Synthesis and Structure-Activity Relationships of β- and α-Piperidine Sulphone Hydroxamic Acid Matrix Metalloproteinase Inhibitors with Oral Antitumor Efficacy

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Abstract
\(\alpha\)-Piperidine-\(\beta\)-sulphone hydroxamates were explored that are potent for MMP-2, -9 and -13 that are sparing of MMP-1 with good pk in the rat. An unexpected decarbonylation led to the hitherto unknown \(\alpha\)-sulphone hydroxamates that are superior to the corresponding \(\beta\)-sulphones in potency for target MMP’s, selectivity versus MMP-1, and oral exposure when dosed orally. \(\alpha\)-Piperidine-\(\alpha\)-sulphone hydroxamate SC-276 was advanced through antitumor and anti-angiogenesis assays and selected for development.

Introduction
Matrix metalloproteinases (MMPs) are zinc-dependent enzymes responsible for the remodeling and degradation of all components of the extracellular matrix.\(^1\) The upregulation of MMPs has been implicated in numerous disease states.\(^2\)\(^-\)\(^6\) Including osteoarthritis\(^7\) and cancer.\(^8\)\(^-\)\(^11\) MMPs are essential for tumor growth and metastasis,\(^12\) and inhibition of MMP-9 can block metastasis.\(^13\)\(^,\)\(^14\) It is recognized that most of the proteolytic activity associated with tumors in located in the stroma, representing either a defense reaction by surrounding tissues, or a recruitment process.

Until recently, clinical trials with MMPi’s for advanced cancer had not been successful in demonstrating efficacy.\(^15\)\(^,\)\(^16\) Bramhall has reported the first placebo-controlled double-blind study reporting success in treating cancer with an MMPi in a study treating gastric cancer patients with the broad-spectrum inhibitor marimastat.\(^17\) A survival benefit has also been recently demonstrated in glioblastoma multiforme patients on marimastat in combination with temozolomide, providing additional support that MMPi’s can improve the outcome of cancer patients.\(^18\) Marimastat afforded a survival rate similar to gemcitabine in patients with unresectable pancreatic cancer.\(^19\) Thus, the proof-of-principle for efficacy in treating human cancers with MMPi’s has now been demonstrated. Clinical studies are also presently underway with BMS-275291 for the treatment of cancer.\(^20\)

Inhibition of MMP-1 has been hypothesized\(^21\) to be the cause of the musculoskeletal syndrome (MSS) observed clinically with broad-spectrum inhibitors including marimastat. We therefore have concentrated our efforts on potently inhibiting selected MMPs while sparing MMP-1. The strategy of avoiding inhibition of MMP-1 has been applied to succinate MMP inhibitors by British Biotech.\(^22\) Cross inhibition of ADAMs and ADAMTSs may also partially account for side effects observed in long-term MMPi therapy.\(^20\)
We have previously described the synthesis and MMP inhibitory activity of a series of α-amino-β-sulphone hydroxamates [Becker BMCL 2001 2719] and α-alkyl-α-amino-β-sulphone hydroxamates23,24 as potent inhibitors of MMP-2 and MMP-13 that spare MMP-1. These compounds had moderate pharmacokinetic parameters and required enantioselective syntheses to access the individual enantiomers. We wanted to remove the chirality and improve the pharmacokinetic profile by incorporating an spiro ring alpha to the hydroxamate to reduce potential metabolic degradation of the hydroxamate moiety. It should be noted in this context that the α-tetrahydropyran β-sulphone RS-130,83025 synthesized by Roche Bio-Science has been advanced to Phase II clinical trials for osteoarthritis.26 During our examination of the β-sulphones series we discovered α-sulphone hydroxamate inhibitors, which are superior to the β-sulphone series in both enzyme profile and ADME properties.27-28 A series of α-sulphone hydroxamates has also been reported by the Wyeth group.29,30

This manuscript will highlight our initial efforts in the β-sulphone and α-sulphone aryl ether hydroxamate series resulting in the discovery of SC-276, an MMP-1 sparing inhibitor which shows excellent efficacy in tumor xenograft models.

Chemistry

The β-sulphone derivatives were prepared from N-BOC ethyl isonipecotate11 as illustrated in Scheme 1. Deprotonation of 1 with LDA and quenching with methylene diiodide gave iodomethyl derivative 2. Alkylation of the sodium salt of 4-mercapto-diphenyl ether with 2 gave the corresponding sulfide which was oxidized directly with MCPBA to afford the sulphone 3. Removal of the BOC group with HCl gave amine 4, and alkylation of the piperidine with an alkylating agent or via reductive amination gave the N-alkyl amine 5. Saponification of the ethyl ester with sodium hydroxide gave the carboxylic acid 6 which was coupled with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine utilizing EDC as the coupling reagent. Deprotection under acidic conditions gave the β-sulphone hydroxamate 7.

We desired the dimethyl ketal 8 as an intermediate for facile elaboration of the α-position via the ketone moiety to afford various a-substituted-β-sulphone hydroxamates. Toward this end we alkylated 4-mercapto diphenyl ether 10 with bromopyruvic acid in methanol (Scheme 2) to afford the α-keto acid 11. Oxidation of the sulfide to the sulphone followed by conditions of esterification with thionyl chloride in methanol proceeded with an unexpected decarbonylation to afford the α-sulphone 12. Direct treatment of the methyl ester 12 with hydroxylamine gave the corresponding hydroxamic acid 13.

The α,α-dimethyl-α-sulphone 17 was prepared as shown in Scheme 3. Alkylation of 4-phenoxytiophenol with t-butyl bromoacetate and oxidation of the resulting sulfide gave the sulphone 14. Dialkylation with methyl iodide and sodium hydride gave the dimethyl sulphone 15. Removal of the t-butyl ester with TFA gave the carboxylic acid which was coupled with hydroxylamine in the presence of EDC to give the α,α-dimethyl hydroxamic acid 17.

The alpha-THP sulphone 21 was prepared as shown in Scheme 4. Alkylation of 4-fluorothiophenol with methyl bromoacetate gave the sulhide which was oxidized with ozone to afford sulphone 18. The acidic methylene was dialkyated with bis(2-bromoethyl)ether to afford the α-sulphone 19. Saponification of the methyl ester with potassium trimethylsilanolate and subsequent coupling of the carboxylic acid with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (THP-hydroxylamine) utilizing the water-soluble carbodiimide reagent (EDC) gave the THP protected hydroxamate 20. Displacement of the fluoride with 4-chlorophenol anion and subsequent treatment with HCl gave the free hydroxamate 21.

N-alkylpiperidine phenyloxynphenyl α-sulphones were synthesized as described in Scheme 5. Ethyl N-BOC isonipecotate 1 was deprotonated with LDA and sulfinylated with the disulfide of 4-mercaptopdiphenyl ether to give the sulfide 22, and oxidation with MCPBA afforded the corresponding α-sulphone 23. Removal of the BOC protecting group under acidic conditions gave the free piperidine 24 which was either directly alkylated or reductively alkylated to afford 25. Saponification of the hindered ethyl ester proceeded under basic conditions and the resulting carboxylic acid 26 was coupled with THP-hydroxylamine employing ECD. Acidic deprotection of the hydroxamate moiety afforded the requisite hydroxamate 27 as the hydrochloride salt.
N-Alkylpiperidine phenylthiophenyl α-sulphones 35a-h were prepared as exemplified in Scheme 4. Ethyl N-BOC isonicotinate 1 was silylated with p-fluorophenylsulfide after deprotonation with LDA to afford the sulfide 29, and subsequent oxidation with MCPBA gave the corresponding α-sulphone 30. Acidic removal of the BOC group gave the free amine 31 as the hydrochloride salt which was then alkylated with an alkyl halide or via reductive amination to yield 32. The p-fluoro was then displaced via a nucleophilic aromatic substitution reaction with thiophenol to yield thioether 33. Basic saponification of the hindered ethyl ester gave the carboxylic acid, which was coupled with THP-hydroxylamine utilizing EDC to give the protected hydroxamate 34. Removal of the THP group with HCl gave the desired α-sulphone hydroxamate 35 as the hydrochloride salt for basic amines. Alternatively, as shown in Scheme 7, the fluoro of N-BOC sulphone 30 was displaced with thiophenol to afford thioether 36. Removal of the BOC with HCl gave the amine hydrochloride 37 which was alkylated to give tertiary amine 33.

**Biology**

Selected α-sulphone and β-sulphone hydroxamates were tested for inhibitory potency versus MMP-1, 2, 3, 8, 9, and 13. Table 1 summarizes the MMP inhibitory potency of β-sulphone analogs, and includes RS-130,830 as a direct comparator. We utilized the diphenyl ether moiety that we had utilized in our earlier ethers with varying substituents on the selectivity. The MMP-2 selectivity ratio of dimethylphenylthiophenyl sulphone to drive deeper into the P1’ selectivity pocket and enhance the typically with >1000-fold selectivity versus MMP-1.

Sulphone work, as it had enabled the production of analogs that were potent for MMP-2 and MMP-13, 21,22 although the potency for MMP-2 was attenuated 3-4X relative to the other analogs. The free NH compound 7b was roughly an order of magnitude less potent versus all enzymes tested, which was surprising. It is possible that the compound was unstable under the conditions of the assay leading to diminished potency. We were hoping for an enhancement in exposure in the rat for the α-piperidine derivatives versus the α-THP RS-130830. Propargyl compound 7e did exhibit a higher C_{max} of 8038 µg/mL, but the concentration at 6 hours was lower for all of these analogs relative to the neutral compound RS-130830.

As mentioned, we originally targeted ketal 8 to further our exploration of β-sulphone hydroxamates via elaboration of the ketone derived from the ketal, but Oxone® oxidation of α-keto acid 11 followed by standard conditions to form the methyl ester afforded the decarbonylated methyl ester 12. When α-sulphone hydroxamate 13 was subsequently prepared and tested, we were not expecting particularly potent inhibition of the target MMPs because the hydroxamate is known to serve as a tight chelator for the zinc in the active site, and one of the sulphone oxygens forms an energetically favorable H-bond with the NH of Ala-161 in the enzyme. This is analogous to the binding of amino acid sulphonamide hydroxamates and corresponds to those well-known MMP inhibitors in terms of digitization. Thus, we were surprised and delighted to find that the unsubstituted α-sulphone 13 maintained good inhibitory potency of 5 nM versus MMP-13, 2.6 nM versus MMP-2, and was selective versus MMP-1 (IC_{50} = 6600 nM). Indeed, we were then the first to report α-sulphone hydroxamates as potent MMP inhibitors.27,28 Aranapakam and coworkers at Wyeth have recently reported novel series of α-sulphones that are potent for MMP-13 and sparing of MMP-1, including a compound that is efficacious in an advanced rabbit osteoarthritis model.29,30

With the potency of α-sulphone 12 established, we prepared the α,α-dimethyl analog 17 which boosted the potency back to sub-nanomolar values, and actually exceeded the potency of the β-sulphones with an IC_{50} values for MMP-13 and MMP-2 of 0.25 nM and 0.1 nM, respectively. The α-sulphone 17 is also more potent for MMP-1 (IC_{50} = 220 nM) but is still >2000X sparing of MMP-1 relative to MMP-13. We thus determined to make the corresponding α-piperidine diaryl ethers and diaryl thioethers 9 (X = O and X = S, respectively). We also prepared the α-THP 21 corresponding to the Roche α-THP RS-130830 for a direct comparison of the b- and α-sulphones (Table 2). We have found, in general, that α-sulphones are more potent versus target MMP isozymes and also have superior pharmacokinetics relative to the β-sulphones. Specifically, relative to RS-130830, compound 21 is approximately 4X more potent versus MMP-2, 3X more potent against MMP-9, and 4X more potent versus MMP-13. Compound 21 is twice as potent versus MMP-1, so the selectivity ratio is actually improved. Potency for MMP-3 remains essentially unchanged.
When administered orally to the rat, compound 21 has twice the C$_{\text{max}}$, although the concentration at 6 hours is comparable. The t$_{1/2}$ is identical at 1.5 h (data was only collected to 6 hours, hence the t$_{1/2}$ is less that would be measured for a full 24 h data collection). Strikingly, the BA for α-sulphone 21 (45.8%) is double the value for RS-130830 (22%) in this direct head-to-head comparison. This higher bioavailability and C$_{\text{max}}$ may be due to greater steric bulk around the hydroxamate, protecting it from the usual modes of hydroxamate metabolism including N-O bond cleavage, hydrolysis, and glucuronidation. It is interesting to note that the α-sulphone is of slightly lower molecular weight relative to the β-sulphone and has one less rotatable bond. Veber has predicted improved BA for compounds with fewer rotatable bonds.\textsuperscript{32}

Table 3 summarizes the MMP inhibitory potency for diphenyl ether α-sulphone analogs and includes rat pk data for selected analogs. It should be noted for the rat pk in Tables 1 through 4 that plasma concentrations were measured only out to 6 hours. This protocol enables a higher throughput of compounds for rat pk, but leads to an underestimation in particular of the half life (t$_{1/2}$) of the compounds. It nonetheless allows a direct comparison among analogs for advancement selection criterion. In general, these analogs are very potent versus the target enzymes MMP-2, MMP-9 and MMP-13, and quite sparing of MMP-1. N-methyl analog 27c, for example, is 4600X selective for MMP-2 and MMP-13 over MMP-1. Comparable potency and selectivity would be expected for most of these analogs, given that the P1’ substituents is held constant, which occupies the S1’ selectivity pocket. As in the β-sulphone series, the secondary amine 27b was notably less potent than the other analogs in the series, and mesyl compound 27i was somewhat less potent as well. Secondary amine 27b did have the longest t$_{1/2}$ of 1.8 h among these compounds, but suffers from a lower BA of 16% as compared with the tertiary amine compounds tested. N-Methyl piperidine 27c showed good exposure and the highest bioavailability (59%) of the series, while N-cyclopropyl piperidine 27e had a C$_{\text{max}}$ of 15,720 ng/mL and a good BA of 36%. N-propargyl piperidine 27g exhibited the highest oral exposure of these analogs, with a very high C$_{\text{max}}$ of 22,882 ng/mL and a significant concentration (345 ng/mL) remaining after 6 h. The N-propargyl analog also had a good BA of 35.5%.

