H₁₈N₃O₆SF₃, 446.0885; found, 446.0872.

N-hydroxy-4-([4-(trifluoromethyl)phenoxy]phenyl)sulfonyl)tetrahydro-2H-pyran-4-carboxamide (9i). According to the general method of Samaritoni[J Het Chem 1997 34(4) 1263-1266] 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 10 (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 (4X). 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 (4X), and the combined extracts were washed with 0.1N HCl, water, and brine, and dried over Na₂SO₄ 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 Oxone® (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 (4X). The combined extracts were washed with water three times, brine, dried over MgSO₄, 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 K₂CO₃ (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, 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·H⁺ calcd for C₂₀H₁₉O₆SF₃, 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 removed 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 Na₂SO₄, 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·NH₄⁺ calcd for C₁₉H₁₇O₆SF₃ 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-2H-pyran-2-
yl)hydroxylamine (41.3 g, 0.353 mol) and EDC (30.6 g, 0.160 mol). After 4h at rt the reaction was concentrated in vacuo. The residue was taken up in EtOAc, washed with water, 5% aqueous KHSO4, saturated NaHCO3, and brine and dried over Na2SO4, filtered and concentrated to give the THP-protected hydroxamate 11i as a white foam (62.6 g, 100%). MS (ES+) M’NH4+ calcd for C24H26NO7SF3, 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 Na2SO4, filtered and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give compound 19p as a white solid (42.79 g, 87%). 1H NMR (400 MHz, DMSO-d6) 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 (2H, d, J=13.3 Hz), 1.84-2.00 (2H, m). MS (ES+) M’NH4+ calcd for C19H18NO6SF3, 463; found, 463. HRMS MH+ calcd for C19H18NO6SF3, 446.0885; found, 446.0871.
N-hydroxy-4-((4-(4-(trifluoromethoxy)phenoxy)phenyl)sulfonyl)tetrahydro-2H-pyran-4-carboxamide (9j). To a solution of fluorophenylsulfone 10 (3.1 g, 8 mmol) in DMAC (20 mL) were added Cs₂CO₃ (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 Na₂SO₄, 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 C₂₄H₂₆NO₈SF₃, 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 minutes at ambient temperature, the reaction was diluted with EtOAc and washed with water, dried over Na₂SO₄, filtered, and concentrated in vacuo. The product was recrystallized (acetone/hexanes) to give the hydroxamate 9j as a white solid (2.2 g, 65%). ¹H NMR (400 MHz, DMSO-d₆) 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+NH₄⁺ calcd for C₁₉H₁₈NO₇SF₃, 479.11; found, 479.11. HRMS MH⁺ calcd for C₁₉H₁₈NO₇SF₃, 462.0834; found, 462.0815.

N-hydroxy-4-((4-[4-(methylthio)phenoxy]phenyl)sulfonyl)tetrahydro-2H-pyran-4-carboxamide (9k). To a solution of fluorophenylsulfone 10 (3.1 g, 8.0 mmol) in DMAC (20 mL) was added Cs₂CO₃ (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 Na₂SO₄, 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 C₂₄H₂₉NO₇S₂, 508.15; 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 Na₂SO₄, filtered and concentrated in vacuo. The residue was recrystallized (acetone/hexanes) to give the hydroxamate 9k as a white solid (1.9 g, 57%). ¹H NMR (400 MHz, DMSO-d₆) 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 C₁₉H₂₁NO₆S₂ 424.09, found 424.09. HRMS MH⁺ calcd for C₁₉H₂₁NO₆S₂ 424.0889, found 424.0874.

N-hydroxy-4-[(4-[(trifluoromethyl)thio]phenoxy)phenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxamide (9l). To a solution of fluorophenylsulfone 10₄₂ (2.0 g, 5.2 mmol) in DMAC (6 mL) was added 4-(trifluoromethylthio)thiophenol (1.5 g, 7.8 mmol) followed by Cs₂CO₃ (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 18h 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$_6$) $\delta$ 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$_3$NO$_6$S, 476; found, 476. HRMS MH$^+$ calcd for C$_{19}$H$_{18}$F$_3$NO$_6$S, 478.0606; found, 478.0615.

