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

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Synthesis and Structure-Activity Relationships of MMP-1 Sparing α-Piperidine Sulphone Hydroxamic Acids: Oral Antitumor Efficacy of Clinical Candidate SC-276

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Abstract
α-Piperidine-β-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 and α-sulphone hydroxamates that are superior to the corresponding β -sulphones in potency for target MMP's, selectivity versus MMP-1, and oral exposure when dosed orally. α-Piperidine-α-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 hydroxamates[23,24] 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-130,830**[25] 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 isonipecotate **1**[31] 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-phenoxythiophenol 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 sulfide which was oxidized with oxone to afford sulphone **18**. The acidic methylene was dialkylated with bis(2-bromoethyl)ether to afford the α-sulphone **19**. Saponification of the methyl ester with potassium trimethylsilanoate 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-chlorophenolate anion and subsequent treatment with HCl gave the free hydroxamate **21**.

N-alkylpiperidine phenyloxyphenyl 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-mercaptodiphenyl 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 isonipecotate **1** was sulfinylated with p-fluorophenyldisulfide 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 β-sulphone work, as it had enabled the production of analogs that were potent for MMP-2 and MMP-13, typically with >1000-fold selectivity versus MMP-1.[23,24] Compounds **7a** through **7e** are phenylthiophenyl ethers with varying substituents on the α-piperidine nitrogen, and compound **7f** employs a 3,4-dimethylphenylthiophenyl sulphone to drive deeper into the P1' selectivity pocket and enhance the selectivity. The MMP-2 selectivity ratio of **7a** through **7d** persists at between 860X (example **7b**) to 2400X (example **7a**) relative to a selectivity ratio of 2000X for **RS-130830**. Somewhat higher selectivity (8500X) was attained with N-propargyl piperidine **7e**, 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 a-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_{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_{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.[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_{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_{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_{max} of 22,882 μg/mL and a concentration at 6 h of 345 μg/mL, compared with a C_{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_{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_{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.[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.[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 C_{max} 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 phenyloxyphenyl 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 cyno and a $t_{1/2}$ 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. ^{1}H NMR spectra were obtained from either General Electric QE-300 or Bruker-400 MHz Ultrashield spectrometers with tetramethylsilane (TMS) as an internal standard. Noise-decoupled and APT ^{13}C NMR spectra were recorded at 75 MHz on a General Electric QE-300 spectrometer. IR spectra were recorded on a Perkin Elmer 685 spectrophotometer. DSC refers to differential scanning calorimetry. MIR refers to multiple internal reflectance infrared spectroscopy. 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 isonipecotate N-t-butyl carbamate **1** (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 $MgSO_4$. Concentration gave the desired iodide **2** (1.5 g, 96.8%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ

4.23 (2H, t, J = 7 Hz), 3.83 (2H, m), 3.30 (2H, s), 3.00 (2H, m), 2.18 (2H, m), 1.42 (9H, s), 1.28 (3H, t, J = 7 Hz).

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 $MgSO_4$. 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 CH_2Cl_2 at 0°C was added 85% MCPBA (5.65 g, 27.8 mmol) and then the reaction was stirred for 2 h at 0°C. The solution was then washed successively with water, saturated NaHCO3, water, and brine, and then dried over $MgSO_4$. Concentration gave a residue (7.86 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 amine hydrochloride **4** (774 mg, 80%) as a colorless solid: ^{1}H NMR (300 MHz, CD_3OD) 7.88 (2H, d, J = 9 Hz), 7.46 (2H, t, J = 8 Hz), 7.27 (1H, t, J = 8 Hz), 7.12 (4H, t, J = 8.5 Hz), 4.19 (2H, q, J = 7 Hz), 3.69 (2H, s), 3.32 (2H, m), 3.16 (2H, td, J = 10, 3 Hz), 2.39 (2H, m), 2.00 (2H, m), 1.31 (3H, t, J = 7 Hz). IR (MIR) 1722, 1583, 1486, 1246, 1146 cm^{-1}. Anal calcd for $C_{21}H_{25}NSO_5$.HCl C, 57.33; H, 5.96; N, 3.18; Cl, 8.06. Found 57.29; H, 5.87; N, 3.17; Cl, 8.17.

tert-Butyl 4-[(hydroxyamino)carbonyl]-4-{[(4-phenoxyphenyl)sulfonyl]methyl}piperidine-1-carboxylate (7a). To a solution of ethyl ester **3** (250 mg, 0.496 mmol) in 1:1 EtOH/THF (6 mL) was added NaOH (198 mg, 4.96 mmol) in water (2 mL) and the solution was heated at 60°C for 18 h. The reaction was diluted with water (20 mL) and acidified with 2N HCl. The mixture was then extracted with CH_2Cl_2 (3X). The combined extracts were washed with brine and dried over $MgSO_4$ and concentrated to afford the carboxylic acid **6a** (236 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, J = 8 Hz), 7.41 (2H, t, J = 8 Hz), 7.22 (1H, t, J = 7 Hz), 7.06 (4H, d, J = 7 Hz), 3.68 (2H, m), 3.48 (2H, s), 3.32 (2H, m), 2.21 (2H, m), 1.71 (2H, m), 1.45 (9H, s).

To a solution of the carboxylic acid **6a** (850 mg, 1.79 mmol) in DMF (7 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 $MgSO_4$. Concentration gave a residue (900 mg) which was chromatographed on reverse phase eluting with MeCN/H_2O (gradient from 30/70 to 80/20) to afford the desired hydroxamate **7a** (300 mg, 34%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) 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 $C_{24}H_{30}N_2SO_7$ C, 58.76; H, 6.16; N, 5.71; S, 6.54. Found C, 58.64; H, 6.24; N, 5.66; S, 6.66.

N-hydroxy-4-{[(4-phenoxyphenyl)sulfonyl]methyl}piperidine-4-carboxamide hydrochloride (7b). Through a solution of N-BOC hydroxamate **7a** (499 mg, 1.02 mmol) in EA (20 mL) at 0°C was bubbled HCl gas for 2 min. The solution was then stirred for 0.5 h at 0°C and then concentrated to dryness. The residue was triturated with ether and dried to afford the hydrochloride salt of hydroxamate **7b** (432 mg, 99%) as a colorless solid: ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.78 (1H, s), 8.65 (1H, br s), 3.18 (2H, m), 2.91 (2H, m), 2.16 (2H, m), 1.95 (2H, m). HRMS calcd for $C_{19}H_{22}N_2SO_5$ 391.1328, found 391.1349. Anal

calcd for C19H22N2SO5.HCl.H_2O C, 51.29; H, 5.66; N, 6.30; Cl, 7.97; S, 7.21. Found C, 50.87; H, 5.24; N, 6.22; Cl, 8.24; S, 7.07.