The improvement of the α-sulphones over the β-sulphones is again clearly borne out in the direct comparison of N-propargyl piperidine phenyloxyphenyl β-sulphone 7e and the corresponding α-sulphone 27g (Figure 3). The α-sulphone 27g is almost twice as potent at MMP-1, but it is 3X as potent at MMP-2, 9X as potent at MMP-9 and over 2X as potent at MMP-13. The exposure in rat after an oral suspension dose of 20 mpk was substantially greater for 31, with a C$_{\text{max}}$ of 22,882 µg/mL and a concentration at 6 h of 345 µg/mL, compared with a C$_{\text{max}}$ of 8038 µg/mL and C6h of 49 µg/mL for 7e.

We then prepared the phenylthiophenyl ether α-sulphones as summarized in Table 4 in order to enhance the selectivity versus MMP-1. These compounds were still highly potent, although slightly less potent relative to the phenyloxyphenyl ethers of Table 3. These thioethers have the advantage of exquisitely MMP-1 sparing, with all examples shown having selectivity ratios of >10,000X for MMP-2 over MMP-1, with the exception of N-mesyl piperidine 35g. N-cyclopropyl piperidine 35d, for example, is very potent for MMP-2 (IC$_{50}$ = 0.1 nM) with an IC$_{50}$ for MMP-1 of >10,000 nM. Cyclopropyl compound 35d is also very potent for MMP-13 (0.2 nM) and has moderate potency for MMP-9 (2.5 nM). The tertiary amines tested exhibit very good pk in the rat after oral suspension dosing. N-Cyclopropyl derivative 35d has a significant C$_{\text{max}}$ of 7647 ng/mL and a substantial amount remaining after 6 h (529 ng/mL), with a good BA of 34.6%. N-methoxyethyl piperidine also enjoyed good exposure, as did N-propargyl piperidine SC-276, with a C$_{\text{max}}$ of 13,630 ng/mL, and 281 ng/mL remaining after 6 h. SC-276 was selected for further study based on its excellent in vitro and in vivo pharmacokinetic parameters.

**Anti-angiogenic and anti-tumor properties of SC-276**

The growth of solid tumors has been shown to be dependent on the development of new blood vessels.\textsuperscript{33}

Avascular, microscopic growing tumors produce diffusible angiogenic factors that induce host capillary endothelial cells to proliferate, migrate and form new vessels in a process called tumor-induced angiogenesis. Once vascularized, tumor size can increase almost exponentially.\textsuperscript{34-36} To address the
question of whether SC-276 is anti-angiogenic in vivo and therefore might inhibit tumor growth by inhibiting angiogenesis, we tested SC-276 in a mouse model of corneal neovascularization.

The mouse corneal micropocket assay is a widely used model of angiogenesis useful for in vivo testing of anti-angiogenic agents. Hydron pellets containing basic fibroblast growth factor (bFGF) were implanted into the corneas of mice. Pronounced neovascularization occurred in the tissue surrounding the pellet of the course of 4 days. Mice were administered vehicle or SC-276, orally, twice a day beginning the evening of pellet implantation. On day 5, animals were sacrificed and corneal neovascularization was determined by computer-aided image analysis. SC-276 inhibited bFGF-induced corneal neovascularization in a dose-dependent manner (Fig 6). SC-276 reduced corneal neovascularization approximately 50% at a dose of 50 mpk and supports the hypothesis that the anti-tumor activity of SC-276 is due, at least in part, to inhibition of tumor angiogenesis.

Inhibition of Tumor Growth by SC-276

Matrix metalloproteinase inhibitors (MMPi) may be most useful in the human clinical setting when used in combination with chemotherapy. We tested SC-276 as single agent and in combination with Taxol, a chemotherapeutic used in the treatment of breast cancer. The Kaplan-Meier survival curves for the various treatment groups are presented in Fig 7. MX-1 carcinomas grew progressively and rapidly in mice that received vehicle only; the median survival time (MDS) was 25.3 days. A MDS value of 32.2 days was calculated for the mice treated with 100 mg/kg of SC-276. All tumors in this group reached the cut cut-off size of 1.5 g. The 32% increase in the MDS of the SC-276-treated mice was statistically significant when compared to the MDS of vehicle-treated mice (p < 0.00001). Eight of the 9 mice treated with Taxol had a MDS of 30.1 days. The 19% increase in survival compared to vehicle-treated mice was statistically significant (p=0.036). One mouse died from unknown causes on Day 13 and was not included in the analysis.
Excellent activity was seen when Taxol and SC-276 were combined. The MDS of the mice treated with Taxol and SC-276 was 46.7 days and represents a survival increase of 53% over the MDS of the mice treated with Taxol alone. These results clearly show that the combination of Taxol and SC-276 exceeds the efficacy of Taxol alone as demonstrated by the increased median survival time of mice bearing MX-1 tumors. Moreover, the survival benefit appears to be more than additive when compared to the efficacy of monotherapy with either agent (Table 5).

Crystallography and Modeling of α-Sulphones and β-sulphones
Joe McDonald Discussion of structure & modeling, selectivity vs. MMP-1 and Arg214 [Refs: a & b, Moy, 2000, etc…….]

Conclusions
The β-sulphone series provided potency for the targeted MMPs and selectivity versus MMP-1, but generally exhibited poor oral exposure (Table 1). In addition, we have observed that some β-sulphones with α-hydrogens can undergo β-elimination. In contrast, the α-sulphones possess both potency and selectivity and provide an improvement in oral exposure demonstrated by higher Cmax value and bioavailability. Both the aryl ether and thioether P1’ moieties provide excellent potency (Tables 3 and 4, respectively), but the thioether moiety exhibits enhanced selectivity over the phenyloxophenyl sulphones. The α-piperidine nitrogen substituents provide improved ADME properties, and compounds exhibiting the highest oral exposures are those with the methoxyethyl, cyclopropyl, allyl and propargyl groups (35c, 35d, 35e and SC-276). This work culminated in the discovery of SC-276, a thioether sulphone hydroxamate that shows excellent efficacy in murine xenograft tumor models and anti-angiogenesis assays.

SC-276 exhibits excellent potency for target enzymes, selectivity versus MMP-1, good pk in multiple species, and excellent efficacy in tumor xenograft models. Primate pk for SC-276 was excellent, with BA = 88% in cyto and a t1/2 of 3.8 h. The compound has been slated for development and has been prepared on a multi-kilo scale. Additional results 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. 1H NMR spectra were obtained from either General Electric QE-300 or Bruker-400 MHz Ultrasound spectrometers with tetramethylsilane (TMS) as an internal standard. Noise-decoupled and APT 13C 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. High-resolution mass spectra were recorded on a Finnigan MAT8430 instrument. Elemental analyses were conducted on a Control Equipment CEC240-XA instrument. Melting points are obtained by differential scanning calorimetry.

1-tert-Butyl 4-ethyl 4-(iodomethyl)piperidine-1,4-dicarboxylate (2). To a solution of ethyl isonipocate N-t-butyl carbamate I (1.00 g, 3.89 mmol) in dry THF (10 mL) at -40°C was added 1.8 M LDA (2.2 mL, 3.9 mmol) dropwise. After 0.5 h at -40°C the reaction was quenched with water and extracted with diethyl ether (3X). The combined extracts were washed with water and brine and dried over MgSO4. Concentration gave the desired iodide 2 (1.5 g, 96.8%) as an oil: 1H NMR (400 MHz, CDCl3) δ
of water (100 mL) and the resulting mixture was extracted with EA (3X). The combined extracts were washed successively with water, 1N KHSO₄, water and brine and dried over MgSO₄.

**1-tert-Butyl 4-ethyl 4-[(4-phenoxyphenyl)sulfonyl]methyl)piperidine-1,4-dicarboxylate (3).** To a suspension of sodium hydride (600 mg of a 60% dispersion, 15.0 mmol) in dry DMF (9 mL) at 0°C was added 4-phenoxy thiophenol (3.03 g, 15.0 mmol) in dry DMF (1 mL) and stirred for 15 min at 0°C. The sodium thiolate solution was then added to a solution of iodide 2 (5.96 g, 15.0 mmol) in DMF (9 mL) at 0°C and the solution was stirred for 1 h at 0°C and 3 h at rt. The reaction was quenched with the addition of water (100 mL) and the resulting mixture was extracted with EA (3X). The combined extracts were washed successively with water, 1N KHSO₄, water and brine and dried over MgSO₄. Concentration gave a residue (7.42 g) which was purified by chromatography on silica gel eluting with EA/hexane (20/80) to afford the desired sulfide (6.27 g, 89%) as a solid: HRMS calcd for C₂₆H₃₃NSO₅ 471.2063, found 471.2052. To a solution of the sulfide (6.2 g, 13.1 mmol) in CH₂Cl₂ at 0°C was added NaOH (198 mg, 4.96 mmol) in water (2 mL) and the solution was heated at 60°C for 18 h. The solution was then washed successively with water, saturated NaHCO₃, water, and brine, and then dried over MgSO₄. Concentration gave a residue (7.86 g) which was chromatographed on silica gel eluting with EA/hexane (30/70) to afford the desired hydroxamate 7(4.g) which was chromatographed on silica gel eluting with EA/hexane (30/70) to afford the β-sulphone 3 (6.4 g, 97%) as a colorless solid.

**Ethyl 4-[(4-phenoxyphenyl)sulfonyl]methyl)piperidine-4-carboxylate hydrochloride (4).** Through a solution of sulphone BOC amine 3 (1.11 g, 4.03 mmol) in EA (30 mL) at 0°C was bubbled HCl gas for 5 min. Concentration gave a colorless solid which was triturated with ether, filtered and dried to afford the ethyl carboxylate 4 (774 mg, 80%) as a colorless solid: ¹H NMR (300 MHz, CDCl₃) δ 7.94 (2H, m, 1.91 (2H, m), 1.45 (9H, s). 1H NMR (400 MHz, CDCl₃) δ 7.85 (2H, d, J = 8 Hz), 7.72 (1H, t, J = 8 Hz), 7.50 (4H, d, J = 7 Hz), 7.06 (4H, d, J = 7 Hz), 3.68 (2H, s), 3.42 (2H, m), 3.32 (2H, m), 3.16 (2H, td, J = 10, 3 Hz), 2.18 (2H, m), 1.42 (9H, s). Anal calcd for C₂₆H₃₄NSO₅HCl C, 57.33; H, 5.96; N, 3.18; Cl, 8.06. Found 57.29; H, 5.87; N, 3.17; Cl, 8.17.

**N-hydroxy-4-[(4-phenoxyphenyl)sulfonyl]methyl)piperidine-4-carboxamide hydrochloride (7b).** Through a solution of N-BOC hydroxamate 7a (300 mg, 495 mmol) in 1:1 EtOH/THF (6 mL) was sequentially added HOBT (290 mg, 2.1 mmol), EDC (480 mg, 2.5 mmol), NMM (0.59 mL, 5.37 mmol) and 50% aqueous hydroxylamine (0.35 mL, 5.37 mmol), and the solution was stirred at rt for 16 h. Water (35 mL) was added and the mixture was extracted with EA (4 X 50 mL). The combined extracts were washed successively with water and brine and dried over MgSO₄. Concentration gave a residue (900 mg) which was chromatographed on reverse phase eluting with MeCN/H₂O (gradient from 30/70 to 80/20) to afford the desired hydroxamate 7a (300 mg, 0.495 mmol) as a colorless solid: ¹H NMR (400 MHz, CDCl₃) δ 7.85 (2H, d, J = 8 Hz), 7.48 (2H, t, J = 8 Hz), 7.28 (1H, t, J = 7 Hz), 7.15 (4H, d, J = 7 Hz), 3.66 (2H, s), 3.42 (2H, m), 3.18 (2H, m), 1.91 (2H, m), 1.65 (2H, m), 1.38 (9H, s); Anal calcd for C₂₆H₃₄N₃O₅C, 58.76; H, 6.16; N, 5.71; S, 6.54. Found C, 58.64; H, 6.24; N, 5.66; S, 6.66.
dried over Na2SO4. The reaction was extracted with ethyl acetate (3X). The combined extracts were washed with water and brine, eluting with EA/hexane (1:1) afforded the N-methoxybenzylamine (MIR) 1731, 1581, 1486, 1242, 1140 cm⁻¹. The combined extracts were washed with water and brine, dried over Na2SO4, and concentrated to afford a colorless oil (1.03 g). Chromatography on silica gel eluting with EA/hexane (1:1) afforded the N-methoxybenzylamine (MIR) 1731, 1581, 1486, 1242, 1140 cm⁻¹. To a solution of 3-methoxybenzylamine (800 mg, 1.53 mmol) in EtOH (10 mL) and THF (15 mL) was added an aqueous solution of NaOH (612 mg, 15.3 mmol) in water (15 mL) and the solution was stirred for an additional 16 h at rt. The reaction mixture was then concentrated. Saturated aqueous sodium bicarbonate (10 mL) was then added and the reaction was extracted with ethyl acetate (3X). The combined extracts were washed with water and brine, dried over Na2SO4, and concentrated to afford a colorless oil (1.03 g). Chromatography on silica gel eluting with EA/hexane (1:1) afforded the N-methoxybenzylamine (MIR) 1731, 1581, 1486, 1242, 1140 cm⁻¹. To a solution of 3-methoxybenzylamine (800 mg, 1.53 mmol) in EtOH (10 mL) and THF (15 mL) was added an aqueous solution of NaOH (612 mg, 15.3 mmol) in water (15 mL) and the solution was heated under reflux for 16 h. The reaction mixture was concentrated, and 5.5N aqueous HCl (15 mL) was added followed by MeOH (20 mL) to affect dissolution of the resulting gum. Purification on a Waters reverse-phase instrument eluting with 15/85 MeCN/H2O with 0.5% HCl afforded the corresponding carboxylic acid 6c as a yellow-orange oil. IR (MIR) 3500 (br), 3200-2300 (br), 1581, 1486, 1244, 1142 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (2H, d, J = 8 Hz), 7.22 (2H, q, J = 8 Hz), 7.05 (5H, m), 6.85 (2H, m), 6.75 (1H, d, J = 8 Hz). MS MH⁺ calcd for C₁₉H₂₂N₂SO₅.HCl.H₂O C, 564.2086; H, 6.32; N, 4.89; Cl, 14.07; S, 7.85. Found C, 563.3140; H, 6.47; N, 4.86; Cl, 13.81; S, 7.89.