4-pyridyl N-hydroxy-4-(4-(pyridin-4-yloxy)phenylsulfonyl)tetrahydro-2H-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$_6$) $\delta$ 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$_2$O$_6$S, 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 (3.00 g, 5.66 mmol) in DMF (10 mL) was added Cs$_2$CO$_3$ (4.7 g, 14.5 mmol) and 4-methoxyphenol (1.80 g, 14.5 mmol) and the solution was heated to 95 $^\circ$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 H₂O (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-2H-pyran-2-yl)hydroxylamine (1.34 g, 9.0 mmol). After the solution was stirred for 15 min, EDC (1.72g, 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 NaHCO₃, H₂O and brine, and then dried over MgSO₄. 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 C₂₂H₂₄N₂O₆S, 445; found, 445. Anal calcd for C₂₂H₂₄N₂O₆S.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 15⁴² (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$_2$CO$_3$ (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 X 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$_2$CO$_3$ (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 X 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, was
acidified to ~pH 3 with HCl, and was concentrated and azeotroped to dryness using acetonitrile.
This crude acid (~5.7 mmol) was combined with O-(tetrahydro-2H-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 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$_3$O$_6$S 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 Hz), 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$_3$O$_6$S·2HCl·1.5 H$_2$O: 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$_3$O$_6$S, 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$_2$CO$_3$ (4.00 g, 28.8 mmol) and 4-ethoxyphenol (3.99 g, 28.8 mmol). The solution was stirred at 90°C for 24 hours. The solution was diluted with H$_2$O (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 minutes. The reaction was stirred at this temperature for 0.5 hours. 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 hours. The precipitate was removed by filtration and the filtrate was concentrated in vacuo. The residue was diluted with H$_2$O (400 mL) and extracted with EtOAc. The organic layer was washed with 1 N NaOH, 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 gm, 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 hours. 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}.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 hours. The solution was diluted with H₂O (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over MgSO₄, 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%). ¹H NMR (400 MHz, CDCl₃) 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_{2}SO_{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 hours, 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-\(d_6\)) \(\delta\) 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\(_2\)SO\(_6\), 460.1677; found, 460.1678. Anal calcd for C\(_{23}\)H\(_{28}\)N\(_2\)SO\(_6\).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 (18d).** 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\(_2\)CO\(_3\) (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-2H-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 NaHCO₃ and water and dried over MgSO₄. 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. **¹H NMR** (400 MHz, DMSO-d₆) 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 C₂₄H₂₈N₂O₅S.HCl.0.9H₂O:  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 C₂₄H₂₈N₂O₅S, 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-\(d_6\)) \(\delta\) 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\(_2\)O\(_6\)S, 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\(_2\)CO\(_3\) (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, water and dried over MgSO₄. 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-2H-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 NaHCO₃, water and dried over MgSO₄. 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 3h. 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: $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 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$_2$O$_5$S, 461.2110; found, 461.2108. Anal. calcd for C$_{24}$H$_{32}$N$_2$O$_5$S.HCl.0.5H$_2$O: 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$_2$CO$_3$ (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) 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-2H-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: \( ^1 \text{H NMR} \) (400 MHz, DMSO-d<sub>6</sub>) \( \delta \) 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<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>7</sub>S.HCl.1.5H<sub>2</sub>O: 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<sup>+</sup> calcd for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>7</sub>S 493, found 493. HRMS calcd for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>7</sub>S, 493.2008; found, 493.1992.

1-cyclopropyl-N-hydroxy-4-[[4-(4-isoproxyphenoxy)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-isopropoxyphenol65 (1.28 g, 8.4 mmol) and Cs$_2$CO$_3$ (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 grams, 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 hours. The solvents were removed in vacuo. Water (50 mL) was added and the mixture was acidified with 2 N HCl 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-2H-pyran-2-yl) hydroxylamine (0.68 g, 4.5 mmol). After stirring for 16 hours at ambient temperature, the reaction mixture was concentrated to a residue that was dissolve 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 HCl/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 \textbf{19h} (0.3 g, 19%). \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) \(\delta\) 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\textsubscript{24}H\textsubscript{30}N\textsubscript{2}O\textsubscript{6}S.HCl: C, 56.41; H, 6.11; N, 5.48. Found:
C, 56.04; H, 5.82; N, 5.44. MS (CI) MH\textsuperscript{+} calcd for C\textsubscript{24}H\textsubscript{30}N\textsubscript{2}O\textsubscript{6}S, 475; found. 475. HRMS MH\textsuperscript{+}
calcd for C\textsubscript{24}H\textsubscript{30}N\textsubscript{2}O\textsubscript{6}S, 475.1903; found, 475.1893.