N-hydroxy-1-(3-methoxybenzyl)-4-{[(4-phenoxyphenyl)sulfonyl]methyl}piperidine-4-carboxamide hydrochloride (7c). To a solution of the ethyl ester piperidine monohydrochloride **4** (748 mg, 1.70 mmol) in methanol (7 mL) was added anisaldehyde (242 mg, 1.78 mmol) followed by borane-pyridine complex (106 uL of a ca. 8 M solution in pyridine, 0.85 mmol). After 18 h at rt, additional quantities of anisaldehyde (112 mg, 0.82 mmol) and borane-pyridine (106 uL, 0.85 mmol) were added and the solution stirred for an additional 18 h at rt. 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 Na_2SO_4, and concentrated to afford a colorless oil (1.03 g). Chromatography on silica gel eluting with EA/hexane (1:1) afforded the N-methoxybenzylamine **5c** (0.82 g, 92%) as a colorless oil: IR (MIR) 1731, 1581, 1486, 1242, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (2H, d, J = 8.7 Hz), 7.42 (2H, t, 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 $C_{29}H_{33}NO_6S$ 524, found 524. Anal calcd for $C_{29}H_{33}NO_6S.0.75H_2O$ C, 64.84; H, 6.47; N, 2.61. Found C, 64.89; H, 6.72, N, 2.51.

To a solution of 3-methoxybenzylamine **5c** (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/H_2O 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}; HRMS calcd for $C_{27}H_{29}NO_6S$ 496.1798, found 496.1794. ^1H NMR (300 MHz, CD_3OD) δ 7.87 (2H, d, J = 8.7 Hz), 7.45 (2H, t, J = 8 Hz), 7.39 (1H, t, J = 8 Hz), 7.26 (2H, m), 6.92 (1H, m), 4.29 (2H, s), 3.83 (3H, s), 3.78 (2H, s), 3.38 (2H, br m), 3.23 (2H, br m), 2.45 (2H, br m), 2.12 (2H, br m).

To a solution of this carboxylic acid **6c** (841 mg, 1.62 mmol) in dry DMF (6 mL) was added HOBT (263 mg, 1.94 mmol) and NMM (655 mg, 6.5 mmol). The solution was then cooled to 0°C and 50% aqueous hydroxylamine (128 uL, 194 mmol) was added followed by EDC (372 mg, 1.94 mmol). After 20 h at rt, additional quantities of HOBT, NMM, hydroxylamine and EDC (same quantities as original) were added and the solution was stirred for an additional 16 h at rt. The reaction mixture was then concentrated. Saturated aqueous NaHCO3 (50 mL) was added and the mixture was extracted with EA (4X). The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated to afford a yellow-orange oil (308 mg) which was purified on a Waters reverse-phase instrument eluting with 15/85 MeCN/H_2O with 0.5% HCl afforded the requisite hydroxamic acid **7c** as a colorless solid: IR (MIR) 1737, 1656, 1583, 1487, 1245, 1144 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.89 (2H, d, J = 8 Hz), 7.5-6.9 (11 H, m), 4.27 (2H, s), 3.84 (3H, s), 3.55-3.25 (4H, m), 3.06 (2H, m), 2.62 (2H, m), 2.16 (2H, m). HRMS calcd for MH+ $C_{27}H_{31}N_2O_6S$ 511.1903, found 511.1907. Anal calcd for $C_{27}H_{30}N_2O_6S.HCl.1.5H_2O$ C, 56.49; H, 5.97; N, 4.88. Found C, 55.92; H, 5.32; N, 4.72.

N-hydroxy-4-{[(4-phenoxyphenyl)sulfonyl]methyl}-1-(2-phenylethyl)piperidine-4-carboxamide hydrochloride (7d). To a suspension of amine hydrochloride **4** (750 mg, 1.70 mmol) in EtOH (30 mL) was added phenyl acetaldehyde (414 mg, 3.4 mmol) followed by borane-pyridine (0.44 mL, 3.4 mmol) and the reaction was stirred at rt for 3 d. The solvent was removed in vacuo and the residue resuspended in H_2O (40 mL). The mixture was extracted with CH_2Cl_2 (3X) and the combined organic extracts were washed successively with water and brine, and dried over $MgSO_4$. Concentration gave a residue which was chromatographed on silica gel eluting with EA/hexane (60/40 to neat EA) to afford the phenethylamine ethyl ester **5d**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, J = 9 Hz), 7.44 (2H, t, J = 9 Hz), 7.31 (1H, m), 7.24 (5H, m), 7.09 (4H, m), 4.30 (2H, q, J = 7 Hz), 3.50 (2H, m), 3.45 (2H, s), 3.24 (2H, m), 3.12 (2H, m), 2.94 (2H, m), 2.55-2.45 (4H, m), 1.36 (3H, t, J = 7 Hz). HRMS calcd for $C_{29}H_{34}NSO_5$ 508.2158, found 508.2161.

To a solution of phenethylamine ethyl ester **5d** (680 mg, 1.30 mmol) in 1:1 EtOH/THF (16 mL) was added an aqueous solution of NaOH (520 mg, 13.0 mmol) in water (3 mL) and the reaction was heated to 60°C

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 $C_{27}H_{29}NSO_5$ 480, found 480.

To a suspension of the carboxylic acid **6d** (850 mg) in DMF (10 mL) was added sequentially HOBT (267 mg, 1.98 mmol), EDC (429 mg, 2.24 mmol), NMM (485 mg, 4.8 mmol) and 50% aqueous hydroxylamine (1.06 mL, 16 mmol). After 16 h the reaction was charged with identical quantities of HOBT, EDC, NMM and hydroxylamine and stirred for an additional 24 h. To the reaction was then added H_2O (50 mL) and the mixture was extracted with CHCl3 (3X). 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_2O /HCl to afford the hydroxamic acid hydrochloride salt **7d** (104 mg, 14% from amine **4**) as a colorless solid: MS MH+ calcd for $_{C27H30N2SO5}$ 495, found 495. Anal calcd for $C_{27}H_{30}N_2SO_5$.HCl.0.75H_2O 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 K2CO3 (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 (400 MHz, $CDCl_3$) δ 7.84 (2H, d, J = 9 Hz), 7.42 (2H, t, 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), 2.37 (2H, m), 1.96 (2H, m), 1.33 (3H, t, J = 7 Hz).