To a solution of amine hydrochloride 4c (748 mg, 1.70 mmol) in EtOH (30 mL) was added phenyl acetaldehyde (0.82 g, 92%) as a colorless oil: IR (MIR) 3500 (br), 3200-2300 (br), 1581, 1486, 1244, 1142 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (2H, d, J = 8 Hz), 7.22 (2H, q, J = 8 Hz), 7.05 (5H, m), 6.85 (2H, m), 6.75 (1H, d, J = 8 Hz). MS MH⁺ calcd for C₁₉H₂₂N₂SO₅.HCl.H₂O C, 564.2086; H, 6.32; N, 4.89; Cl, 14.07; S, 7.85. Found C, 563.3140; H, 6.47; N, 4.86; Cl, 13.81; S, 7.89.
for 16 h. The reaction was then concentrated to dryness and acidified with 2N HCl. Trituration with ether afforded the carboxylic acid 6d as a beige solid (894 mg): MS MH+ calcd for C$_{27}$H$_{30}$N$_2$SO$_5$ 495, found 495. Anal calcd for C$_{27}$H$_{30}$N$_2$SO$_5$-H$_2$O (429 mg, 92%) as a colorless solid: MS MH+ calcd for C$_{27}$H$_{30}$N$_2$SO$_5$-H$_2$O 495, found 495. Anal calcd for C$_{27}$H$_{30}$N$_2$SO$_5$.HCl.0.5H$_2$O C, 59.55; H, 6.02; N, 5.14. Found C, 59.29; H, 6.04; H, 5.19. IR (MIR) 1647, 1580 cm$^{-1}$.

N-hydroxy-4-[[4-(phenoxyphenyl)sulfonyl]methyl]-1-prop-2-ynylpiperidine-4-carboxamide hydrochloride (7e). To a solution of amine hydrochloride 4 (750 mg, 1.70 mmol) in DMF (10 mL) was added K$_2$CO$_3$ (469 mg, 3.4 mmol) followed by 80% propargyl bromide in toluene (0.25 mL, 1.7 mmol). The reaction was stirred at rt for 5 h and then diluted with EA (40 mL) and washed successively with water and brine and dried over MgSO$_4$. Concentration gave a residue (730 mg) which was chromatographed on silica gel eluting with EA to afford the N-propargyl amine ethyl ester 5e (620 mg, 82%) as a solid: IR (MIR) 3278, 1733, 1581, 1467, 1242, 1142 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.84 (2H, d, J = 9 Hz), 7.23 (1H, t, J = 7 Hz), 7.06 (4H, d, J = 9 Hz), 4.21 (2H, q, J = 7 Hz), 3.47 (2H, s), 3.41 (1H, m), 2.83 (2H, m), 2.69 (2H, m), 1.96 (2H, m), 1.33 (3H, t, J = 7 Hz). HRMS calcd for C$_{22}$H$_{23}$NSO$_5$ 429.1484, found 429.1480. Anal calcd for C$_{22}$H$_{23}$NSO$_5$.H$_2$O (50 mL) and the mixture was extracted with CHCl$_3$ (3X), and the combined extracts were washed successively with water and brine, dried over MgSO$_4$, and concentrated to afford a residue (380 mg) which was chromatographed on reverse phase eluting with a gradient of MeCN/H$_2$O/HCl to afford the hydroxamic acid hydrochloride salt 7d (104 mg, 14% from amine 4) as a colorless solid: MS MH+ calcd for C$_{27}$H$_{30}$N$_2$SO$_5$.HCl.0.5H$_2$O C, 59.55; H, 6.02; N, 5.14. Found C, 59.29; H, 6.04; H, 5.19. IR (MIR) 1647, 1580 cm$^{-1}$.
extracted with EA (3X). The combined extracts were washed with brine and dried over MgSO₄.

Concentration gave a viscous oil which was purified by chromatography on silica gel eluting with EA/hexane (15/85) to afford the corresponding sulfide (6.45 g, 13.0 mmol) by propargyl bromide (0.98 mL, 23.0 mmol). The reaction was stirred for 4 h at rt and then diluted with water (75 mL) and extracted with EA (3X). The combined extracts were washed successively with water and brine and dried over MgSO₄. Concentration gave a residue (10.5 g) which was chromatographed on silica gel eluting with EA/hexane (20/80) to afford the corresponding sulphone (86%): HRMS calcd for C₂₈H₃₇NSO₅C₂₄H₂₈N₂SO₅.HCl.0.5H₂O C, 63.36; H, 7.11; N, 2.44; S, 5.16.

Through a solution of the sulphone (5.7 g, 98%) as a colorless solid: HRMS calcd for C₃₁H₃₇NSO₅.C₂₈H₃₇NSO₅.HCl.0.5H₂O C, 65.50; H, 7.02; N, 2.66; S, 6.15.

To a solution of this sulfide (6.45 g, 13.0 mmol) in CH₂Cl₂ (100 mL) at 0°C was added 3-chloroperbenzoic acid (4.45 g, 26.0 mmol) and the reaction was stirred at 0°C for 3 h. The solution was then washed with water (75 mL) and brine and dried over MgSO₄. Concentration gave a residue (441.1651) which was chromatographed on silica gel eluting with EA/hexane (15/85) to afford the corresponding sulfide (6.45 g, 86%): HRMS calcd for C₂₈H₃₇NSO₅.HCl.0.5H₂O C, 63.36; H, 7.49; N, 2.86; S, 5.59.

N-hydroxy-2-[4-phenoxypyphenyl)sulfonyl]acetamide (13). To a solution of 3-bromopyruvic acid hydrate (1.95 g, 11.7 mmol) cooled to 0°C in MeOH (50 mL) was added 4-phenoxybenzenethiol (2.35 g, 11.7 mmol). The solution was stirred for 15 minutes followed by concentration in vacuo. The residue was partitioned between EA and H₂O and the organic layer was dried over MgSO₄. Concentration in vacuo provided the crude suloxide (2.35 g, 89%) as a colorless solid: HRMS calcd for C₂₄H₂₈N₂SO₅.HCl.0.5H₂O C, 57.36; H, 6.32; N, 5.68; Cl, 6.84.

To a solution of the HCl salt of amine (3.8 g, 100%) as a colorless solid. HRMS calcd for C₂₄H₂₈N₂SO₅.HCl.0.5H₂O C, 63.14; H, 6.18; N, 5.58; Cl, 6.84.

To a solution of carboxylic acid (4.13 g, 8.79 mmol) in 1:1 EtOH/THF (100 mL) was added acetyl chloride (35 uL, 0.49 mmol) to MeOH (1 mL). The solution was concentrated to afford a solid which was triturated with ether, filtered and dried to afford the monohydrochloride salt of the hydroxamic acid (191 mg, 86%) as a colorless solid: MS MH+ calcd for C₂₈H₃₇NSO₅.C₂₄H₂₈N₂SO₅.HCl.0.5H₂O.C₂₄H₂₈N₂SO₅.HCl.0.5H₂O C, 57.36; H, 6.32; N, 5.68; Cl, 6.84.

To a suspension of 3-bromopyruvic acid hydrate (1.95 g, 11.7 mmol) cooled to 0°C in MeOH (50 mL) was added 4-phenoxypbenzenethiol (2.35 g, 11.7 mmol). The solution was stirred for 15 minutes followed by concentration in vacuo. The residue was partitioned between EA and H₂O and the organic layer was dried over MgSO₄. Concentration in vacuo provided the crude sulﬁde (1.2 g) as a yellow solid that was used without any additional purification. To a solution of this sulﬁde (1.2 g) in methanol/H₂O cooled to 0°C was added Oxone (3.5 g, 5.72 mmol). The solution was stirred for 1 h followed by removal of excess Oxone by filtration. The filtrate was
concentrated and the residue was dissolved into EA and washed with saturated NaHCO₃ and brine and dried over MgSO₄. After concentration in vacuo the resulting residue was dissolved into MeOH and thionyl chloride (1.9 mL, 26 mmol) was added. Chromatography (on silica, EA/hexane) provided the decarbonylated sulphone 12 as a solid (350 mg, 44%). MS(Cl) MH+ calculated for C₁₅H₁₄O₅S 307, found 307. To a solution of the sulphone 12 (350 mg, 1.1 mmol) in MeOH (2 mL) and THF (2 mL) was added 50% aqueous hydroxylamine (1 mL). The solution was stirred overnight. Trituration with EA provided the hydroxamic acid 13 as a white solid (270 mg, 77%). HPLC 65 purity: >97%. MS(Cl) MH+ calculated for C₁₄H₁₃NO₅S: 308, found 308.

N-hydroxy-2-methyl-2-(4-phenoxyphenyl)sulfonyl]propanamide (17). To a solution of 4-(phenoxy)benzenethiol (3.8 g, 18.8 mmol) in MeOH (60 mL) cooled to 0°C was added t-butyl bromoacetate (2.8 mL, 18.8 mmol) and triethylamine (2.6 mL, 19.0 mmol). The solution was stirred for 30 minutes and was then concentrated in vacuo. The residue was partitioned between EA and H₂O and the organic layer was washed with brine and dried over MgSO₄. Concentration in vacuo provided the sulfide as an oil. To a solution of the sulfide in CH₂Cl₂ (85 mL) was added m-chloroperbenzoic acid (13.8 g, 43.2 mmol) over 15 minutes. The solution was stirred at rt for 2 h. The reaction was quenched by the addition of aqueous Na₂S0₃. After 30 minutes the solution was filtered through Celite. The filtrate was washed with 25 percent aqueous ammonia, IN HCl, and brine and dried over MgSO₄. Chromatography on silica gel eluting with EA/hexane provided the sulphone 14 as a white solid (4.0 g, 68%).

To a solution of the sulphone 14 (3.2 g, 9.2 mmol) in THF (65 mL) cooled to 0°C was added sodium hydride (730 mg of a 60 percent dispersion in mineral oil, 18.4 mmol). After 10 minutes, methyl iodide (2.28 mL, 36.8 mmol) was added dropwise and the mixture was stirred for 18 h at rt. The reaction was quenched with H₂O and concentrated in vacuo. The aqueous residue was diluted with EA and the organic phase was washed with H₂O and dried over Na₂S0₄. Concentration in vacuo provided the dimethyl sulphone 15 as an off-white solid (3.2 g, 92%). HPLC purity: 95%.

To a solution of the dimethyl sulphone 15 (3.2 g, 8.5 mmol) in anisole (10 mL) was added trifluoroacetic acid (30 mL) and the solution was stirred for 30 minutes. Concentration in vacuo followed by trituration (ethyl ether) provided the carboxylic acid 16 as a white solid (750 mg, 28%). HPLC purity: 99%. MS(Cl) MH+ calculated for C₁₆H₁₆O₅S: 321, found 321.

α-THP PhOPhCl (21)

In dry equipment under nitrogen, sodium metal (8.97 g, 390 mmol) was added to MeOH (1 l) at 0°C. The reaction was allowed to warm to rt over 45 minutes by which time the sodium had completely dissolved. The solution was chilled to 0°C and p-fluorothiophenol (41.5 mL, 0.39 mmol) was added, followed by methyl 2-chloroacetate (34.2 mL, 0.39 mol). The reaction was stirred at rt for 4 h, filtered, and concentrated in vacuo to give the desired sulfide (75.8 g, 97%) as a clear colorless oil. To a solution of this sulfide (75.8 g, 0.38 mol) in MeOH (1 L) was added water (100 mL) and Oxone (720 g, 1.17 mol). An exotherm to 67 °C was noted. After 2 h, the reaction was filtered and the cake was rinsed with MeOH. The filtrate was concentrated in vacuo. The residue was taken up in EA and washed with brine, dried over MgS0₄, filtered, and concentrated to give the sulphone 18 as a crystalline solid (82.74 g, 94%).

To a solution of the sulphone 18 (28.5 g, 0.123 mol) in DMF (200 mL) was added KO₂CO₃ (37.3 g, 0.27 mol), bis-(2-bromoethyl) ether (19.3 mL, 0.147 mol), DMAP (0.75 g, 6 mmol), and tetra-n-butylammonium bromide (1.98 g, 6 25 mmol). The reaction was stirred for 18 h at rt. The reaction was then slowly poured into 1N HCl (300 mL) and the resultant solid filtered and the cake washed well with
hexanes. The solid was recrystallized from EA/hexane to give the pyran 19 as a beige solid (28.7 g, 77%). MS MH+ calcd for C_{13}H_{15}O_{3}SF 303, found 303.