\textbf{N-hydroxy-4-(4-(4-(methylsulfonyl)phenoxy)phenylsulfonyl)-1-(prop-2-ynyl)piperidine-4-}
carboxamide (\textbf{19i}). To a solution of N-propargyl ethyl ester p-fluorosulfone 22i\textsuperscript{12} (2.5 g, 6.4
mmol) in DMF (15 mL) were added 4-methylsulfonylphenol (3.5 g, 20.3 mmol) and Cs\textsubscript{2}CO\textsubscript{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 \textbf{20i} (2.5
g, 77%).

To a solution of the diaryl ether ethyl ester \textbf{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 \textbf{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-2H-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<sub>6</sub>) 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<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>S<sub>2</sub>·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<sup>+</sup> calcd for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>S<sub>2</sub>, 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<sup>42</sup> (25.0 g, 67.3 mmol) and powdered K<sub>2</sub>CO<sub>3</sub> (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 MgSO4. 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 MgSO4. 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-2H-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 X 40 mL) and brine (30 mL). The solution was dried over Na2SO4 and concentrated to give THP-protected hydroxamate 18j as a nearly colorless foam (1.54 g, 100%): DSC 221.01°C. MIR ν 3285, 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 255.96°C; IR ν 3213, 3107, 1653, 1144 cm⁻¹; MS
MH⁺ calcd for C₁₉H₂₀N₂O₇S, 421; found, 421; C₁₉H₂₀N₂O₇S, 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), K₂CO₃ (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 X 100 mL). The combined organic phases were dried over MgSO₄, then filtered through silica, and concentrated. Chromatography afforded diaryl ether 20k as an oil (9.38 g, 100%). Elem. Anal. calcd for C₂₄H₂₅NO₇S: 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 (2.0g, 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-2H-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 NaHCO₃ (20 mL) and
EtOAc (2 X 50 mL). The combined organic phase was dried over MgSO₄, 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 minute. 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. ¹H NMR (400 MHz, DMSO-d₆) 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 C₂₂H₂₂N₂O₇S, 459; found, 459. HRMS calcd for C₂₂H₂₂N₂O₇S, 459.1226; found, 459.1222. Anal. calcd for C₂₂H₂₂N₂O₇S·HCl·1.5 H₂O: 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 K₂CO₃ (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 MgSO₄. 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-2H-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 NaHCO₃ and water and dried over MgSO₄. 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: ¹H NMR (400 MHz, DMSO-d₆) 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_{2}O_{8}S.HCl.H_{2}O: 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_{2}O_{8}S, 479.1488; found, 479.1497.