To a solution of N-propargyl amine ethyl ester **5e** (620 mg, 1.4 mmol) in 1:1 EtOH/THF (20 mL) was added NaOH (560 mg, 14.0 mmol) in water (10 mL) and the reaction was heated to 60°C for 18 h. The reaction mixture was then concentrated to a residue. Water (40 mL) was added and the mixture acidified with 2N HCl to pH 4. The resulting precipitate was filtered and dried to afford carboxylic acid **6e** (473 mg, 82%) as a solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (2H, d, J = 9 Hz), 7.48 (2H, t, J = 8 Hz), 7.28 (1H, t, J = 6 Hz), 7.16 (4H, d, J = 9 Hz), 3.53 (2H, s), 3.20 (2H, s), 3.09 (1H, s), 2.48 (2H, m), 2.33 (2H, m), 2.01 (2H, m), 1.06 (2H, m). HRMS calcd for $C_{22}H_{24}NSO_5$ 414.1375, found 414.1382. Anal calcd for $_{C22H23NSO5}$.HCl.0.5H_2O C, 57.57; H, 5.49; N, 3.05; S, 6.99. Found C, 57.59; H, 4.91; N, 2.72; S, 6.76.

To a solution of solution of carboxylic acid **7e** (460 mg, 1.10 mmol) in DMF (10 mL) was added sequentially HOBT (180 mg, 1.33 mmol), EDC (299 mg, 1.56 mmol), NMM (0.49 mL, 4.45 mmol) and 50% aqueous hydroxylamine (0.22 mL, 3.3 mmol) and the reaction was stirred on at rt. The reaction was then charged again with identical amounts of HOBT, EDC, NMM and aqueous hydroxylamine and stirred an additional 48 h. Water (30 mL) was added and the reaction was extracted with CHCl3 (3X), and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford a residue (500 mg) which was chromatographed on reverse phase eluting with MeCN/H_2O (20/80) to afford the N-propargyl hydroxamic acid free base of **7e** (173 mg, 36%) as a colorless solid: ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.63 (1H, s), 7.82 (2H, d, J = 9 Hz), 7.48 (2H, t, J = 9 Hz), 7.27 (1H, t, J = 8 Hz), 7.14 (4H, d, J = 9 Hz), 3.57 (2H, s), 3.19 (2H, s), 3.11 (1H, s), 2.47 (2H, m), 2.32 (2H, m), 201 (2H, m), 1.72 (2H, m). HRMS calcd for C22H25N2SO5 429.1484, found 429.1480. Anal calcd for C22H24N2SO5 C, 61.66; H, 5.64; N, 6.54; S, 7.48. Found C, 61.33; H, 5.68; N, 6.36; S, 7.35. To a solution of this free base hydroxamate in MeOH (5 mL) was added a solution of HCl in MeOH [prepared by adding 46 mg (0.66 mmol) of acetyl chloride to MeOH (2 mL) at 0°C]. Concentration and trituration with ether afforded the hydroxamic acid amine hydrochloride salt **7e** (153 mg, 100%) as a colorless solid: Anal calcd for $C_{22}H_{24}N_2SO_5$.HCl.0.5H_2O C, 55.75; H, 5.53; N, 5.91; Cl, 7.48. Found C, 55.42; H, 5.63; N, 5.79; Cl, 8.00.

4-({[4-(3,4-dimethylphenoxy)phenyl]sulfonyl}methyl)-N-hydroxy-1-prop-2-ynylpiperidine-4-carboxamide hydrochloride (7f). To a suspension of 60% NaH (600 mg, 15.0 mmol) in DMF (10 mL) at 0°C was added 4-(3,4-dimethylphenoxy)thiophenol (3.45 g, 15.0 mmol). To this solution of sodium thiolate was then added a solution of iodide **2** in DMF (10 mL). The reaction, which became thick, was stirred for 0.5 h at 0°C and then warmed to rt for 4 h. Water (100 mL) was then added and the mixture was

extracted with EA (3X). The combined extracts were washed with brine and dried over $MgSO_4$. 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, 86%): HRMS calcd for C28H37NSO5 400.1946, found 400.1948. Anal calcd for $C_{28}H_{37}NSO_4.1.75H_2O$ C, 63.31; H, 7.68; N, 2.64; S, 6.04. Found C, 63.36; H, 7.49; N, 2.86; S, 5.59.

To a solution of this sulfide (6.45 g, 13.0 mmol) in CH_2Cl_2 (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 (2X) and brine and dried over $MgSO_4$. Concentration gave a residue (10.5 g) which was chromatographed on silica gel eluting with EA/hexane (20/80) to afford the corresponding sulphone **3f** (5.7 g, 98%) as a colorless solid. Anal calcd for $C_{28}H_{37}NSO_7.H_2O$ C, 61.18; H, 7.15; N, 2.55; S, 5.83. Found C, 61.32; H, 7.11; N, 2.44; S, 5.16.

Through a solution of the sulphone **3f** (5.7 g, 13.0 mmol) in EA (120 mL) at 0°C was bubbled HCl gas for 15 min. Concentration and trituration of the residue with ether afforded the hydrochloride salt of the secondary amine **4f** (5.4 g, 89%) as a colorless solid: HRMS calcd for $C_{23}H_{30}NSO_5$ 432.1845, found 432.1828.

To a solution of the HCl salt of amine **4f** in DMF (70 mL) was added K2CO3 (3.17 g, 23.0 mmol) followed 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 organic extracts were washed successively with water and brine and dried over $MgSO_4$. Concentration gave a residue (6.28 g) which was chromatographed on silica gel eluting with 1:1 EA/hexane to afford the propargyl amine ethyl ester **5f** (4.28 g, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, J = 9 Hz), 7.15 (1H, d), 7.04 (2H, d, J = 9 Hz), 6.86 (1H, s), 6.80 (1H, m), 4.19 (2H, q, J = 7 Hz), 3.44 (2H, s), 3.32 (2H, br s), 2.74 (2H, m), 2.69 (2H, m), 2.38-2.30 (3H, m), 2.31 (3H, s), 2.28 (3H, s), 1.86 (2H, m), 1.31 (3H, t, J = 7 Hz). HRMS calcd for $C_{24}H_{31}NSO_5$ 469.1923, found 469.1908. Anal calcd for $C_{24}H_{31}NSO_5.0.5$EA (consistent with NMR) C, 65.47; H, 6.87; N, 2.73; S, 6.24. Found C, 65.50; H, 7.02; N, 2.66; S, 6.15.

To a solution of the propargyl amine ethyl ester **5f** (4.13 g, 8.79 mmol) in 1:1 EtOH/THF (100 mL) was added a solution of NaOH (3.52 g, 87.9 mmol) in H_2O (30 mL) and the reaction was heated to 65°C for 40 h. The reaction was then concentrated to dryness and water (50 mL) was added, which was then acidified to pH 2 with 2N HCl. Concentration gave a residue which was triturated with ether, filtered and dried to afford the carboxylic acid **6f** (3.8 g, 100%) as a colorless solid. HRMS calcd for $C_{24}H_{27}NSO_5$ 441.1608, found 441.1651.