To the pyran methyl ester 19 (8.0 g, 26.5 mmol) in THF (250 mL) was added a solution of potassium trimethylsilanolate (10.2 g, 79.5 mmol) in dry THF (15 mL). After 1.5 h, water (100 mL) was added and the solution concentrated in vacuo. The residue was taken up in water and washed with EA. The aqueous solution was acidified with 6N HCl to pH 1 and the resulting slurry was extracted with EA. The combined extracts were washed with water, dried over Na2SO4 and concentrated in vacuo. The residue was triturated with hot ether and the resulting solid filtered and dried to give the carboxylic acid (7.5 g, 94.8 mmol), 94.8 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxyIamine (11.5 g, 98 mmol), and EDC (8.48 g, 44.2 mmol). After three h at rt the reaction was concentrated in vacuo. The residue was taken up in EA, washed successively with water, 5% KHSO4, saturated aqueous NaHCO3, brine, dried over Na2SO4. Concentration gave a residue which was purified by chromatography on silica gel eluting with EA/hexane to prove the THP-hydroxamate 20 (9.7 g, 80%) as a crystalline solid: HRMS MH+ calculated for C_{17}H_{22}N_{6}O_{5}SF: 388.12, found 388.12.

Other-Sulfide PhOPh 22
To a solution of the THP-hydroxamate p-fluorophenyl sulphone 20 (2.9 g, 7.5 mmol) in DMF (15 mL) was added p-chlorophenol (1.93 g, 15 mmol) and cesium carbonate (7.3 g, 22.5 mmol). The reaction was heated with hot ether and the resulting solid filtered and dried to give the carboxylic acid (5.78 g, 76%) as a crystalline solid. HRMS MH+ calcd for C_{12}H_{13}O_{5}SF: 287.04, found 287.04. To a solution of the THP-hydroxamate p-fluorophenyl sulphone THP-protected hydroxamate (2.9 g, 78%). To a solution of this THP-protected hydroxamate (2.9 g, 5.7 mmol) in dioxane (5 mL) was added 4N HCl in dioxane (5 mL, 20 mL, 94.8 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxyIamine (11.5 g, 98 mmol), and EDC (8.48 g, 44.2 mmol). After three h at rt the reaction was diluted with H2O and the resulting mixture was heated to 90°C for 1.5 h. Additional DMF (20 mL) was added, followed by additional cesium carbonate (2 g, 6.2 mmol). After three h at rt the reaction was concentrated in vacuo. The residue was taken up in EA, washed successively with water, 5% KHSO4, saturated aqueous NaHCO3, brine, dried over Na2SO4. Concentration gave a residue which was purified by chromatography on silica gel eluting with EA/hexane to prove the THP-hydroxamate 20 (9.7 g, 80%) as a crystalline solid: HRMS MH+ calculated for C_{17}H_{22}N_{6}O_{5}SF: 388.12, found 388.12.

N-BOC α-sulphone PhOPh 23
To a solution of sulfide 22 (1.8 g, 3.95 mmol) in CH_2Cl_2 (75 mL) at 0°C was added 3-chloroperbenzoic acid (1.7 g, 7.9 mmol). The reaction was stirred for 1 h at 0°C, then 0.5 h at rt. The reaction solution was then washed with water and brine and dried over MgSO4. Concentration gave a residue which was purified by chromatography on silica gel eluting with EA/hexane (10/90) to give the desired sulfide 22 (24.7 g, 86%): MS calcd for [C_{25}H_{31}NSO_2-C_6H_5O_2(BOC)] 358, found 358. ^1H NMR (400 MHz, CDCl_3) δ 7.87 (4H, m), 7.16 (1H, t, J = 7 Hz), 7.03 (2H, m), 6.92 (2H, m), 4.14 (2H, q, J = 7 Hz), 3.79 (2H, m), 3.12 (2H, m), 2.09 (2H, m), 1.72 (2H, m), 1.46 (9H, s), 1.23 (3H, t, J = 7 Hz).

NH.HCl ethyl ester α-sulphone PhOPh 24
To a solution of ethyl isonipecotate 1 (26.2 g, 102 mmol) in THF (470 mL) at -45°C was added 2M LDA in THF (60 mL, 120 mmol) with stirring. The solution was warmed to 0°C over 2 h and then recooled to -40°C, whereupon a solution of 4-phenyloxythiophenol disulfide (25.5 g, 63.0 mmol) in THF (30 mL) was added. The reaction was then stirred at 0°C for 1 h, then warmed to rt for 16 h. Water (600 mL) was added and the mixture was extracted with EA (3 X 500 mL). The combined organic extracts were washed with brine and dried over MgSO4. Concentration gave a dark yellow oil (53 g) which was purified by chromatography on silica gel eluting with EA/hexane to afford the p-chlorophenoxypseudon sulphone THP-protected hydroxamate (2.9 g, 78%). To a solution of this THP-protected hydroxamate (2.9 g, 5.7 mmol) in dioxane (5 mL) was added 4N HCl in dioxane (5 mL, 20 mmol), followed by MeOH (7.5 mL). The resulting solution was stirred at rt for 1 hour. Concentration and reverse-phase chromatography eluting with MeCN/H2O provided the p-chlorophenoxypseudon sulphone hydroxamic acid 21 (1.35 g, 58%) as a white solid: MS (FAB) MH+ for C_{18}H_{18}N_6O_5S: 315, found 315.

Alpha-Sulfide PhOPh 22
To a solution of ethyl isonipecotate 1 (26.2 g, 102 mmol) in THF (470 mL) at -45°C was added 2M LDA in THF (60 mL, 120 mmol) with stirring. The solution was warmed to 0°C over 2 h and then recooled to -40°C, whereupon a solution of 4-phenyloxythiophenol disulfide (25.5 g, 63.0 mmol) in THF (30 mL) was added. The reaction was then stirred at 0°C for 1 h, then warmed to rt for 16 h. Water (600 mL) was added and the mixture was extracted with EA (3 X 500 mL). The combined organic extracts were washed with brine and dried over MgSO4. Concentration gave a dark yellow oil (53 g) which was purified by chromatography on silica gel eluting with EA/hexane to afford the p-chlorophenoxypseudon sulphone THP-protected hydroxamate (2.9 g, 78%). To a solution of this THP-protected hydroxamate (2.9 g, 5.7 mmol) in dioxane (5 mL) was added 4N HCl in dioxane (5 mL, 20 mmol), followed by MeOH (7.5 mL). The resulting solution was stirred at rt for 1 hour. Concentration and reverse-phase chromatography eluting with MeCN/H2O provided the p-chlorophenoxypseudon sulphone hydroxamic acid 21 (1.35 g, 58%) as a white solid: MS (FAB) MH+ for C_{18}H_{18}N_6O_5S: 315, found 315.
Through a solution of N-BOC ethyl ester 23 (3.65 g, 7.00 mmol) in EA (100 mL) at 0°C was bubbled HCl gas for 5 min. The solution was concentrated to give a residue which was triturated with ether to afford amine hydrochloride salt 24 (3.1 g, 100%) as a colorless solid: HRMS calc'd for C_{29}H_{37}NO_5S, 390.1375, found 390.1357.  ^1H NMR (400 MHz, d_6-DMSO) δ 7.77 (2H, d, J = 11 Hz), 7.51 (2H, m), 7.32 (1H, t, J = 6 Hz), 7.18 (4H, d, J = 11 Hz), 4.12 (2H, q, J = 7 Hz), 3.41 (2H, br d, J = 14 Hz), 2.72 (2H, t, J = 14 Hz), 2.36 (2H, d, J = 14 Hz), 2.22 (2H, td, J = 11, 3 Hz), 1.08 (3H, t, J = 7 Hz).

**N-BOC α-sulphone PhOPh (27a).** To a solution of ethyl ester sulphone 23 (800 mg, 1.63 mmol) in 1:1 EtOH/THF (17 mL) was added NaOH (654 mg, 16.3 mmol) in H_2O (3 mL) and the solution was heated to 65°C for 16 h. Concentration gave a beige semi-solid. Water (25 mL) was added and the mixture was acidified to pH = 4 with 2N HCl and extracted with EA (2X). The combined organic extracts were washed with brine and dried over MgSO_4. Concentration gave the corresponding carboxylic acid 26a (754 mg, 100%) as a white foam: Anal calc'd for C_{23}H_{28}O_5NSO, 377.1171; C, 57.97; H, 5.92; N, 5.88; S, 6.73. Found C, 57.95; H, 6.02; N, 5.81; S, 6.56. MS MH+ calc'd for [C_{23}H_{28}O_5NSO]^+ 377.1170, found 377.1170.  ^1H NMR (400 MHz, d_6-DMSO) δ 7.74 (2H, d, J = 10 Hz), 7.42 (2H, t, J = 8 Hz), 7.25 (1H, m), 7.09 (2H, d, J = 8 Hz), 7.03 (2H, d, J = 9 Hz), 4.18 (2H, m), 2.73 (2H, m), 2.28 (2H, m), 2.05 (2H, m), 1.45 (9H, s).

To a solution of carboxylic acid 26a (730 mg, 1.58 mmol) in DMF (9 mL) was added sequentially HOBT (424 mg, 2.21 mmol), EDC (479 mg, 4.70 mmol) and 50% aqueous hydroxylamine (1.04 mL, 15.8 mmol). After stirring for 16 h, the reaction was recharged with equivalent additional quantities of HOBT, EDC, NMM and hydroxylamine. After an additional 20 h at rt, water (50 mL) was added and the mixture was extracted with EA (2X 120 mL), and the combined extracts were washed with brine and dried over MgSO_4. Concentration gave a residue (820 mg) which was purified by reverse-phase chromatography eluting with a gradient of MeCN/H_2O (30/70 to 80/20) to afford the desired hydroxamate 27a (460 mg, 61%): MS MH+ calc'd for [C_{33}H_{28}N_2O_5S(CHO)]^+ 362.1210, found 362.1204.  ^1H NMR (400 MHz, CDCl_3) δ 9.14 (1H, br s), 7.71 (2H, d, J = 8 Hz), 7.49 (2H, t, J = 8 Hz), 7.28 (1H, t, J = 6 Hz), 7.16 (2H, d, J = 6 Hz), 7.11 (2H, d, J = 10 Hz), 3.96 (2H, m), 2.58 (2H, m), 2.28 (2H, m), 1.69 (2H, m), 1.39 (9H, s).

**Hydroxamate NH.HCl α-sulphone PhOPh (27b).** Through a solution of N-BOC hydroxamate 27a in EA (25 mL) at 0°C was bubbled HCl gas for 5 min. The solution was concentrated to give a residue which was triturated with ether to afford the hydroxamate hydrochloride salt 27b (330 mg, 99%) as a light pink solid: HRMS calc'd for C_{18}H_{20}N_2O_5S.CI, 377.1170, found 377.1170.  ^1H NMR (400 MHz, d_6-DMSO) δ 9.28 (1H, s), 8.98 (1H, br s), 8.65 (1H, br s), 7.72 (2H, d, J = 10 Hz), 7.51 (2H, m), 7.31 (1H, t, J = 7 Hz), 7.20-7.11 (4H, m), 3.38 (2H, m), 2.63 (2H, m), 2.45 (2H, m), 2.10 (2H, m). Anal calc'd for C_{18}H_{20}N_2O_5S.HCl.CI, 52.36; H, 5.13; N, 6.78; Cl, 8.59; S, 7.77. Found C, 51.95; H, 5.25; N, 6.55; Cl, 8.37; S, 7.63.

**N-Me α-sulphone PhOPh (27c).** To a solution of N-BOC α-sulphone 23 (2.67 g, 5.5 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (5 mL), and the solution was stirred at rt for 2 h. The solution was concentrated in vacuo and the residue was triturated with ether to afford the crude amine trifluoroacetic acid salt. To a solution of the crude amine salt in MeOH (10 mL) was added formaldehyde (37% aqueous solution, 2.0 mL, 27.5mmol) and borane pyridine (2.2 mL, 22 mmol), and the solution was stirred at rt for 18 h. The solution was concentrated in vacuo. The residue was dissolved in EA, washed with H_2O and dried over MgSO_4. Concentration in vacuo provided the N-methyl amine 25c as a yellow oil (2.17 g, 98%).

To a solution of the N-methyl α-sulphone 25c (2.17 g, 5.4 mmol) in EtOH (10 mL) and THF (10 mL) was added NaOH (2.0 g, 50 mmol), and the reaction mixture was stirred at 65°C for 18 h. The solution was concentrated in vacuo. The residue was dissolved in H_2O and extracted with ether. The aqueous solution was acidified to pH 2 and the resulting solid was collected by vacuum filtration to provide the acid 26c (1.8 g, 90%) as a white solid.
To a solution of the acid 26c (0.5 g, 1.3 mmol) in DMF(10 mL) was added EDC (1.06 g, 5.5 mmol) followed by O-tetrahydro-2H-pyran-2-yl-hydroxylamine (490 mg, 4.2 mmol) and 4-methylmorpholine (0.76 mL) and the solution was stirred at rt for 18 h. The solution was concentrated in vacuo and the residue was dissolved in EA, washed with H2O and dried over MgSO4. Concentration in vacuo provided the crude protected hydroxamate. To a solution of the crude hydroxamate in MeOH (10 mL) was added acetyl chloride (0.28 mL, 3.9 mmol), and the solution was stirred for 3 h at rt. The solution was concentrated in vacuo. Reverse phase chromatography eluting with MeCN/H2O (0.01% HCl) provided the α-sulphone hydroxamic acid 27c as a white solid (261 mg, 46%). MS(CI) MH+ calculated for C19H22NO5S:391, found 391.