4-(4-(benzo[d][1,3]dioxol-5-yl)oxy)phenylsulfonyl)-1-cyclopropyl-N-hydroxypiperidine-4-carboxamide (19m). To a solution of N-BOC 4-fluorophenylsulfone ethyl ester 15 (9.0 g, 22.0 mmol) in DMF (30 mL) was added K_{2}CO_{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_{2}O (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) \(\delta\) 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 (4H, 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$_{3}$) \(\delta\) 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 4A 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 MgSO₄, filtered and concentrated in vacuo. Chromatography on silica gel eluting with EtOAc provided N-cyclopropyl amine \textbf{20m} (7.9 g, 100\%) as a white solid: $^1\text{H}$ NMR (400 MHz, CDCl$_3$) $\delta$ 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 \textbf{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 \textbf{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 \textbf{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-2H-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 MgSO4, 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. ¹H NMR (400 MHz, CDCl₃) 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 C₂₂H₂₄N₂SO₇, 461.1382; found, 461.1386. Anal. calcd for C₂₂H₂₄N₂SO₇.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 21 ¹¹² (14.36 g, 40 mmol) in methanol (50 mL) was added acetic acid (24.5 g, 400 mmol), a portion of 4A molecular sieves (2 g), (1-ethoxycyclopropyl)-oxytrimethylsilane (25.8 mL, 148 mmol) and sodium cyanoborohydride (7.105 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
MgSO₄, 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 C₁₇H₂₂NO₄SF₃, 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 Cs₂CO₃ (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 Na₂SO₄. 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 C₂₅H₂₉NO₇S, 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 C₂₃H₂₅NO₇S, 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-2H-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 Na₂SO₄.
Chromatography on silica gel eluting with EtOAc/hexane provided the THP-protected hydroxamate 18n as a yellow oil (940 mg, 70%). MS (Cl) MH⁺ calcd for C₂₈H₃₄N₂O₂S, 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%). ¹H NMR (400 MHz, DMSO-d₆) 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 (Cl) MH⁺ calcd for C₂₃H₂₆N₂O₇S, 475; found, 475. HRMS calcd for C₂₃H₂₆N₂O₇S, 475.1539; found, 475.1553. Anal. calcd for C₂₃H₂₆N₂O₇S.1.15HCl.05H₂O: 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 K₂CO₃ (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 cooled and diluted with H₂O (400 mL) and extracted with EtOAc. This organic phase was washed with water and brine and dried over MgSO₄, 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=2.0. 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_{5}F_{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-2H-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 H₂O (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over MgSO₄, 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 (3.33 g, 96%) as a white solid: DSC 207.29-211.84°C at 373.8 J/g. ¹H NMR (400 MHz, DMSO-d₆) 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}N₂SO_{5}F_{3}, 485; found, 485.
N-hydroxy-4-([4-(trifluoromethyl)phenoxy]phenyl)sulfonyl)piperidine-4-carboxamide (19p). To a solution of N-BOC 4-fluorophenylsulfone ethyl ester 15 (1.5 g, 3.61 mmol) in DMF (10 mL) was added Cs$_2$CO$_3$ (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$_2$SO$_4$. 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$_7$SF$_3$, 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$_2$SO$_4$. Concentration in vacuo provided the carboxylic acid 17p as a solid (2.11 g, 100%). MS (Cl) MH$^+$ calcd for C$_{24}$H$_{26}$NO$_7$SF$_3$, 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-2H-pyran-2-yl)hydroxylamine (634 mg, 5.41 mmol). After stirring for 1h 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 (Cl) MH\(^+\) calcd for C\(_{29}\)H\(_{35}\)N\(_2\)O\(_8\)SF\(_3\), 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 2h. 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\(_6\)) \(\delta\) 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 (Cl) MH\(^+\) calcd for C\(_{19}\)H\(_{19}\)N\(_2\)O\(_5\)SF\(_3\), 445; found, 445. HRMS calcd for C\(_{19}\)H\(_{19}\)N\(_2\)O\(_5\)SF\(_3\), 445.1045; found, 445.1052. Anal. calcd for C\(_{19}\)H\(_{19}\)N\(_2\)O\(_5\)SF\(_3\),0.5H\(_2\)O.