To a suspension of carboxylic acid **6f** (1.0 g, 2.26 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (0.95 mL, 6.78 mmol) and 50% aqueous hydroxylamine (1.5 mL, 22.6 mmol) followed by PyBroP (1.16 g, 2.48 mmol). After 3 d the reaction was concentrated to afford a residue which was chromatographed on a reverse phase column eluting with a gradient of MeCN/H_2O (30/70 to neat MeCN) to afford the requisite hydroxamic acid free base **7f** (215 mg, 21%) as a solid: Anal calcd for C24H28N2SO5 C, 63.14; H, 6.18; N, 6.14; S, 7.02. Found C, 62.78; H, 6.06; N, 6.17; S, 6.86. To a suspension of this free base hydroxamic acid (205 mg, 0.449 mmol) in MeOH (4 mL) at 0°C was added a solution of HCl in MeOH [prepared by adding acetyl chloride (35 uL, 0.49 mmol) to MeOH (1 mL)]. The solution was concentrated to afford a solid which was triturated with ether and dried to afford the monohydrochloride salt of the hydroxamic acid **7f** (191 mg, 86%) as a colorless solid: MS MH+ calcd for $C_{24}H_{28}N_2SO_5$ 457, found 457. Anal calcd for $C_{24}H_{28}N_2SO_5.HCl.0.5H_2O$ C, 57.42; H, 6.02; N, 5.58; Cl, 7.06. Found C, 57.36; H, 6.32; N, 5.68; Cl, 6.84.

N-hydroxy-2-[(4-phenoxyphenyl)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 **10** (2.35 g, 11.7mmol). The solution was stirred for 15 minutes followed by concentration in vacuo. The residue was partitioned between EA and H_2O and the organic layer was dried over $MgSO_4$. Concentration in vacuo provided the crude sulfide **11** as a yellow solid that was used without any additional purification. To a solution of this sulfide of (1.2 g) in methanol/H_2O 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 $NaHC0_3$ and brine and dried over $MgSO_4$. 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(CI) MH+ calculated for $C_{15}H_{14}0_5S$ 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(CI) MH+ calculated for $C_{14}H_{13}NO_5S$: 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 H_2O and the organic layer was washed with brine and dried over $MgSO_4$. Concentration in vacuo provided the sulfide as an oil. To a solution of the sulfide in CH_2Cl_2 (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 $MgSO_4$. 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 H_2O and concentrated in vacuo. The aqueous residue was diluted with EA and the organic phase was washed with H_2O 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(CI) MH+ calculated for $C_{16}H_{16}0_5S$: 321, found 321.

To a solution of the acid **16** (723 mg, 2.26 mmol) in DMF (4.5 mL) was added HOBT (366 mg, 2.71 mmol) and EDC (476 mg, 2.49 mmol). After the solution was stirred for 1 hour at rt 50% aqueous hydroxylamine (0.40 mL, 6.8 mmol) was added. After 15 minutes the solution was partitioned between EA and H_2O. The organic layer was washed with H_2O and brine and dried over Na_2S0_4. Reverse phase chromatography ($MeCN/H_2O$) provided the hydroxamic acid **17** as a white foam (434 mg, 57%). HPLC purity: 99%. MS(CI) MH+ calculated for $C_{16}H_{17}NO_5S$: 342, found 342.

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 $MgS0_4$, 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 K_2CO_3 (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 $C_{13}H_{15}O_5SF$ 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 trimethylsilanoate (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 Na2S04 and concentrated in vacuo. The residue was triturated 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 C12H1305SF: 287.04, found 287.04. To a solution of the carboxylic acid (9.1 g, 31.6 mmol) in DMF (70 mL) was added HOBT (5.1 g, 37.9 mmol), NMM (10.4 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 concentrated in vacuo. The residue was taken up in EA, washed successively with water, 5% KHS04, saturated aqueous NaHC03, brine, dried over Na2S04. 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 $C_{17}H_{22}N0_6SF$: 388.12, found 388.12.

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 to 90°C for 1.5 h. Additional DMF (20 mL) was added, followed by additional cesium carbonate (2 g, 6.2 mmol). The resulting mixture was heated to 95°C for 3 h. The reaction was then diluted with H_2O and extracted with EA. The organic layer was washed with brine and dried over Na_2SO_4. Concentration gave a residue which was purified by chromatography on silica gel eluting with EA/hexane to afford the p-chlorophenoxyphenyl 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/H_2O provided the p-chlorophenoxyphenyl sulphone hydroxamic acid **21** (1.35 g, 58%) as a white solid: MS (FAB) MH+ for $C_{18}H1_8N0_6SCl$ 412, found 412.

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 $MgSO_4$. Concentration gave a dark yellow oil (53 g) 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 [$C_{25}H_{31}NSO_5$-$C_5H_9O_2$(BOC)] 358, found 358. ^{1}H 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).

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 $MgSO_4$. Concentration gave a residue which was purified by chromatography on silica gel eluting with EA/hexane (20/80) to afford the sulphone **23** (1.68 g, 87%) as a colorless solid: DSC 137.1-139.3°C; MS MH+ calcd for [$C_{25}H_{31}NSO_7$-$C_5H_9O_2$(BOC)] 390, found 390. Anal calcd for $C_{25}H_{31}NSO_7$ C, 61.33; H, 6.38; N, 2.79; S, 6.55. Found C, 61.39; H, 6.45; N, 2.77; S, 6.54. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (2H, d, J = 8 Hz), 7.43 (2H, m), 7.25 (1H, m), 7.12-7.02 (4H, m), 4.21 (2H, q, J = 7 Hz), 4.16 (2H, m), 2.63 (2H, m), 2.32 (2H, m), 2.03 (2H, m), 1.44 (9H, s), 1.26 (3H, t, J = 7 Hz).