α-sulphone N-methoxethyl PhOPh [patent EXAMPLE 30] (27d). To a solution of the amine HCl salt 24 (2.5 g, 5.87 mmol) and K2CO3 (1.6 g, 11.57 mmol) in DMF(25 mL) was added 2-bromoethylmethyl ether (0.66 mL, 7.0 mmol) and then stirred at rt for 18 h. The solvent was evaporated and the residue was diluted with EA. The organic layer was washed with water and dried over MgSO4. Concentration in vacuo provided the methoxy ethyl amine 25c as light yellow oil (2.63 g, 100%).

To a solution of the methoxy ethyl amine 25c (2.63 g, 5.87 mmol) in THF (18 mL) and ethanol (18 mL) was added NaOH (2.1 g, 5.25 mmol) in water (6 mL). The solution was heated to reflux for 12 h. The solution was concentrated in vacuo and diluted with water. The aqueous layer was extracted with ether (2 X 100 mL) and was acidified to pH=2. Vacuum filtration of the resulting precipitation provided the acid 26d as a white solid (2.4 g, 100%).

To a solution of the acid of part B (2.0 g, 4.33 mmol), also containing NMM (1.8 mL, 16.4 mmol), and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.767 g, 6.44 mmol) in DMF (20 mL) was added EDC (3.1 g, 16.2 mmol), and the solution was stirred at rt for 20 h. The solution was concentrated under high vacuum and the residue was dissolved in EA. The organic layer was washed with H2O and dried over MgSO4. Concentration in vacuo provided the THP-hydroxamic acid as off white foam (1.60 g, 71.1%). To a solution of this protected hydroxamate (1.58 g, 3.05 mmol) in MeOH (20 mL) at 0°C was added acetyl chloride (0.65 mL, 9.15 mmol) and the solution was stirred at 0°C for 3 h. Concentration gave a residue which was purified on reverse-phase chromatography on C-18 eluting with MeCN/H2O (0.01% HCl) to afford the hydroxamate HCl salt 27d as a white solid (830 mg, 58%) as a solid. HRMS calcd for C21H26NO6S.HCl:0.75H2O: C, 52.06; H, 5.93; N, 5.78; S, 6.62. Found C, 51.94; H, 5.67; N, 5.91; S, 6.66.

N-cyclopropyl α-sulphone hydroxamate PhOPh (27e). To a solution of amine hydrochloride 24 (2.13 g, 5.0 mmol) in MeOH (25 mL) was added 3A molecular sieves (2 g) followed sequentially by acetic acid (2.86 mL, 50 mmol), [(1-ethoxycyclopropyl)oxy]-trimethylsilane (6.08 mL, 30 mmol), and sodium cyanoborohydride (1.41 g, 22.0 mmol) and the reaction was heated under reflux for 16 h. The mixture was cooled and filtered, and then concentrated to give a residue (2.08 g) which was purified by chromatography on silica gel eluting with EA/hexane (20/80) to afford the N-cyclopropyl amine 25e (1.90 g, 86%) as a white solid: DSC 131.4-133.5°C. HRMS calcd for C23H27NO5S4:429.1653, found 429.1600.

To a solution of N-cyclopropyl ethyl ester 25e (1.9 g, 4.2 mmol) in 1:1 EtOH/THF (25 mL) was added a solution of NaOH (1.71 g, 4.3 mmol) in H2O (10 mL) and the reaction was heated to 65°C for 16 h. The organic solvents were removed in vacuo and the reaction was diluted with additional water (20 mL). Concentration to pH 5 with 1N HCl gave a solid which was filtered and dried to give the carboxylic acid 26e (1.49 g, 82%) as a colorless solid: HRMS calcd for C21H22NSO5 402.1375, found 402.1350.

To a solution of N-cyclopropyl carboxylic acid 26e (1.49 g, 3.4 mmol) in CH2Cl2 (50 mL) was added Et3N (1.42 mL, 10.2 mmol) followed by 50% aqueous hydroxylamine (2.25 mL, 34.0 mmol) and PyBroP (3.17 g, 6.8 mmol). The reaction was stirred for 3 d at rt. Water (70 mL) was added and the reaction was extracted with CH2Cl2 (3X). The combined organic extracts were washed with brine and dried over MgSO4 and concentrated to give an oil (4.0 g) which was chromatographed on reverse phase eluting with MeCN/H2O (20/80 to neat MeCN) to afford the free base hydroxamic acid (830 mg, 58%) as a solid. To a
solution of this hydroxamic acid amine (830 mg, 2.0 mmol) in MeOH (20 mL) was added methanolic HCl [prepared by the addition of acetyl chloride (170 µL, 2.0 mmol) to MeOH (2 mL)]. The resulting precipitate was filtered and dried to give the desired N-cyclopropylamine hydroxamic acid hydrochloride salt 27e (595 mg, 66%) as a white powder: HRMS calcd for \( \text{C}_2\text{H}_{12}\text{N}_2\text{SO}_4 \) 416.1407, found 416.1398. Anal calcd for \( \text{C}_2\text{H}_{12}\text{N}_2\text{SO}_4 \cdot \text{HCl} \) C, 55.68; H, 5.56; N, 6.18; Cl, 7.83; S, 7.08. Found C, 55.39; H, 5.72; N, 6.15; Cl, 8.17; S, 7.29.

**N-cyclopropylmethyl hydroxamate PhOPh (27f)**. To a solution of amine hydrochloride 24 (2.13 g, 5.0 mmol) in DMF (10 mL) at rt was added K2CO3 (1.4 g, 10.0 mmol) followed by bromomethylcyclopropane (675 mg, 5.0 mmol) and the reaction was stirred for 16 h. Water (40 mL) was added and the mixture was extracted with EA (2X). The combined extracts were washed with water and brine and dried over MgSO₄. Concentration gave a residue (2.94 g) which was purified by chromatography on silica gel eluting with EA/hexane (20/80) to afford the cyclopropylmethyl amine 25f (2.09 g, 91%) as an oil which solidified: MS MH⁺ calcd for C₂₄H₂₉NSO₅ 444, found 444. Anal calcd for C₂₄H₂₉NSO₅ C, 64.99; H, 6.59; N, 3.16; S, 7.28.

To a solution of cyclopropyl amine ethyl ester 25g (2.0 g, 4.4 mmol) in EtOH/THF (25 mL) was added a solution of NaOH (1.75 g, 4.4 mmol) in water (10 mL) and the reaction was heated to 65°C. The organic solvents were removed in vacuo and additional water (20 mL) was added. Acidification to pH 4 gave a precipitate which was filtered and dried to give the carboxylic acid 26f (1.58 g, 79%) as a colorless solid: HRMS MH⁺ calcd for C₂₄H₂₉NSO₅ 414.1375, found 414.1334. Anal calcd for C₂₄H₂₉NSO₅·HCl·0.5H₂O C, 57.32; H, 5.90; N, 3.04. Found C, 57.44; H, 5.63; N, 3.13.

To a solution of carboxylic acid 26f (1.58 g, 3.50 mmol) in CH₂Cl₂ (50 mL) was added Et₃N (1.46 mL, 10.5 mmol) followed by 50% aqueous hydroxyamine (2.31 mL, 3.50 mmol) and PyBroP (2.04 g, 6.99 mmol). After 3 d at rt the reaction was still a suspension so DMF (20 mL) was added and the reaction was quenched with equivalents of Et₃N, aqueous hydroxyamine and PyBroP. After 24 h at rt, water was added and the mixture was extracted with CH₂Cl₂. The combined extracts were washed with water and brine and dried over MgSO₄. Concentration gave an oil (5.0 g) which was purified by reverse phase chromatography eluting with MeCN/H₂O to afford the free base of the hydroxamate (3.2 g; theo = 1.51 g) contaminated with phosphoramide. To a solution of this free base in MeOH (5 mL) was added a methanolic solution of HCl [prepared by adding acetyl chloride (0.25 mL, 3.5 mmol) to MeOH (20 mL) at 0°C]. Concentration gave an oil which was dissolved in a minimum amount of MeOH (2.5 mL) and added slowly to ether (300 mL) with rapid stirring. The resulting solid was filtered and dried to afford the requisite hydroxamic acid 27f (677 mg, 42% from 27i???) as a colorless powder.

**N-propargyl ethyl ester PhOPh (27g)**. To a solution of amine hydrochloride salt 24 (850 mg, 1.99 mmol) in DMF (20 mL) was added K₂CO₃ (300 mg, 2.0 mmol) followed by 80% propargyl bromide in toluene (300 µL, 238 mg, 2.00 mmol) and the reaction was stirred for 4 h at rt. The reaction was quenched with the addition of water and extracted with EA (3X). The combined organic extracts were washed with water and brine and dried over MgSO₄. Concentration gave a residue which was purified by chromatography on silica gel eluting with EA/hexane (20/80) to afford N-propargyl amine 25g (740 mg, 86.5%) as colorless crystals: DSC 94.4-98.3°C. IR (MIR) 3278, 1729 cm⁻¹. Anal calcd for C₂₄H₂₉NSO₅·HCl·0.5H₂O C, 64.62; H, 5.89; N, 3.28; S, 7.50. Found C, 64.41; H, 5.65; N, 3.11; S, 7.27. \(^1\)H NMR (400 MHz, CDCl₃) δ 7.73 (2H, d, J = 10 Hz), 7.42 (2H, t, J = 9 Hz), 7.23 (1H, m), 7.11 (2H, d, J = 7 Hz), 7.06 (2H, d, J = 9 Hz), 4.24 (2H, m), 3.28 (2H, m), 3.13 (2H, m), 2.52 (2H, m), 2.39 (2H, m).

To a solution of N-propargylamine ethyl ester 25g (660 mg, 1.50 mmol) in 1:1 EtOH/THF (20 mL) was added NaOH (600 mg, 15.0 mmol) in water (10 mL) and the reaction was heated to 65°C for 18 h. Water (40 mL) was added and the aqeous layer was washed with EA. Acidification of the aqueous layer to pH 5 with 2N HCl gave a solid which was filtered and rinsed successively with water and ether to afford carboxylic acid 26g (519 mg, 80%) as a colorless solid: DSC 197.6-203.3°C. HRMS calcd for C₂₄H₂₉NSO₅ 414.1129, found 414.1120. \(^1\)H NMR (400 MHz, d₂-MSO) δ 7.75 (2H, d, J = 10 Hz), 7.49 (2H, d, J = 8 Hz), 7.28 (1H, t, J = 6 Hz), 7.18 (2H, d, J = 9 Hz), 7.12 (2H, d, J = 9 Hz), 3.28 (2H, s), 3.11
Concentration gave a residue (3.5 g) which was purified by reverse-phase chromatography to afford the
extracted with CH$_2$Cl$_2$ (3.16 g, 6.76 mmol). The reaction was stirred at rt for 3 d. Water (70 mL) was added and the mixture was
sequentially Et$_3$N (1.41 mL, 10.1 mmol), 50% aqueous hydroxylamine (0.73 mL, 11.1 mmol) was added and the reaction was stirred for another 24 h at rt.
Water was added and the mixture was extracted with CH$_2$Cl$_2$. The combined extracts were washed with brine and dried over MgSO$_4$ and concentrated to afford a residue (380 mg) which was purified by reverse-phase chromatography eluting with MeCN/aqueous HCl (30/70 to 80/20) to afford the requisite N-propargyl amine hydroxamic acid hydrochloride salt 27g (275 mg, 57%) as a colorless solid: HRMS calcd for C$_{12}$H$_{22}$N$_2$SO$_3$HCl:0.5H$_2$O C, 54.84; H, 5.26; N, 6.09. Found C, 54.90; H, 5.37; N, 6.07.

N-Ac EXAMPLE N-Ac α-sulphone PhOPh (27h). To a solution of N-BOC α-sulphone 23 (2.75 g, 5.6 mmol) in THF (10 mL) and EtOH (10 mL) was added NaOH (2.25 g, 56 mmol), and the solution was heated to 70°C for 18 h. The solution was concentrated in vacuo, the residue was dissolved into H$_2$O and extracted with ethyl ether. The aqueous solution was acidified to a pH value of 2 and extracted with EA. The organic layer was dried over MgSO$_4$. Concentration in vacuo provided the crude acid as a solid. A solution of the acid in CH$_2$Cl$_2$ (6 mL) and trifluoroacetic acid (6 mL) was stirred for 1 hour at rt. Concentration in vacuo provided the amine hydrochloride salt as a solid (2.3 g, 100%). To a solution of this amine hydrochloride salt (2.3 g, <5.6 mmol) in acetone (10 mL) and H$_2$O (10 mL) cooled to 0 °C was added triethylamine (1.17 mL, 8.4 mmol) and acetyl chloride (0.60 mL, 8.4 mmol), and the solution was stirred at rt for 18 h. The solution was concentrated in vacuo to remove the acetone and the aqueous solution was extracted with ethyl ether. The aqueous layer was acidified to pH 2 and extracted with EA. The organic layer was dried over MgSO$_4$ and concentration in vacuo provided the N-acetyl carboxylic acid 26h as a white solid (1.5 g, 65.2%).

To a solution of the N-acetyl carboxylic acid 26h (0.6 g, 1.49 mmol) in DMF (10 mL) was added EDC (401 mg, 2.1 mmol) followed by 50% aqueous hydroxylamine (0.9 mL) and 4-methylmorpholine (0.7 mL, 6.4 mmol), and the solution was stirred for 18 h at rt. The solution was concentrated in vacuo and the residue was dissolved into EA. The organic layer was washed with H$_2$O and dried over MgSO$_4$. Reverse phase chromatography eluting with MeCN/H$_2$O provided the N-acetyl hydroxamic acid 27h (101 mg, 16%) as a white solid: MS MH+ calcd for C$_{20}$H$_{22}$N$_2$O$_6$S, 419, found 419.