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\(_6\)) \(\delta\) 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\(_3\)N\(_3\)O\(_6\)S, 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, brine and dried over MgSO₄, 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 Cs₂CO₃ (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 H₂O (400 mL) and extracted with EtOAc. The organic layer was washed with water, brine and dried over MgSO₄, 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%). ¹H NMR (400 MHz, CDCl₃) 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 C₂₄H₂₈NSO₅F₃, 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 H₂O (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_{5}F_{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-tetrahydropyanyl 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 H₂O (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over MgSO₄, 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: ¹H NMR (400 MHz, CDCl₃) 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, 1Hz), 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}N₂SO₅F₃, 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: ¹H NMR (400 MHz, DMSO-d₆) 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 C₂₂H₂₅SN₂O₅F₃, 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 15₂₂ (48 g, 115 mmol) in EtOAc (750 mL) at 0°C was bubbled HCl gas for 45 min, 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 K₂CO₃ (12.4 g, 90.0 mmol) and bromoethane (3.4 mL, 45.0 mmol). The solution was stirred at rt for 18 h, then diluted with H₂O (200 mL) and extracted with EtOAc. The organic layer was washed with H₂O, brine and dried over MgSO₄, filtered and concentrated in vacuo to provide the desired N-ethyl piperidine 22s (15.4 g, 100%) as an oil. ¹H NMR (400 MHz, CDCl₃) 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, 1Hz), 1.24 (3H, t, J = 7 Hz), 1.03 (3H, t, J = 7 Hz). HRMS calcd for C₁₆H₂₂NSO₄F, 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 Cs₂CO₃ (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 H₂O (400 mL) and extracted with EtOAc. The organic layer was washed with water, brine and dried over MgSO₄, 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\(_3\)) \(\delta\) 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\(_{39}\)NSO\(_5\)F\(_3\), 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 = 4.0. 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\(_5\)F\(_3\), 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-2H-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\(_2\)O (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\(_2\)SO\(_6\), 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$_2$SO$_5$F$_3$, 473.1358; found, 473.1361. Anal calcd for C$_{21}$H$_{23}$N$_2$SO$_5$F$_3$.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$_2$CO$_3$ (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 24h. The solution was concentrated under high vacuum and the residue was dissolved in EtOAc. The organic phase was washed with 1N aqueous NaOH, 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-2H-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 NaHCO₃, water, and dried over MgSO₄. 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 3h. Concentration in vacuo gave a residue which was triturated with diethyl ether to afford the N-methoxyethyl piperidine hydroxamate (3.95 g, 92.1%) as a white solid: ¹H NMR (400 MHz, DMSO-d₆) 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 C₂₂H₂₅F₃N₂O₆S₂, 535.1184; found, 535.1179. Anal calcd for C₂₂H₂₅F₃N₂O₆S₂.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 (1.5 g, 3.61 mmol) in
DMF (10 mL) was added Cs₂CO₃ (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 Na₂SO₄. Filtration through a pad of silica gel eluting with EtOAc provided the diaryl ether 16u as a yellow oil (2.11 g, 100%). MS(Cl) MNa⁺ calcd for C₂₆H₃₀F₃NO₈S, 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 Na₂SO₄. Concentration in vacuo provided the carboxylic acid 17u as a solid (2.2 g, 100%). MS(Cl) MH⁺ calcd for C₂₄H₂₆NO₈SF₃, 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-2H-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 MgSO₄. 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$_2$O$_6$SF$_3$, 461; found, 461. HRMS calcd for C$_{19}$H$_{19}$N$_2$O$_6$SF$_3$, 461.0994; found, 461.0997. Anal calcd for C$_{19}$H$_{19}$N$_2$O$_6$SF$_3$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 (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$_2$CO$_3$ (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 K₂CO₃ (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, brine and dried over MgSO₄. 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 H₂O (28 mL). The solution was then heated to 60°C for 18h. 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 16v (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-2H-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 NaHCO₃ and water and dried over MgSO₄. 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 3h. 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:

$$\text{^1H NMR (400 MHz, DMSO-}d_6\text{)} \delta 11.20 (1H, \text{br s}), 9.33 (1H, \text{br s}), 7.77 (2H, \text{d, J=8.6 Hz}), 7.51 (2H, \text{d, J=8.99 Hz}), 7.32 (2H, \text{d, J=9.4 Hz}), 7.21 (2H, \text{d, J=8.99 Hz}), 3.55-3.66 (4H, m), 3.23-3.31 (5H, m), 2.71-2.85 (2H, m), 2.52-2.59 (2H, m), 2.18-2.30 (2H, m).$$

HRMS $M^+$ calcd for $C_{22}H_{25}F_3N_2O_7S$, 519.1413; found, 519.1399. Anal. calcd for $C_{22}H_{25}F_3N_2O_7S\cdot HCl \cdot 0.5H_2O$: 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$_2$CO$_3$ (3.42 g, 18.0 mmol) and 4-(trifluoromethoxy)-phenol (3.7 g, 24.8 mmol). The solution was stirred at 90$^\circ$C for 40 h. The mixture was then diluted with H$_2$O (600 mL) and extracted with EtOAc. The organic layer was washed with water, 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 $M^+$ 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$_2$O (20 mL) and the solution was heated to 60$^\circ$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 C₂₂H₂₂NSO₆F₃, 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-2H-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 H₂O (400 mL) and extracted with EtOAc. The organic layer was washed with brine and dried over MgSO₄, 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, 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. ¹H NMR (400 MHz, DMSO-d₆) 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 C₂₂H₂₃N₂SO₆F₃, 501.1307; found, 501.1324. Anal. calcd for C₂₂H₂₃N₂SO₆F₃.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-methoxyphenoxy)phenyl]sulfonyl]-4-piperidinecarboxamide, Dihydrochloride (19x). To a solution of 4-fluorophenylsulfone \(15^{12}\) (6.22 g, 15 mmol) in DMF (7 mL) was added powdered \(\text{K}_2\text{CO}_3\) (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 \(\text{K}_2\text{CO}_3\) (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, 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 \(\text{K}_2\text{CO}_3\) (828 mg, 6.0 mmol), 2-picoly hydrochloride (492 mg, 3.0 mmol), and DMF (3 mL), and the mixture was stirred at ambient temperature for 2 h, 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 MgSO₄, 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 ten minutes, EDC (0.57 g, 3.0 mmol) was added, and the mixture was stirred overnight. The reaction was then diluted with half-saturated aqueous NaHCO₃ (50 mL) and extracted with EtOAc (100 mL, then 25 mL). The combined organic layers were dried over MgSO₄, 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 two minutes. The reaction was stirred for 2 hours at ambient temperature, then concentrated to afford the hydroxamate as the dihydrochloride salt 19x (1.20 g, 100%) as a white crystalline solid. ¹H NMR (400 MHz, DMSO-d₆) 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\textsubscript{25}H\textsubscript{24}F\textsubscript{3}N\textsubscript{3}O\textsubscript{6}, 552.1416; found, 522.1428. Anal. calcd for C\textsubscript{25}H\textsubscript{24}F\textsubscript{3}N\textsubscript{3}O\textsubscript{6}S\textsuperscript{2}HCl.1/3H\textsubscript{2}O: 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-picoly chloride (1.5 g, 8.8 mmol) and K\textsubscript{2}CO\textsubscript{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 (3X). The combined organic layers were washed with water and brine and dried over MgSO\textsubscript{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-picoly piperidine 20y as an amber oil (1.6 g, 60%): MS MH\textsuperscript{+} calcd for C\textsubscript{27}H\textsubscript{27}N\textsubscript{2}O\textsubscript{6}SF\textsubscript{3}, 565; found, 565. Anal. calcd for C\textsubscript{27}H\textsubscript{27}N\textsubscript{2}O\textsubscript{6}SF\textsubscript{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-picoly 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_{2}O_{6}SF_{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-2H-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_{3}O_{7}SF_{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%).

{\textsuperscript{1}}H NMR (400 MHz, DMSO-d_{6}) \delta 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_{3}O_{6}SF_{3} 552.1416, found 552.1417. Anal. calcd for C_{25}H_{24}N_{3}O_{6}SF_{3}.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 hour. 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$_2$CO$_3$ (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 hours. 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 22 as a light yellow gel (0.68 g, 65.4%).

To a solution of 4-fluorophenylsulfone 22 (0.68 g, 1.56 mmol) and powdered K$_2$CO$_3$ (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 hours. The solution was concentrated under high vacuum and the residue was dissolved in EtOAc. The organic layer was washed with 1N NaOH, 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 hours. 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 NaHCO₃, water and dried over MgSO₄. 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%). ¹H NMR (400 MHz, DMSO-d₆) 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 C₂₃H₂₇N₂O₇SF₃, 533.1459; found, 533.1566. Anal. calcd for C₂₃H₂₇N₂O₇SF₃.HCl.H₂O: 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 K₂CO₃ (3.45 g, 25 mmol) and 2-(2-bromoethoxy)tetrahydro-2H-pyran (1.85 mL, 12 mmol) and the
mixture was stirred for 48 hours 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 MgSO₄, 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 hours in the presence of powdered K₂CO₃ (2.07 g, 15 mmol) and 4-(trifluoromethoxy)phenol (2.67 mL, 15 mmol). The mixture was diluted with saturated NaHCO₃ (50 mL) and was extracted with EtOAc (150, then 50 mL). The combined organic layers were dried over MgSO₄, 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 hours, the reaction was cooled to 0°C. Concentrated hydrochloric acid was added drop-wise 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 16h. 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 minutes. After 4 hours 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$_{6}$) $\delta$ 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$_{3}$N$_{2}$O$_{7}$S, 505.1256; found, 505.1250.