NH.HCl ethyl ester α-sulphone PhOPh 24

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 calcd for $C_{20}H_{23}NSO_5$ 390.1375, found 390.1357. ^{1}H 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 = 11 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 calcd for $C_{23}H_{27}NSO_7$ C, 59.86; H, 5.90; N, 3.04; S, 6.95. Found C, 59.49; H, 6.37; N, 2.81; S, 6.56. MS MH+ calcd for [$C_{23}H_{27}NSO_7$–$C_5H_9O_2$ (BOC)] 362, found 362. ^{1}H NMR (400 MHz, $CDCl_3$) 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 (256 mg, 1.90 mmol), EDC (424 mg, 2.21 mmol), NMM (479 mg, 4.70 mmol) and 50% aqueous hydroxylamine (1.04 mL, 15.8 mmol). After stirring for 16 h at rt, 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 (2 X 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+ calcd for [$C_{23}H_{28}N_2SO_7$-$C_4H_9O_2$(BOC)] 377, found 377. Anal calcd for C23H28N2SO7 C, 57.97; H, 5.92; N, 5.88; S, 6.73. Found 57.95; H, 6.02; N, 5.81; S, 6.85. IR (MIR) 1637, 1658 cm^{-1}. ^{1}H NMR (400 MHz, d_6-DMSO) 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 allowed to stand at 0°C for 0.5 h and was then 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 calcd for $C_{18}H_{20}N_2SO_5$ 377.1171, found 377.1170. ^{1}H 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 calcd for $_{C18H20N2SO5}$:HCl C, 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 ethyl ether to provide 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 w as 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 sb1ution was concentrated in vacuo and the residue was dissolved to EA, washed with H_2O and dried over $MgSO_4$. Concentration in vacuo provided the crude protected hydroxamate. To a solution of the crude hydroxamate in MeOH (10 mL) was added acetyl chloride (0.28mL, 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/H_2O (0.01% HCl) provided the α-sulphone hydroxamic acid **27c** as a white solid (261 mg, 46%). MS(CI) MH+ calculated for $C_{19}H_{22}N$-0_5S:391, found 391.

α-sulphone N-methoxyethyl PhOPh [patent EXAMPLE 30] (27d). To a solution of the amine HCI 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 $MgSO_4$. 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-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 H_2O and dried over MgS04. 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/H_2O (0.01% HCl) to afford the hydroxamate HCl salt **27d** (0.65 g, 45.5%) as a white solid: Anal calcd for $C_{21}H_{26}N_2O_6S$:HCl:0.75H_2O 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. HRMS calcd for $C_{21}H_{26}N_2O_6S$ 435.1590, found 435.1571.

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 $C_{23}H_{27}NSO_5$ 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 H_2O (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 C21H23NSO5 402.1375, found 402.1350.

To a solution of N-cyclopropyl carboxylic acid **26e** (1.49 g, 3.4 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (3X). The combined organic extracts were washed with brine and dried over $MgSO_4$ and concentrated to give an oil (4.0 g) which was chromatographed on reverse phase eluting with MeCN/H_2O (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 uL, 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 $C_{21}H_{24}N_2SO_5$ 416.1407, found 416.1398. Anal calcd for $C_{21}H_{24}N_2SO_5$.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 $MgSO_4$. 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, 7.23. Found C, 64.99; H, 6.92; N, 3.18; N, 3.11; S, 7.28.

To a solution of cyclopropyl amine ethyl ester **25f** (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 for 16 h at 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 $C_{22}H_{25}NSO_5$ 414.1375, found 414.1334. Anal calcd for $C2_2H_{25}NSO_5$:HCl:0.5H_2O 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 CH_2Cl_2 (50 mL) was added Et3N (1.46 mL, 10.5 mmol) followed by 50% aqueous hydroxylamine (2.31 mL, 3.50 mmol) and PyBroP (3.26 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 charged again with equivalent quantities of Et3N, aqueous hydroxylamine and PyBroP. After 24 h at rt, water was added and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with water and brine and dried over $MgSO_4$. Concentration gave an oil (5.0 g) which was purified by reverse phase chromatography eluting with MeCN/H_2O 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 **17i???**) 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 uL, 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 $MgSO_4$. 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 $C_{23}H_{25}NSO_5$ 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, $CDCl_3$) 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 aqueous 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 $C_{21}H_{22}NSO_5$ 400.1219, found 400.1210. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.75 (2H, d, J = 10 Hz), 7.49 (2H, d, J = 8Hz), 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

(1H, s), 2.80 (2H, m), 2.18 (2H, m), 2.06 (2H, m), 1.90 (2H, m). Anal calcd for $C_{21}H_{21}NSO_5$:H_2O C, 60.42; H, 5.55; N, 3.36; S, 7.68. Found C, 60.60; H, 4.91; N, 3.33; S, 7.34.

To a suspension of carboxylic acid **26g** (485 mg, 1.10 mmol) in DMF (10 mL) was added sequentially EDC (326 mg, 1.70 mmol), NMM (364 uL, 3.30 mmol), and 50% aqueous hydroxylamine (0.73 mL, 11.1 mmol) and the reaction was stirred for 16 h at rt. An additional quantity of EDC (326 mg, 1.70 mmol) and 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_2Cl_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 $C_{21}H_{23}N_2SO_5$ 415.1328, found 415.1331. Anal calcd for $C_{21}H_{22}N_2SO_5$:HCl:0.5H_2O 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_2O 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_2Cl_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_2O (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_2O and dried over $MgSO_4$. Reverse phase chromatography eluting with MeCN/H_2O provided the N-acetyl hydroxamic acid **27h** (101 mg, 16%) as a white solid: MS MH+ calcd for $C_{20}H_{22}N2O_6S$ 419, found 419.

N-methanesulphonyl hydroxamate PhOPh (27i). To a solution of amine hydrochloride **24** (2.13 g, 7.5 mmol) in CH_2Cl_2 (35 mL) was added triethylamine (2.34 mL, 16.5 mmol) followed by methanesulphonyl chloride (0.70 mL, 9.0 mmol). After 16 h at rt the solution was washed with water (2X) 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 $C_{21}H_{25}NS_2O_7$ 468, found 468. Anal calcd for $C2_1H_{25}NS_2O_7$ 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 $C_{19}H_{21}NS_2O_7$ 440.0838; found 440.0820. Anal calcd for $C_{19}H_{21}NS_2O_7$ 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_2Cl_2 (50 mL) was added sequentially Et3N (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_2Cl_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

desired methanesulphonamide hydroxamic acid **27i** (215 mg, 14%) as a colorless solid: Anal calcd for $C_{19}H_{22}N_2S_2O_7.H_2O$ C, 48.29; H, 5.12; N, 5.93; S, 13.57. Found C, 48.72; H, 5.36; N, 5.61; S, 12.81.