N-methanesulphonyl hydroxamate PhOPh (27i). To a solution of amine hydrochloride 24 (2.13 g, 7.5 mmol) in CH$_2$Cl$_2$ (35 mL) was added triethylamine (2.34 mL, 16.5 mmol) and concentration in vacuo provided the residue as a white solid. A solution of the residue was added triethylamine (2.34 mL, 16.5 mmol) and 50% aqueous hydroxylamine (2.34 mL, 16.5 mmol) in CH$_2$Cl$_2$ (35 mL) was added triethylamine (2.34 mL, 16.5 mmol) and the solution was stirred for 18 h at rt. The solution was concentrated in vacuo and the residue was dissolved into EA. The organic layer was washed with H$_2$O and dried over MgSO$_4$. Concentration gave a dark oil (3.6 g) which was chromatographed on silica gel eluting with EA/hexane (20/80 to 50/50) to afford the N-methanesulphonamide 25i (58%): MS calcd for C$_{12}$H$_{23}$NS$_2$O$_7$ 468, found 468. Anal calcd for C$_{12}$H$_{23}$NS$_2$O$_7$: C, 53.95; H, 5.39; N, 3.00. Found C, 53.97; N, 5.43; N, 3.09.

To a solution of N-mesyl ethyl ester 25i (2.0 g, 4.15 mmol) in 1:1 EtOH/THF (25 mL) was added a solution of NaOH (1.66 g, 41.5 mmol) in water (10 mL) and the reaction was heated to 65°C for 16 h. The organic solvents were removed in vacuo, then additional water (20 mL) was added. The aqueous solution was then acidified to pH 4 and extracted with EA (3X). The combined extracts were washed with brine, dried over MgSO$_4$ and concentrated to give the desired carboxylic acid 26i (1.46 g, 80%) as a light yellow foam: HRMS calcd for C$_{19}$H$_{21}$NS$_2$O$_7$: 440.0838; found 440.0820. Anal calcd for C$_{19}$H$_{21}$NS$_2$O$_7$: C, 51.92; H, 4.82; N, 3.19; S, 14.59. Found C, 52.62; H, 5.18; N, 3.02; S, 13.85.

To a solution of N-mesyl carboxylic acid 26i (1.46 g, 3.38 mmol) in CH$_2$Cl$_2$ (50 mL) was added sequentially Et$_3$N (1.41 mL, 10.1 mmol), 50% aqueous hydroxylamine (2.2 mL, 33.8 mmol) and PyBroP (3.16 g, 6.76 mmol). The reaction was stirred at rt for 3 d. Water (70 mL) was added and the mixture was extracted with CH$_2$Cl$_2$ (3X). The combined extracts were washed with brine and dried over MgSO$_4$. Concentration gave a residue (3.5 g) which was purified by reverse-phase chromatography to afford the

p-fluoro disulfide 28
A solution of 4-fluorothiophenol (50.29 g, 390 mmol) in DMSO (500 mL) was heated to 65°C for 6 hours. The reaction was quenched by pouring into ice and the resulting solid was collected by vacuum filtration to provide the disulfide 28 as a white solid (34.4 g, 68.9%): 1H NMR (300 MHz, CDCl3) δ 7.44 (4H, m), 7.01 (4H, m).

1-tert-butyl 4-ethyl 4-[(4-fluorophenyl)thio]piperidine-1,4-dicarboxylate (29).
To a solution of ethyl N-BOC-isonipecotate 1 (16.0 g, 62 mmol) in THF (300 mL) at -50°C was added LDA (41.3 mL, 74 mmol) and the solution was stirred for 1.5 h at 0°C. To this solution was added p-fluorophenyl disulfide 28 (15.8 g, 62 mmol), and the resulting solution was stirred at ambient temperature for 20 hours. The reaction was quenched with the addition of H2O and the solution was concentrated in vacuo. The aqueous residue was extracted with ethyl acetate and the organic layer was washed with 0.5N KOH, H2O, and brine. Chromatography on silica gel eluting with hexane/ethyl acetate provided the sulfide 29 as an oil (18.0 g, 75%): Anal calcd for C19H26NO4 C, 59.51; H, 6.83; N, 3.65; S, 8.36. Found C, 59.49; H, 7.03; N, 3.69; S, 8.28.

1-tert-butyl 4-ethyl 4-[(4-fluorophenyl)sulfonyl]piperidine-1,4-dicarboxylate (30).
To a solution of the sulfide 29 (16.5 g, 43 mmol) in dichloromethane (500 mL) cooled to 0°C was added MCPBA (18.0 g, 86 mmol) and the solution was stirred for 20 hours. The solution was diluted with H2O and extracted with dichloromethane. The organic layer was washed with 10 percent Na2SO3, H2O, and saturated NaCl and dried over magnesium sulfate. Chromatography on silica gel eluting with EA/hexane provided the sulphone 30 as a solid (10.7 g, 60%). Anal calcd for C19H26O6NSF C, 54.93; H, 6.31; N, 3.37; S, 7.72. Found 54.89; H, 6.43; N, 3.15; S, 7.57.

ethyl 4-[(4-fluorophenyl)sulfonyl]piperidine-4-carboxylate (31).
Into a solution of the sulphone 30 (10 g, 24.0 mmol) in ethyl acetate (250 mL) was bubbled HCl gas for 10 minutes followed by stirring at ambient temperature for 4 hours. Concentration in vacuo provided the amine hydrochloride salt 31 as a white solid (7.27 g, 86%). Anal calcd for C14H18O4NSF.HCl C, 47.80; H, 5.44; N, 3.98; Cl, 10.08; S, 9.11. Found C, 47.85; H, 5.65; N, 3.87; Cl, 10.35; S, 9.42.

N-hydroxy-1-methyl-4-[

To a solution of amine salt 37 (2.67 g, 5.14 mmol) and 37% aqueous formaldehyde (2.0 mL, 25.7 mmol) in MeOH (20 mL) was added borane pyridine complex (2.6 mL, 25.7 mmol). The solution was then stirred at rt for 18 h. The solution was acidified and then concentrated to afford a residue that was partitioned between aqueous NaHCO3 and EA. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with H2O and dried over MgSO4. Concentration gave the N-methyl amine 33a as off-white foam (1.6 g, 76%).

To a solution of the methyl amine 33a (1.63 g, 3.88 mmol) in EtOH (20 mL) was added KOH (1.31 g, 23.2 mmol) in water (4 mL), and the resulting solution was heated to 50°C for 8 h, and then 70°C for 4 h. The solution was acidified and concentrated providing the acid as white solid. To a solution of the crude acid in DMF (50 mL) was added O-tetrahydro-2H-pyran-2-yl-hydroxylamine (0.92 g, 7.76 mmol), NMM (1.05 mL, 7.76 mmol), and EDC (1.5 g, 7.76 mmol). The solution was then stirred for 72 h and then concentrated. The residue was dissolved in EA and washed with aqueous NaHCO3, H2O and dried over MgSO4. Concentration in vacuo and chromatography on silica gel eluting with CH2Cl2/MeOH provided the THP-hydroxamic acid 34a as white solid (0.46 g, 24.2%).

To a solution of the THP hydroxamic acid 34a (0.22 g, 0.45 mmol) in MeOH (5 mL) cooled to 0°C was added acetyl chloride (0.096 mL, 1.35 mmol), and the resulting solution was stirred at rt for 3 h. The solution was concentrated in vacuo and chromatographed on reverse phase eluting with MeCN/H2O (0.01% HCl) to afford the hydroxamate N-methyl amine hydrochloride salt 35a (0.12 g, 60.6%) as a white solid: HRMS calculated for C19H22N3O4S2 407.1099, found 407.1105.
To a solution of the methoxyethyl amine was concentrated and resuspended in HNaOH (3.7 g, 92.5 mmol) in water (9 mL). The solution resulting was heated to 60 °C for 12 h. The solution of this carboxylic acid (3.4 g, 7.8 mmol) in DMF (20 mL) was added NMM (2.6 mL, 23.4 mmol), HOBT (3.16 g, 23.4 mmol), and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.85 g, 15.5 mmol) and EDC. The reaction was stirred for 6 d and then filtered to recover unreacted starting material. The filtrate was concentrated, then water was added and the solution extracted with EA. The combined extracts were washed with brine and dried over MgSO₄. Concentration provided the THP-protected hydroxamic acid (3.5 g, 87.5%) as a white solid. HRMS calcd for C₂₀H₂₃NS₂O₄ 406.1140, found 406.1147.

To a suspension of the carboxylic acid (5.3 g, 11.8 mmol) in DMF (45 mL) was added 2-bromoethyl methyl ether (1.9 mL, 20.2 mmol). The solution was stirred at rt for 48 h. Then DMF was evaporated and the residue was diluted with EA. The organic layer was washed with saturated NaHCO₃, H₂O and dried over MgSO₄. Concentration gave the THP-hydroxamate 34b (2.33 g, 39%) as a white solid: HRMS calcd for C₂₅H₃₀N₂O₄·HCl·O.9H₂O 505.1831, found 505.1831.

N-hydroxy-1-(2-methoxyethyl)-4-[[4-(phenylthio)phenyl]sulfonyl]piperidine-4-carboxamide hydrochloride (35c). To the solution of the amine hydrochloride salt (37 (4.3 g, 9.43 mmol) and K₂CO₃ (2.62 g, 19.0mmol) in DMF(40 mL) was added 2-bromoethyl methyl ether (1.9 mL, 20.2 mmol). The solution was stirred at rt for 48 h. Then DMF was evaporated and the residue was diluted with EA. The organic layer was washed with water and dried over MgSO₄. Concentration in vacuo provided the methoxyethyl amine 33c (4.26 g, 95.3%) as a solid. MS calcd for C₂₉H₃₀N₂O₄·HCl·0.5H₂O 434.1460, found 434.1452.

To a solution of the methoxyethyl amine 33c (4.26 g, 9.2 mmol) in 1:1 EtOH/THF (10 mL) was added NaOH (3.7 g, 92.5 mmol) in water (9 mL). The solution resulted was heated to 60 °C for 12 h. The solution was concentrated in vacuo, diluted with water, washed with ether, and acidified to pH 2. Filtration of the resulting precipitate provided the corresponding carboxylic acid (3.4 g, 87.5%) as a white solid. To a solution of this carboxylic acid (3.4 g, 7.8 mmol) in DMF (20 mL) was added NMM (2.6 mL, 23.4 mmol), HOBT (3.16 g, 23.4 mmol), and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.85 g, 15.5 mmol) and EDC (4.47 g, 23.4 mmol). The solution was stirred at rt for 36 h. The solution was concentrated and the residue dissolved in EA. The organic layer was washed with water and dried over MgSO₄. Concentration provided the THP-protected hydroxamic acid 34c as off-white solid (2.98 g, 71.5%). To this free base (2.98 g, 5.6 mmol) in MeOH (40 mL) at 0°C was added acetyl chloride (1.19 mL, 16.8 mmol), and the resulting solution was stirred at the rt for 3 h. The solution was concentrated and purified on reverse-phase chromatography eluting with MeCN/H₂O (containing 0.01% HCl) provided the desired hydroxamate N-methoxyethyl monohydrochloride salt 35c (2.29 g, 84.6%) as a white solid: Anal calcd for C₂₉H₂₉N₂O₄·HCl·O₂H·0.5H₂O C, 51.59; H, 5.73; N, 5.70; S, 12.71; Cl, 7.61. Found: C, 51.59; H, 5.73; N, 5.70; S, 12.71; Cl, 7.60.

1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]piperidine-4-carboxamide hydrochloride (35d). To a solution of the amine TFA salt (37 (6 g, 11.9 mmol) was added acetyl chloride (6.8 mL, 119 mmol). After 5 minutes stirring at rt, (1-ethoxycyclopropyl)oxytrimethylsilane (14.3 mL, 71.4 mmol) was added followed 5 minutes later by the addition of sodium cyanoborohydride (3.35 g, 53.6 mmol). Then the solution was heated under reflux for 18 h. The solvent was evaporated and residue was dissolved in EA. The organic layer was washed with IN NaOH, H₂O and dried 40 over MgSO₄. Concentration in vacuo gave the N-cyclopropylamine 33d as an off-white powder (4.9 g, 92.6%).
To a solution of the cyclopropylamine 33d (4.88 g, 10.9 mmol) in THF (12 mL) and EtOH (12 mL) was added NaOH (4.3 g, 100 mmol) in 45 water (25 mL). The solution was then heated to 55°C for 12 h and was stirred at rt for 18 h. The solution was acidified to pH 2 and concentrated in vacuo to provide the acid as white solid. To a solution of this crude acid in MeCN (50 mL) was added O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.95 g, 16.3 mmol), NMM (2.4 mL, 21.9 mmol), and EDC (3.14 g, 16.3 mmol) in sequence. The solution was then stirred at rt for 18 h. The solution was concentrated in vacuo and the residue was dissolved in EA. The organic layer was washed with H2O and dried over MgSO4.

Concentration in vacuo provided the THP-protected hydroxamate 34d as a white solid (3.0 g, 60 53.1%).

To a solution of the THP-protected hydroxamate 34d (3 g, 5.8 mmol) in MeOH (45 mL) at 0°C was added acetyl chloride (1.5 mL, 21.1 mmol), and the solution was stirred at rt for 2.5 h. Vacuum filtration of the resulting precipitate provided the hydroxamic acid N-cyclopropylamine monohydrochloride salt 35d as a white solid (1.84 g, 68.3%).