1-acetyl-N-hydroxy-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$_{2}$CO$_{3}$ (65.2 g, 200 mmol) and 4-(trifluoromethoxy)phenol (21.4 g, 120 mmol). The solution was mechanically stirred at 60°C for 24 hours. The solution was then diluted with water (1 L) and extracted with EtOAc. The organic layer was washed with water, brine and dried over MgSO$_{4}$, 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 hours. The solution was concentrated in vacuo and the aqueous residue was acidified to pH=5.0 and extracted with EtOAc. The organic extract was washed with brine and dried over MgSO$_{4}$, 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 minutes. The reaction was stirred at this temperature for 2.5 hours. 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 hours. 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, 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-2H-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 hours. 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$_4$, 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 hours 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$_2$SO$_7$F$_3$, 502.1021; found, 502.0979. Anal. calcd for C$_{21}$H$_{21}$N$_2$SO$_7$F$_3$: 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$_3$N$_2$O$_6$S, 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$_{22}$H$_{21}$F$_3$N$_2$O$_6$S, 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_{3}N_{2}O_{6}S 503.1464, found 503.1461.

1H 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]-2H-pyran-4-carboxamide, hydrochloride complex were grown at 4°C by sitting drop vapor diffusion using 5 mg/mL protein and a reservoir solution of 1.4M lithium sulfate, 0.1M Hepes, pH 7.7. The crystallization drop consisted of 5µL protein plus 1µL reservoir solution. Rod-like crystals appeared within four to six weeks. Crystals were pre-equilibrated in a soaking solution containing 1.5M lithium sulfate, 0.1M Hepes, pH 7.7 without inhibitor at room temperature for more than two hours. These crystals were then transferred to a second solution containing 1.5M lithium sulfate, 0.1M Hepes, pH 7.7 and 2.5mM of replacement inhibitor (19v) and were left to incubate at room temperature for five to seven days. The cryo solution consisted of 20% sucrose, 1.5M lithium sulfate, and 0.1M 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 integrated and scaled with HKL-2000, 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\textsuperscript{68} and Coot\textsuperscript{69}, and the structures were refined (Table 4) initially with X-PLOR\textsuperscript{70} and were further optimized in Refmac\textsuperscript{71}.

**Table 4.** Crystallographic data and refinement statistics

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**Refinement statistics**

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Ramachandran plot statistics

- Most favored regions (#,%) 484, 88.8
- Disallowed regions (#,%) 3, 0.6

* Highest resolution bin.  
  $R_{syn} = \frac{\Sigma(|I_i| - \langle I \rangle)}{\Sigma I_i}$. All reflections with $I/\sigma_I < -1.0$ eliminated from scaling.

**Enzyme Assays.** Inhibitors were assayed against purified hMMP-1, hMMP-2, hMMP-8, hMMP-9, and hMMP-13 and MMP-14 using an enzyme assay based on cleavage of the fluorogenic peptide MCA-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂. Human MMP-3 activity was measured using a fluorogenic substrate containing glutamic acid and (S)-2-aminopentanoic acid as reported by Nagase. Assay conditions were similar to those described in G. Knight et al. 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. 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.

The enzyme substrate was a methoxycoumarin-containing polypeptide having the following sequence: MCA-ProLeuGlyLeuDpaAlaArgNH₂ where, “MCA” is methoxycoumarin and “Dpa” is 3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl alanine as purchased from Baychem (Redwood City, Calif.) 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 CaCl₂, 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 um of the MMP substrate. The control likewise was incubated at room temperature in separate plates with the MMP and 4 uM 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, Conn.) L550 plate reader. The IC₅₀’s were the calculated from these measurements.
Pharmacokinetic (pk) evaluation of MMP Inhibitors in Rats

Under metofane anesthesia, the femoral artery (all 8 rats) and femoral vein (only 4 of 8 rats) are isolated and canulated with PESO tubing and secured with 3.0 silk suture. The following determinations require 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 are then placed in restraining cages that permit minimal movement and allowed to recover from anesthesia for approximately 30 minutes. At time 0 (prior to dosing), blood samples (400 µL) are collected from arterial cannula.

One group of rats (4 rats per group) receives 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 receives 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 are collected from the arterial cannula at 15, 30, 60, 120, 240, and 360 minutes from the oral group with an additional 3 minute sample being collected from IV group. After each sample, the cannulas are flushed with PBS containing 10 units/mL heparin. The animals are subjected to euthanasia with an excess of anesthesia or carbon monoxide asphyxiation when the study is terminated at 6 hours. Blood samples from each time point are assayed for MMP-13 enzyme inhibitory activity and the circulating concentration of compound plus active metabolites is estimated based on the standard curve. Pharmacokinetic (pk) parameters are 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 i.p. on the day of pair-match (Day 1) on a qd x 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 b.i.d. to end with vehicle or compound 19w at doses of 50, 25, 12.5 and 6 mg/kg (b.i.d. 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 x 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 b.i.d. from evening of day 0 to day 25-30, when the animal were euthanized and tumors weighed. Vehicle and compound 19w
formulated in vehicle (MC/TW 80 vehicle; 0.5% methyl cellulose: 0.1% polysorbate 80). Tumor measurements begin on day 7 and continue every 3rd to 4th 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 i.p. diluted in PBS) on day 8 post cell injection.