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%): ^{1}H NMR (300 MHz, $CDCl_3$) 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 H_2O 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, H_2O, and brine. Chromatography on silica eluting with hexane/ethyl acetate provided the sulfide **29** as an oil (18.0 g, 75%): Anal calcd for $C_{19}H_{26}NO_4$ 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 H_2O and extracted with dichloromethane. The organic layer was washed with 10 percent Na_2SO_3, H_2O, 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 $C_{19}H_{26}O_6NSF$ 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 $C_{14}H_{18}O_4NSF.HCl$ 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-{[4-(phenylthio)phenyl]sulfonyl}piperidine-4-carboxamide hydrochloride (35a). 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 EA, and the combined organic layers were washed with H_2O and dried over $MgSO_4$. 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 stirred at rt for 72 h and then concentrated. The residue was dissolved in EA and washed with aqueous NaHC03, H_2O and dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel eluting with CH_2Cl_2/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, 13.5 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/H_2O (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 $C_{19}H_{22}N_20_4S_2$ 407.1099, found 407.1105.

1-ethyl-N-hydroxy-4-{[4-(phenylthio)phenyl]sulfonyl}piperidine-4-carboxamide hydrochloride (35b). To a solution of amine hydrochloride **37** (6.2 g, 14 mmol) in DMF (20 mL) was added K2CO3 (3.87 g, 28 mmol) and iodoethane (2.4 g, 15.4 mmol) and the reaction was stirred at rt for 3 h. The mixture was then diluted with EA (100 mL), washed with water and brine, and dried over $MgSO_4$. Concentration gave the N-ethyl amine **33b** (6.1 g, 100%) as a solid: HRMS calcd for $C_{22}H_{27}NS_2O_4$ 434.1460, found 434.1452.

To a solution of the N-ethylamine **33b** (2.98 g, 6.9 mmol) in 1:1 EtOH/THF (40 mL) was added a solution of NaOH (2.76 g, 69 mmol) in H_2O (15 mL) and the reaction was heated to 65°C for 18 h. The reaction was concentrated and resuspended in H_2O (30 mL), acidified to pH 3. The resulting solid was filtered and dried to afford the carboxylic acid (1.7 g, 61%) as a 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 sequentially HOBT (1.94 mg, 1.44 mmol), NMM (3.90 g, 35.4 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (2.07 g, 5.7 mmol) and EDC (3.17 g, 16.3 mmol). 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 $MgSO_4$ and concentrated to give a residue (970 mg) which was purified by chromatography on silica gel eluting with MeOH/EA (3/97) to give the THP-hydroxamate **34b** (2.33 g, 39%) as a white solid: HRMS calcd for $C_{25}H_{32}N_2S_2O_5$ 505.1831, found 505.1831.

To a solution of THP-hydroxamate **34b** (2.33 g, 4.6 mmol) in 1/3 MeOH/1,4-dioxane (20 mL) was added 4N HCl/1,4-dioxane (10 mL, 40 mmol). After stirring for 2 h at rt the reaction was concentrated to a semi-solid which was purified by reverse-phase chromatography eluting with MeCN/H_2O (HCl) (5/95 to 100% MeCN) to afford the hydroxamic acid **235b** (1.29 g, 55%) as a colorless foam: MS calcd for $C2_0H_{24}N_2S_2O_4$ 421, found 421. Anal calcd for $C_{20}H_{24}N_2S_2O_4$:HCl:0.5H_2O C, 51.55; H, 5.62; N, 6.01; S, 13.76; Cl, 7.61. Found C, 51.59; H, 5.73; N, 5.70; S, 13.71; Cl, 7.60.

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 $MgSO_4$. Concentration in vacuo provided the methoxyethyl amine **33c** (4.26 g, 95.3%) as white foam.

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 resulting 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 (3.5 g,87.5%) as a while 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 saturated NaHC03, H_2O, and dried over $MgSO_4$. 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/H_2O (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 $C_{21}H_{26}N_20_5S_2$:HCl.O.9H_2O C, 50.12; H, 5.77; N, 5.57; S, 12.74. Found: C, 50.41; H, 5.85; N, 5.73; S,12.83.

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 acetic acid (6.8 mL, 119 mmol). After 5 minutes stirring at rt, (l-ethoxylcyclopropyl)oxytriomethylsilane (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, H_2O and dried 40 over $MgSO_4$. 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 H_2O and dried over $MgSO_4$. 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, 10.8 mmol). The reaction was stirred at rt for 5 h, then diluted with EA an washed successively with water and brine and dried over $MgSO_4$. 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+ calcd for $C_{23}H_{22}NS_2O_4$ 446, found 446. Anal calcd for $C2_3H2_2NS_2O_4$ C, 62.00; H, 6.11; N, 3.14; S, 14.39. Found C, 62.22; H, 6.28; N, 3.04; S, 4.09. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.64 (2H, d, J = 8 Hz), 7.58 (2H, m), 7.53 (3H, m), 7.31 (2H, 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 N-allyl amine ethyl ester **33e** (4.8 g, 10.8 mmol) in 1:1 EtOH/THF (50 mL) was added a solution of NaOH (4.3 g, 10.8 mmol) in water (20 mL) and the reaction was heated at 65°C for 16 h. The reaction was then concentrated to dryness and resuspended in water (100 mL) Acidification with 2N HCl to pH 3 gave a precipitate which was filtered and dried to afford carboxylic acid (4.1 g, 84%) as a beige solid: MS MH+ calcd for $C_{21}H_{23}NS_2O_4$ 418, found 418. Anal calcd for $C_{21}H_{23}NS_2O_4$.HCl:H_2O 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 (2.97 mL, 27 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 CH_2Cl_2 and washed with water and brine and dried over $MgSO_4$. 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 **34e** (4.11 g, 88%) as a colorless foam: HRMS MH+ calcd for $C2_6H3_2N_2S_2O_5$ 517.1831, found 517.1830. Anal calcd for $C_{26}H_{32}N_2S_2O_5$:0.25H_2O 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. ^{1}H NMR (400 MHz, d_6-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, t, 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+ calcd for C21H24N2S2O4 433, found 433. Anal calcd for $C_{21}H2_4N_2S_2O_4$:HCl:0.5H_2O 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 H_2O, and the organic layer was washed with H_2O 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 $CsCO_3$ (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 H_2O. The organic layer was washed with H_2O 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 $C_{23}H_{25}NO_4S_2$ 444, found 444. Anal calcd for $C_{23}H_{25}NO_4S_2$ C, 62.28; H, 5.68; N, 3.16; S, 14.46. Found C, 62.27; H, 5.81; N, 3.09; S, 14.32. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (2H, d, m), 7.54 (2H, m), 7.46 (3H, m), 7.20 (2H, m), 4.21 (2H, q, J = 7 Hz), 3.26 (2H, d, J = 2 Hz), 2.89 (2H, m), 2.34 (2H, m), 2.21 (1H, t, J = 2 Hz), 2.17-2.11 (4H, m), 1.23 (3H, t, J = 7 Hz).