N-hydroxy-4-[(4-(phenylthio)phenyl)sulfonyl]-1-(vinylmethyl)piperidine-4-carboxamide hydrochloride (35e). To a solution of amine hydrochloride 37 (4.78 g, 10.8 mmol) in DMF (25 mL) was added K2CO3 (2.98 g, 21.6 mmol) followed by allyl bromide (0.935 mL, 9.35 mL, 10.8 mmol). The reaction was stirred at rt for 5 h, then diluted with EA and washed successively with water and brine and dried over MgSO4.

Concentration gave an oil which was purified by chromatography on silica gel eluting with EA/hexane (40/60) to give the desired N-allyl amine 33e (4.80 g, 99%) as an oil. MS MH+ calc'd for C26H23N4O4, found 446. Anal calcd for C26H23N4O4: H, 5.48; N, 5.86; S, 13.42; Cl, 7.42. Found C, 52.76; H, 6.29; N, 5.37; S, 12.31. Found C, 59.92; H, 6.29; N, 5.37; H, 6.25; N, 5.79; S, 11.51. 1H NMR (400 MHz, d6-DMSO) δ 7.64 (2H, d, J = 8 Hz), 7.58 (2H, m), 7.53 (3H, m), 7.31 (2H, d, d, J = 8 Hz), 5.74 (1H, m), 5.13 (1H, d, J = 15 Hz), 5.10 (1H, d, J = 11 Hz), 4.07 (2H, q, J = 7 Hz), 2.92-2.85 (4H, m), 2.17 (2H, m), 1.94 (2H, m), 1.72 (2H, m), 1.08 (3H, t, J = 7 Hz).

To a solution of amine hydrochloride 37 (4.78 g, 10.8 mmol) in 1:1 EtOH/THF (50 mL) was added a methanolic solution of NaOH (4.3 g, 10.8 mmol) at 0°C and washed with water and brine and dried over MgSO4. Concentration gave a residue (5.97 g) which was purified by chromatography on silica gel eluting with MeOH/EA (2/98 to 5/95) to afford the THP-hydroxamate 33d (4.11 g, 88%) as a colorless foam: HRMS MH+ calc'd for C26H23N4O4.HCl.H2O C, 53.44; H, 5.55; N, 2.97; Cl, 7.51; S, 13.59. Found C, 53.36; H, 4.71; N, 2.90; Cl, 7.64; S, 14.13. To a suspension of this carboxylic acid (4.1 g, 9.0 mmol) in DMF (90 mL) was added sequentially HOBT (1.46 g, 11 mmol), EDC (2.42 g, 13 mmol), NMM (2.4 mL, 21.9 mmol), and O-tetrahydro-2H-pyran-2-yl-hydroxylamine (1.58 g, 13.5 mmol). The reaction was stirred for 3 d at rt and then concentrated to dryness. The residue was redissolved in CH2Cl2 and washed with water and brine and dried over MgSO4. Concentration gave a residue (5.97 g) which was purified by chromatography on silica gel eluting with MeOH/EA (2/98 to 5/95) to afford the THP-hydroxamate 33e (4.11 g, 88%) as a colorless foam: HRMS MH+ calc'd for C21H28N5O6.HCl.H2O C, 59.92; H, 6.29; N, 5.37; S, 12.31. Found C, 59.63; H, 6.25; N, 5.79; S, 11.51. 1H NMR (400 MHz, d6-DMSO) δ 7.64 (2H, d, J = 8 Hz), 7.58 (2H, 2H, m), 7.52 (3H, m), 7.28 (2H, d, J = 8 Hz), 5.75 (1H, m), 5.12 (1H, d, J = 18 Hz), 5.19 (1H, d, J = 9 Hz), 4.89 (1H, s), 4.00 (1H, d, J = 6 Hz), 3.46 (1H, d, J = 12 Hz), 3.83 (2H, d, J = 7 Hz), 3.80 (1H, d, J = 12 Hz), 2.25 (2H, d, J = 10 Hz), 1.92-1.74 (4H, m), 1.77 (4H, m), 1.52 (4H, m).

To a solution of THP-hydroxamate 34e (4.11 g, 8.0 mmol) in EA (100 mL) at 0°C was added a methanolic solution of HCl [generated by the addition of acetyl chloride (1.71 mL, 24.0 mmol) to methanol (20 mL)]. The solution was concentrated to give a gum which was triturated with ether to afford hydroxamate N-allyl amine hydrochloride 35e (3.53 g, 95%) as a colorless powder: MS MH+ calc'd for C21H24N2S2O4 433, found 433. Anal calc'd for C21H24N2S2O4.HCl:O.5H2O C, 52.76; H, 5.48; N, 5.86; S, 13.42; Cl, 7.42. Found C, 52.57; H, 5.69; N, 6.29; S, 12.59; Cl, 7.80. N-hydroxy-4-[(4-(phenylthio)phenyl)sulfonyl]-1- (2-propynyl)-4-piperidinecarboxamide, monohydrochloride (SC-276, hydrochloride salt). To a solution of the amine hydrochloride salt 31 (5.98 g, 17.0 mmol) in DMF (120 mL) was added potassium carbonate (4.7 g, 34.0 mmol) followed by propargyl bromide (2.02 g, 17.0 mmol) and the solution was stirred for 4 hours at ambient temperature. The solution
was partitioned between EA and H2O, and the organic layer was washed with H2O and brine and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the propargyl amine 32f as a yellow oil (5.2 g, 86%).

To a solution of the propargyl amine 32f (2.75 g, 7.78 mmol) in DMF (15 mL) was added thiophenol (0.80 mL, 7.78 mmol) and Cs2CO3 (2.79 g, 8.56 mmol) and the solution was heated to 70°C for 6 hours. The solution was partitioned between ethyl ether and H2O. The organic layer was washed with H2O and saturated NaCl, and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexane) provided the thioether 33f as an oil (1.95 g, 56%). MS MH+ calcd for C15H13NO3S2 444, found 444. Anal calcd for C15H12NO3S2 C, 52.99; H, 5.08; N, 5.88; S, 13.47. Found C, 53.02; H, 5.21; N, 5.82; S, 13.08. 1H NMR (300 MHz, CDCl3) δ 7.67 (2H, d, J = 8 Hz), 7.57 (2H, m), 7.53-7.47 (3H, m), 7.18 (2H, d, J = 8 Hz), 4.98 (1H, br s), 3.99 (1H, t, J = 11 Hz), 3.68 (1H, d, J = 11 Hz), 3.22 (2H, d, J = 2 Hz), 2.91 (2H, dd, J = 10, 2 Hz), 2.32 (2H, td, J = 11 Hz), 2.27-2.16 (4H, m), 1.92-1.73 (3H, m), 1.68-1.55 (3H, m).

To a solution of the THP-hydroxamate 34f (9.65 g, 18.7 mmol) in methanol (148 mL) cooled to 0°C was added acetyl chloride (4.0 mL, 56.2 mmol), and the solution was stirred for 45 minutes at rt. Concentration followed by trituration with ethyl ether provided 35f (SC-276) as a white solid (8.10 g, 94%). MS(CI) MH+ calcd for C22H22N2O4S2 431, found 431. Anal calcd for C22H21N2O4S2.HCl C, 52.99; H, 5.08; N, 5.88; S, 13.47. Found C, 52.02; H, 5.21; N, 5.82; S, 13.08. 1H NMR (300 MHz, CDCl3) δ 7.67 (2H, d, J = 8 Hz), 7.57 (2H, m), 7.53-7.47 (3H, m), 7.26 (2H, d, J = 7 Hz), 4.08 (2H, d, J = 2 Hz), 3.74 (2H, br d, J = 3 Hz), 3.39 (1H, t, J = 13 Hz), 3.02 (2H, br t, J = 13 Hz), 2.61 (2H, br d, J = 14 Hz), 2.39 (2H, br t, J = 13 Hz).

N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide, methanesulphonate (SC-276, mesylate salt). To a solution of the free base of SC-276 (1.61 g, 3.7 mmol) in MeOH (10 mL) was added methan sulphonic acid (395 mg, 4.1 mmol). After 3 h at rt the precipitate was isolated by filtration to afford the mesylate salt of SC-276 (1.60 g, 81%) as a colorless crystalline solid: Crystalline by powder X-ray diffraction. DSC 219.7°C. Anal calcd for C23H19N2O5S.HClO2.HC2O4 C, 48.51; H, 5.18; N, 5.14; S, 17.66. Found C, 48.88; H, 5.15; N, 5.23; S, 17.81.

1-acetyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]piperidine-4-carboxamide (35f). To a solution of N-BOC ethyl ester 30 (40 g, 96 mmol) and K2CO3 (26 g, 188 mmol) in DMF (200 mL) at 0°C was added thiophenol (19.8 mL, 192 mmol) and the reaction was stirred at rt for 36 h. Concentration gave a residue which was dissolved in EA and washed with water and brine and dried over MgSO4. Chromatography on silica gel eluting with EA/hexane gave the diaryl sulfide (44.3 g, 91%) as a white solid. To a solution of the diaryl sulfide ethyl ester (7 g, 1.29 mmol) in 1:1 EtOH/THF (50 mL) was added NaOH (5.1 g, 12.9 mmol) in H2O (50 mL). The solution was heated to reflux for 20 h. The solution was then concentrated in vacuo and the residue was dissolved in H2O. The aqueous layer was extracted with ether, and then acidified to pH 2 and extracted with EA. The combined organic extracts were washed with water and brine and dried over MgSO4. Concentration provided the carboxylic acid (3.9 g, 60%) as white foam. To a solution of this N-BOC carboxylic acid (2.3 g, 4.98 mmol) in CH2Cl2 (6 mL) was added TFA (6 mL, 77.8 mmol), and the solution was stirred at rt for 1 h. Concentration in vacuo provided the amine
To a solution of the THP-hydroxamate NaOH (1.72 g, 43 mmol) in H2O (10 mL) and the reaction was heated on at 60 °C for 3 h. Concentration in vacuo provided the N-acetamide carboxylic acid (5.0 g, 100%) as a solid:

\[
\text{HRMS calcd for } C_{471.0718}, \text{ found } 471.0728. \text{ Anal calcd for } C_{107.555}, \text{ found } 555.\]

To a solution of the THP-hydroxamate 34g (6.07 g, 11.7 mmol) in MeOH (100 mL) at 0 °C was added acetyl chloride (2.5 mL, 35.1 mmol), and the solution was stirred at rt for 2 h. Concentration gave a residue which was purified by chromatography on silica gel eluting with methanol/CH2Cl2 to provide the N-acetyl hydroxamic acid (3.3 g, 65%) as a white solid.

**N-hydroxy-1-(methylsulfonyl)-4-[[4-(phenylthio)phenyl]sulfonyl]piperidine-4-carboxamide (35g).** To a solution of amine hydrochloride 37 (2.0 g, 4.7 mmol) in CH2Cl2 (35 mL) was added NMM (1.29 mL, 11.7 mmol) followed by methanesulphonyl chloride (0.55 mL, 7.05 mmol). The reaction was stirred for 2 d at rt and then concentrated. Water was added and the mixture was extracted with EA (3X). The combined extracts were washed with water and dried over MgSO4. Concentration in vacuo provided the N-acetylated hydroxamic acid (3.3 g, 65%) as a white solid.

To a solution of mesyl ethyl ester 33h (2.1 g, 4.3 mmol) in 1:1 EtOH/THF (50 mL) was added a solution of NaOH (1.72 g, 43 mmol) in H2O (10 mL) and the reaction was heated on at 60°C. Concentration gave a residue which was acidified to pH 2 with 2N HCl and extracted with EA. The combined extracts were washed with water and dried over MgSO4. Concentration gave a yellow oil (3.86 g) which was purified by chromatography on silica gel eluting with methanol/CH2Cl2 to provide the N-acetyl hydroxamic acid (2.1 g, 100%) as a solid:

\[
\text{H NMR (400 MHz, CDCl}_3) \delta 7.67-7.52 (4H, m), 7.47 (3H, m), 7.21 (2H, d, J = 9 Hz), 4.23 (2H, q, J = 7 Hz), 3.85 (2H, m), 2.77 (3H, s), 2.63 (2H, t, J = 11 Hz), 2.46 (2H, d, J = 13 Hz), 2.17 (2H, m), 1.26 (3H, t, J = 7 Hz). \]

To a solution of sulphone 30 (40 g, 96 mmol) and powdered K2CO3 (26 g, 188 mmol) in DMF (200 mL) cooled to 0°C was added thiophenol (19.8 mL, 192 mmol), and the resulting composition was then stirred at rt for 36 h. That solution was concentrated under high vacuum and the residue was dissolved in EA. The organic layer was washed with H2O and dried over MgSO4. Chromatography on silica gel eluting with EA/hexane provided the phenylthiophenyl BOC-sulphone 36 as a white solid (44.3 g, 91%).
**ethyl 4-[[4-(phenylthio)phenyl]sulfonyl]piperidine-4-carboxylate hydrochloride (37, hydrochloride salt).** Through a solution of N-BOC ethyl ester 36 (31.2 g, 66 mmol) in EA (500 mL) at 0°C was bubbled HCl gas for 0.5 h. The solution was allowed to stand for an additional 1.5 h and was then concentrated to afford a residue which was triturated with ether to afford amine hydrochloride 37 (26.9 g, 96%) as a white foam.

**ethyl 4-[[4-(phenylthio)phenyl]sulfonyl]piperidine-4-carboxylate trifluoroacetate (37, trifluoroacetate salt).** To a solution of the phenylthiophenyl BOC-sulphone (8.6 g, 17 mmol) in CH₂Cl₂ (30 mL) cooled to 0°C was added TFA (30 mL), and the resulting solution was stirred at rt for 2 h. Concentration in vacuo provided the amine TFA salt as a light yellow gel (8.7 g, 100%).