**Bovine Nasal Cartilage Degradation Assay**

Based on the method described by Bottomley, et al, fresh bovine nasal cartilage disks (1 mm thick x 8 mm in diameter) were sterilely prepared and incubated for 72 hours in DMEM containing 5% heat-inactivated FBS containing penicillin (100 IU/mL), streptomycin (100 ug/mL) and amphotericin B (0.25 ug/mL). Disks were weighed to insure 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% CO₂ 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 hours. The presence and amount of hydroxyproline in hydrolysates was measured by mass spectrometry. Cartilage degradation was calculated as a percentage of the hydroxyproline 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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Table 1. IC$_{50}$ values (nM) versus MMPs for $\alpha$-tetrahydropyranyl sulfones

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* clogP: calculated log P
|   | Structure       | 1140 | <0.1 | 35   | -    | 0.9 | 0.2 | <0.1 | 10.6 | 1.83 | 8584 | 1172 | 1.87 | 35.9 |
|---|----------------|------|------|------|------|-----|-----|------|------|------|------|------|------|------|------|
| 9j| OCF<sub>3</sub> | 2500 | <0.1 | -    | -    | -   | <0.1| <0.1 | 3.63 | 1.36 | -    | -    | -    | -    | -    |
| 9k| SCH<sub>3</sub> | 5000 | 0.4  | 20   | -    | 0.4 | 0.25| 0.25 | 200  | 2.47 | 7272 | 3113 | 1.71 | 49.0 |
| 9l| SCF<sub>3</sub> | 5000 | 0.6  | -    | -    | -   | -   | 1.0  | -    | -0.47| 1610 | 3    | 0.25 | 42.3 |

<sup>a</sup>calculated by ACD Labs.

<sup>b</sup>Some data for 9c previously reported<sup>42</sup>
Table 2. IC$_{50}$ values (nM) and Oral Rat PK Data of $\alpha$-Piperidine Sulfones (20 mpk suspension)

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\(^a\)Data for 6 taken from Becker et. al.\(^{42}\) except for MMP-14
Some hemolysis was observed as evidenced by blood in the urine after iv dosing.
Table 3. Pharmacokinetic Parameters of 19v After a Single Oral Administration of 20 mg/kg<sup>a</sup>

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<th>$C_{\text{max}}$ (µg/mL)</th>
<th>$\text{AUC}_{0-\infty}$ (hr*µg/mL)</th>
<th>BA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse (M)</td>
<td>0.167</td>
<td>26.6</td>
<td>29.3</td>
<td>51.7</td>
</tr>
<tr>
<td>Mouse (F)</td>
<td>0.167</td>
<td>41.0</td>
<td>36.1</td>
<td>80.8</td>
</tr>
<tr>
<td>Rat (M)</td>
<td>2.00</td>
<td>42.4</td>
<td>273</td>
<td>66.6</td>
</tr>
<tr>
<td>Rat (F)</td>
<td>4.00</td>
<td>69.8</td>
<td>668</td>
<td>82.2</td>
</tr>
<tr>
<td>Dog (M)</td>
<td>0.833 ± 0.167</td>
<td>60.6 ± 5.9</td>
<td>228 ± 41</td>
<td>64.0 ± 6.1</td>
</tr>
<tr>
<td>Dog (F)</td>
<td>0.500 ± 0.000</td>
<td>68.9 ± 1.2</td>
<td>156 ± 16</td>
<td>69.2 ± 2.1</td>
</tr>
<tr>
<td>Cyno Monkey (M)</td>
<td>1.67 ± 0.33</td>
<td>37.1 ± 2.9</td>
<td>191 ± 35</td>
<td>53.8 ± 0.7</td>
</tr>
</tbody>
</table>

<sup>a</sup>blood sampled out to 24 h.