To a solution of the ethyl ester **33f** (1.81 g, 4.06 mmol) in ethanol (21 mL) and H_2O (3.5 mL) was added KOH (1.37 g, 24.5 mmol) and the solution was heated to 105 degrees Celsius for 4.5 hours. The solution was acidified to a pH value of 1 with concentrated HCl solution and then concentrated to provide the acid as a yellow residue that was used without additional purification (1.82 g). To a solution of the carboxylic acid (1.82 g, 4.06 mmol) in acetonitrile (20 mL) was added O-tetrahydro-2H-pyran-2-yl-hydroxylamine (723 mg, 6.17 mmol) and triethylamine (0.67 mL, 4.86 mmol). To this solution was added EDC (1.18 g, 6.17 mmol) and the solution was stirred for 18 hours. The solution was partitioned between H_2O and ethyl acetate. The organic layer was washed with H_2O, saturated $NaHCO_3$ and brine and dried over magnesium sulfate. Chromatography on silica eluting with ethyl acetate/hexane provided the THP-hydroxamate **34f** (1.32 g, 63%) as a white solid: MS MH+ calcd for $C_{26}H3_1N_2O_5S_2$ 515, found 515. ^{1}H NMR (300 MHz, $CDCl_3$) 7.65 (2H, d, J = 8 Hz), 7.55 (2H, m), 7.50-7.43 (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, 2 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^+ calculated for $C_{21}H_{22}N_2O_4S_2$: 431, found 431. Anal calcd for $C2_1H_{22}N_2O_4S_2$.HCl 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. ^{1}H NMR (300 MHz, MeOD) 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 = 2 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 methane 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 $C_{21}H_{22}N_2O_4S_2.CH_3SO_3H$ 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 $MgSO_4$. 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 H_2O (50 mL). The solution was heated to reflux for 20 h. The solution was then concentrated in vacuo and the residue was dissolved in H_2O. 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 $MgSO_4$. 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 CH_2Cl_2 (6 mL) was 5 added TFA (6 mL, 77.8 mmol), and the solution was stirred at rt for 1 h. Concentration in vacuo provided the amine

trifluoroacetate salt (2.44 g, 100%) as white foam. To a solution of this trifluoroacetate salt (5.0 g, 12.1 mmol) and triethylamine (8.7 mL, 60.4 mmol) in 1:1 acetone/water (20 mL) at 0°C was added acetyl chloride (4.6 mL, 36 mmol), and the solution was stirred at rt for 40 h. The mixture was concentrated and the aqueous layer acidified to pH 2. This aqueous layer was extracted with EA and the combined organic extracts were washed with water and dried over MgS04. Concentration in vacuo provided the N-acetamide carboxylic acid (5.0 g, 100%) as light yellow foam. To a solution of the acetamide (5 g, 11.9 mmol) in DMF (50 mL) was added NMM (5.3 mL, 47.6 mmol), HOBT (4.8 g, 35.7 mmol), O-tetrahydro-2H-pyran-yl-hydroxylamine (2.8 g, 23.5 mmol) and EDC (6.8 g, 35.7 mmol), and the solution was stirred at rt for 20 h. The reaction was concentrated under vacuum and the residue was dissolved in EA. The organic layer was washed with saturated NaHC03, KHS04, H_2O and dried over $MgSO_4$. Concentration in vacuo provided the THP-protected hydroxamic acid **34g** (6.07 g, 98.2%) as a colorless foam.

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 3 h. Concentration gave a residue which was purified by chromatography on silica gel eluting with methanol/ CH_2Cl_2 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 CH_2Cl_2 (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 brine and dried over $MgSO_4$. Concentration gave the methanesulphonamide **33h** (2.17 g, 95%) as colorless crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.52 (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 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 brine and dried over $MgSO_4$ and concentrated to give the desired carboxylic acid (2.1 g, 100%) as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (2H, d, J = 8 Hz, 7.56 (2H, m), 7.57 (3H, m), 7.24 (2H, d, J = 11 Hz), 3.89 (2H, dt, J = 14, 3 Hz), 2.97 (1H, t, J = 12 Hz), 2.69 (2H, t, J = 11 Hz), 2.14 (2H, br d, J = 13 Hz), 1.75 (2H, qd, J = 11, 3 Hz). To a solution of this carboxylic acid (1.98 g, 4.3 mmol) in DMF (30 mL) was added HOBT (705 mg, 5.2 mmol), NMM (1.42 g, 12.9 mmol), O-tetrahydro-2H-pyran-2-yl-hydroxylamine (755 mg, 6.5 mmol) and EDC (1.17 g, 6.1 mmol). The reaction was stirred 4d at rt, then diluted with water and extracted with EA. The combined organic extracts were washed with water and brine and dried over $MgSO_4$. Concentration gave a yellow oil (3.86 g) which was purified by chromatography on silica gel eluting with EA/hexane (30/70) to afford the THP-hydroxamate **34h** (1.99g, MS MH+ calcd for $C_{24}H_{30}N_2S_3O_7$ 555, found 555. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (1H, s), 7.65 (2H, d, J = 6 Hz), 7.57 (2H, m), 7.57 (3H, m), 7.19 (2H, d, J = 7 Hz), 4.98 (1H, s), 3.98 (1H, t, J = 10 Hz), 3.82 (2H, m), 3.69 (1H, m), 3.86 (2H, qd, J = 10, 3Hz), 2.73 (3H, s), 2.28 (2H, m), 2.19 (2H, m), 1.90-1.76 (3H, m), 1.72-1.58 (3H, m).

To a solution of the THP-hydroxamate **34h** (1.86 g, 3.5 mmol) in MeOH/1,4-dioxane (40 mL) was added 4N HCl in 1,4-dioxane (20 mL, 80 mmol). The reaction was stirred for 2.5 h at rt and then concentrated to dryness. Trituration with ether gave the desired N-mesyl hydroxamic acid **35h** (1.48 g, 91%) as a light pink solid: HRMS calcd for $C_{19}H_{22}N_2S_3O_6$ 471.0718, found 471.0728. Anal calcd for $C_{19}H_{22}N_2S_3O_6$:Et_2O C, 50.72; H, 5.92; N, 5.14; S, 17.66. Found C, 50.25; H, 5.59; N, 5.12; S, 17.83.

1-tert-butyl 4-ethyl 4-{[4-(phenylthio)phenyl]sulfonyl}piperidine-1,4-dicarboxylate (36). To a solution of sulphone **30** (40 g, 96 mmol) and powdered K_2CO_3 (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 H_2O and dried over $MgSO_4$. 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 CH_2Cl_2 (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-NH_2. 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 the Institutional Animal Care and Use Committee and conform to the HIH 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 -90ºC. 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 mm^3 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) = $[w^2 X L]/2$, 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.