**Enzyme Assays.** Inhibitors were assayed against purified hMMP-1 hMMP-2, hMMP-8, hMMP-9, and hMMP-13 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 [Nagase, H., Fields, C.G., and Fields, G.B. Design and characterization of a fluorogenic substrate selectively hydrolysed by stromelysin 1 (matrix metalloproteinase-3). *J. Biol. Chem.* 1994, 269, 20952-20957.] Assay conditions were similar to those described in G. Knight et al. in *FEBS Lett.* 1992, 296, 263. All basic compounds were tested as their hydrochloride salts unless otherwise indicated.

**Mouse Corneal Neovascularization Model.** Animal work was carried out in accordance with institutional guidelines. All animal procedures were approved by the Institutional Animal Care and Use Committee and conform to the NIH Guidelines for the Ethical Care and Treatment of Animals. A Hydron [poly(hydroxyethyl)methacrylate: IFN Sciences, New Brunswick, NJ] implant containing 60 ng of human recombinant bFGF (Life Technologies, Gaithersburg MD) and 200 µg of sucralfate (Carafate: Marion Merrel Dow, Cincinnati, OH) were prepared and stored at -90°C. C57BL/6 male mice (Charles River Laboratories, Raleigh, NC) weighing 200-250 g were anesthetized, and a 2-mm keratotomy was made 1 mm from the center of the globe with #15 surgical blade. An intrastromal pocket was tunneled toward the lateral canthus using a modified corneal knife (1 X 15), and a single Hydron pellet was inserted ~2mm from the conral-scleral junction. In some cases, mice were implanted with Hydron pellets prepared without bFGF. Treatment of mice with SC-276 or vehicle was initiated the evening of the same day. SC-276 was prepared in vehicle (0.5% methylcellulose, 0.1% polysorbate 80 in water; sterile filtered). Seven days later, the mice were injected in the ipsilateral carotid artery with 50% India ink to stain the blood vessels. The rats were sacrificed; the corneas were removed and mounted on microscope slides; and the area of corneal vascularization was measured using computer-assisted image analysis.

**MX-1 human breast carcinoma model**
Female NCR-nude mice were implanted subcutaneously with 1 mm³ MX-1 human breast carcinoma fragments in the flank. Tumors were monitored initially twice weekly, and then daily as the neoplasms approached the desired size. When the majority of the carcinomas reached a mass of 32-126 mg in calculated tumor weight, the animals were pair-matched into treatment groups. Estimated tumor weight was calculated using the formula: tumor weight (mg) = [w² X L]/2, where w= tumor width and L = tumor length, measured in mm.

**SC-276** was prepared in vehicle (0.5% methylcellulose, 0.1% polysorbate 80 in water; sterile filtered). Taxol (Taxol®; Bristol Myers Squibb) was obtained as the marketed pharmaceutical drug. Taxol was given ip on a daily X 5 schedule at a dose of 9 mg/kg. **SC-276** was given b.i.d. orally at 100 mg/kg until the study end-point was reached. All drugs were administered starting the day of pair match (Day 1). In the combination group, the oral dose of **SC-276** immediately followed the Taxol injection. The vehicle-treated mice served as controls and were dosed orally b.i.d. with vehicle until the study end point was reached.

The median survivals of various groups were compared to each other and to the median survival time of MX-1 growth control mice. Mice were euthanized when MX-1 tumors reached a calculated size of 1.5 g and is considered a cancer death. The median survival (MDS) is the day at which half the mice in a group have died. Survival curves were compared using Graphpad Prism.

**References**


Figure 1: MMP Inhibitors

**marimastat**

**RS-130,830**

**AG-3340/prinomastat**

**BMS 275,291**

Scheme 1. General Method to Synthesize α-piperidine-β-sulphones 6

1) LDA, CH₂I₂ → EtO₂C-N→CO₂Et  
2) NaH → EtO₂C-I  
3) PhOAr → EtO₂C-PhOAr  
4) MCPBA → 1) RBr, K₂CO₃ or RCHO, BH₃, Py

**Figure 2.** Initial α-ketal-β-sulphone target 7 and new α-sulphone scaffold 8
Scheme 2. Original Synthesis of α-sulphone 12

\[
\begin{align*}
\text{HO} & = O \quad \text{Br} \quad + \quad \text{HS} & \text{O} \quad \text{S} \quad \text{O} \quad \text{O} \quad \text{NH} \\
& \quad \text{HO} \quad \text{O} \quad \text{SMeO} \\
\text{O} & \quad \text{O} \\
\text{MeOH} & \quad \text{11} \\
1) & \quad \text{Oxone} \quad 2) \quad \text{SOCl}_2, \text{MeOH} \\
\end{align*}
\]

Scheme 3. Synthesis of α,α-dialkyl-α-sulphone 17

\[
\begin{align*}
\text{Et}_3 & \text{N} \quad \text{then MCPBA} \\
\end{align*}
\]
Scheme 4: Preparation of a-tetrahydropyran-α-sulphone 21

H₂S

1) Me₂O₂CCH₂Br
2) NaOMe
MeO₂C<br>

18

1) Oxone
K₂CO₃, DMAP
MeO₂C<br>

19

1) TMSOK
2) THPONH₂
EDC

Scheme 5: Synthesis of N-alkylpiperidine-phenyloxyphenyl-α-sulphones 27
Scheme 6: Synthesis of N-alkylpiperidine-phenylthiophenyl-α-sulphones 35a-h, including SC-276

Scheme 7: Alternate Synthesis of N-Alkyl Piperidine Ethyl Esters Intermediates 33
Table 1. In Vitro MMP Inhibitory Data [IC$_{50}$ Values (nM)] and Oral Rat PK Data [$C_{\text{max}}$ and C6h ($\mu$g/mL)] of $\beta$-sulphones 7

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Table 2. In Vitro MMP Inhibitory Data (IC$_{50}$ Values, nM) and Oral Rat PK of RS 130,830 and the corresponding $\alpha$-sulphone 21

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<th>MMP-13</th>
<th>$C_{\text{max}}$</th>
<th>C6h</th>
<th>$t_{1/2}$ (h)</th>
<th>BA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS-130830</td>
<td>800</td>
<td>0.4</td>
<td>17.5</td>
<td>1.0</td>
<td>0.60</td>
<td>1372</td>
<td>537</td>
<td>1.5</td>
<td>22.1</td>
</tr>
<tr>
<td>21</td>
<td>435</td>
<td>&lt;0.1</td>
<td>18.1</td>
<td>0.3</td>
<td>0.15</td>
<td>3119</td>
<td>506</td>
<td>1.5</td>
<td>45.8</td>
</tr>
</tbody>
</table>
Table 3. In Vitro MMP Inhibitory Data [IC_{50} Values (nM)] and Oral Rat PK Data [C_{max} and C6h (µg/mL)] of Phenylxyphenyl α-sulphones 27a-i

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>R</th>
<th>MMP-1</th>
<th>MMP-2</th>
<th>MMP-3</th>
<th>MMP-8</th>
<th>MMP-9</th>
<th>MMP-13</th>
<th>C_{max} (ng/mL)</th>
<th>C6h (ng/mL)</th>
<th>t_{1/2} (h)</th>
<th>BA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27a</td>
<td>BOC</td>
<td>1140</td>
<td>0.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.3</td>
<td>-</td>
<td>-</td>
<td>1.8</td>
<td>16</td>
</tr>
<tr>
<td>27b</td>
<td>H</td>
<td>880</td>
<td>0.2</td>
<td>59</td>
<td>3.5</td>
<td>5.0</td>
<td>0.04</td>
<td>1839</td>
<td>254</td>
<td>1.25</td>
<td>59</td>
</tr>
<tr>
<td>27c</td>
<td>CH₃</td>
<td>464</td>
<td>&lt;0.1</td>
<td>-</td>
<td>-</td>
<td>0.29</td>
<td>0.1</td>
<td>4130</td>
<td>102</td>
<td>1.8</td>
<td>16</td>
</tr>
<tr>
<td>27d</td>
<td>Methoxyethyl</td>
<td>350</td>
<td>0.1</td>
<td>0.3</td>
<td>9.4</td>
<td>0.7</td>
<td>0.1</td>
<td>3111</td>
<td>97</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>27e</td>
<td>Cyclopropyl</td>
<td>400</td>
<td>0.2</td>
<td>0.3</td>
<td>12.1</td>
<td>0.6</td>
<td>0.3</td>
<td>15,720</td>
<td>135</td>
<td>0.74</td>
<td>36</td>
</tr>
<tr>
<td>27f</td>
<td>Cyclopropylmethyl</td>
<td>268</td>
<td>0.1</td>
<td>11.4</td>
<td>1.3</td>
<td>0.5</td>
<td>0.25</td>
<td>22,882</td>
<td>345</td>
<td>1.19</td>
<td>35.5</td>
</tr>
<tr>
<td>27g</td>
<td>Propargyl</td>
<td>464</td>
<td>&lt;0.1</td>
<td>-</td>
<td>-</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>998</td>
<td>121</td>
<td>0.86</td>
<td>11.1</td>
</tr>
<tr>
<td>27h</td>
<td>Acetyl</td>
<td>7300</td>
<td>0.4</td>
<td>23.0</td>
<td>5.0</td>
<td>8.0</td>
<td>0.6</td>
<td>162</td>
<td>72</td>
<td>0.65</td>
<td>12.7</td>
</tr>
<tr>
<td>27i</td>
<td>Mesyl</td>
<td>800</td>
<td>0.3</td>
<td>-</td>
<td>-</td>
<td>1.0</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4. In Vitro MMP Inhibitory Data (IC_{50} Values (nM)) and Oral Rat PK Data (C_{max} and C6h (µg/mL)) of Phenylthiophenyl α-sulphones 35a-g

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>R</th>
<th>MMP-1</th>
<th>MMP-2</th>
<th>MMP-3</th>
<th>MMP-8</th>
<th>MMP-9</th>
<th>MMP-13</th>
<th>C_{max} (ng/mL)</th>
<th>C6h (ng/mL)</th>
<th>t_{1/2} (h)</th>
<th>BA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35a</td>
<td>CH₃</td>
<td>&gt;10,000</td>
<td>0.5</td>
<td>39.3</td>
<td>11.4</td>
<td>9.4</td>
<td>0.55</td>
<td>3330</td>
<td>543</td>
<td>1.91</td>
<td>27.5</td>
</tr>
<tr>
<td>35b</td>
<td>Et</td>
<td>&gt;10,000</td>
<td>0.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>35c</td>
<td>Methoxyethyl</td>
<td>&gt;10,000</td>
<td>0.3</td>
<td>20.0</td>
<td>4.0</td>
<td>3.0</td>
<td>0.5</td>
<td>12,589</td>
<td>1,237</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>35d</td>
<td>Cyclopropyl</td>
<td>&gt;10,000</td>
<td>0.1</td>
<td>23.5</td>
<td>3.5</td>
<td>2.5</td>
<td>0.2</td>
<td>7647</td>
<td>529</td>
<td>1.03</td>
<td>34.6</td>
</tr>
<tr>
<td>35e</td>
<td>Allyl</td>
<td>&gt;10,000</td>
<td>0.15</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.3</td>
<td>10,015</td>
<td>537</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SC-276</td>
<td>Propargyl</td>
<td>9000</td>
<td>0.2</td>
<td>13.0</td>
<td>1.8</td>
<td>1.5</td>
<td>0.3</td>
<td>13,630</td>
<td>281</td>
<td>1.1</td>
<td>28</td>
</tr>
<tr>
<td>35f</td>
<td>Acetyl</td>
<td>7300</td>
<td>0.4</td>
<td>23.0</td>
<td>5.0</td>
<td>8.0</td>
<td>0.6</td>
<td>162</td>
<td>72</td>
<td>0.65</td>
<td>12.7</td>
</tr>
<tr>
<td>35g</td>
<td>Mesyl</td>
<td>&gt;10,000</td>
<td>2.0</td>
<td>32.0</td>
<td>4.0</td>
<td>14.7</td>
<td>2.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Figure 3: β-sulphone versus α-sulphones (MMP IC₅₀ values, nM; rat PK 20 mpk suspension, µg/mL)
SC-276 inhibits angiogenesis in the mouse cornea. Neovascularization was initiated in the mouse cornea by implanting a Hydron pellet containing basic FGF pellet. SC-276, at doses of 1-50 mg/kg in 0.5% methylcellulose/0.08% tween 80 was administered orally twice a day for 5 days.
Neovascularization in the control and treated groups was measured and the extent of neovascularization in treatment groups was normalized to vehicle-treated control (set at 100%). This is representative data from two independent experiments.

**Figure 7**

SC-276 extends the survival of MX-1 breast-tumor bearing mice treated with Taxol. Mice were implanted with MX-1 tumor fragment and then pair-matched on Day 1 when the tumors reached approx 60mg. Groups were administered vehicle, SC-276, Taxol or the combination of Taxol and SC-276 from Day 1 until the end point was reached.
Table 5  Summary of Treatment Response

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>MDS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>-</td>
<td>26.0</td>
<td>-</td>
</tr>
<tr>
<td>Taxol</td>
<td>-</td>
<td>31.0</td>
<td>*p=0.0001</td>
</tr>
<tr>
<td>-</td>
<td>SC-276</td>
<td>33.0</td>
<td>**p&lt;0.0001</td>
</tr>
<tr>
<td>Taxol</td>
<td>SC-276</td>
<td>54.5</td>
<td>***p=0.0004</td>
</tr>
</tbody>
</table>

*p, Vehicle vs Taxol  
**p, Vehicle vs SC-276  
***p, Taxol vs combination Taxol/SC-276