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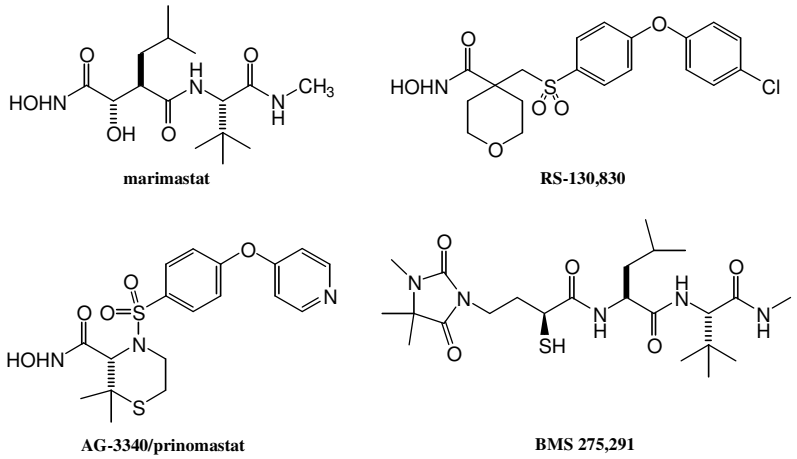
Figure 1: MMP Inhibitors



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

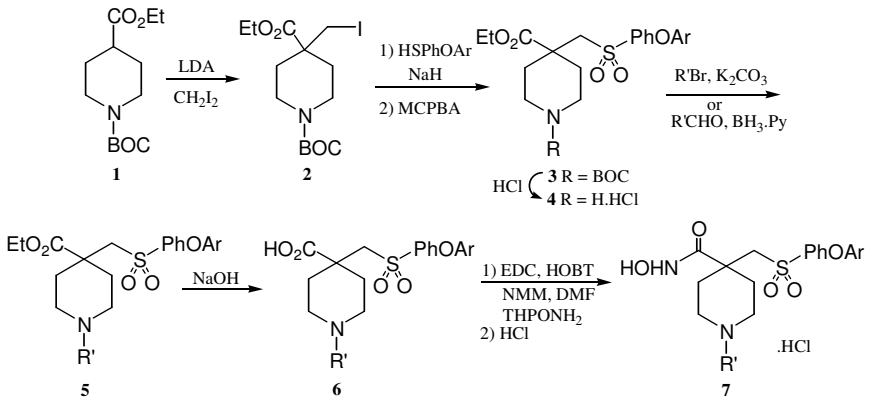
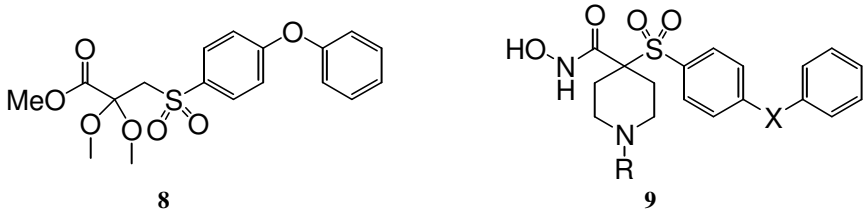
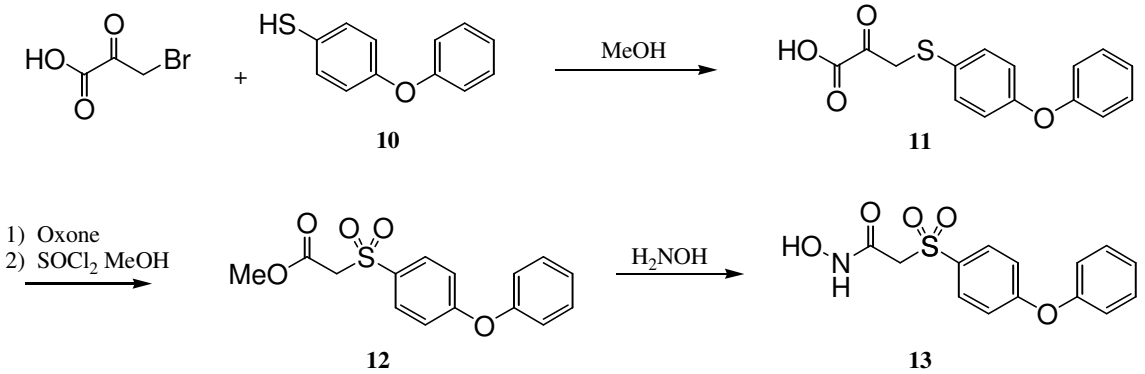


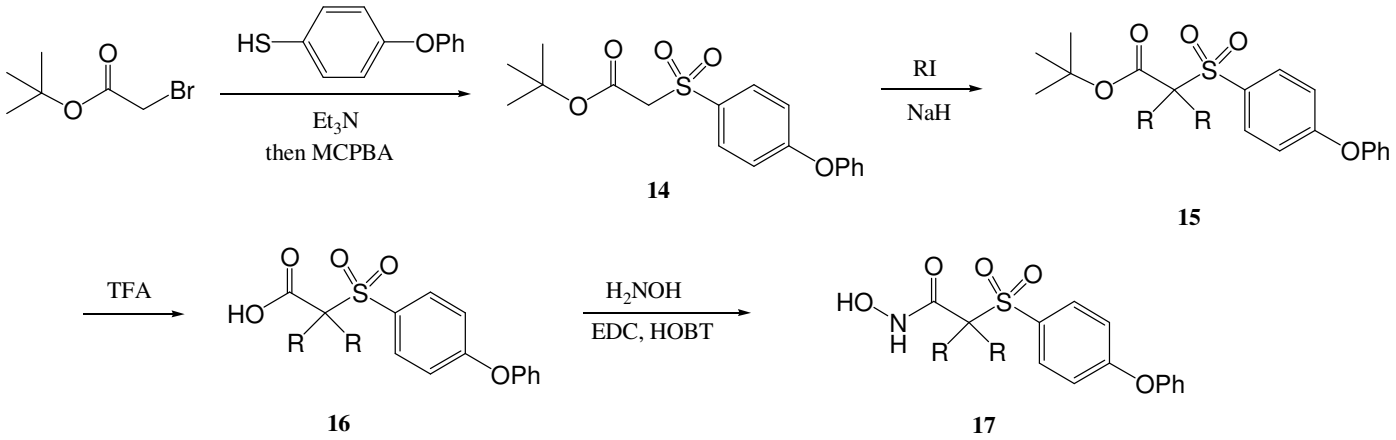
Figure 2. Initial a-ketal-β-sulphone target **7** and new α-sulphone scaffold **8**



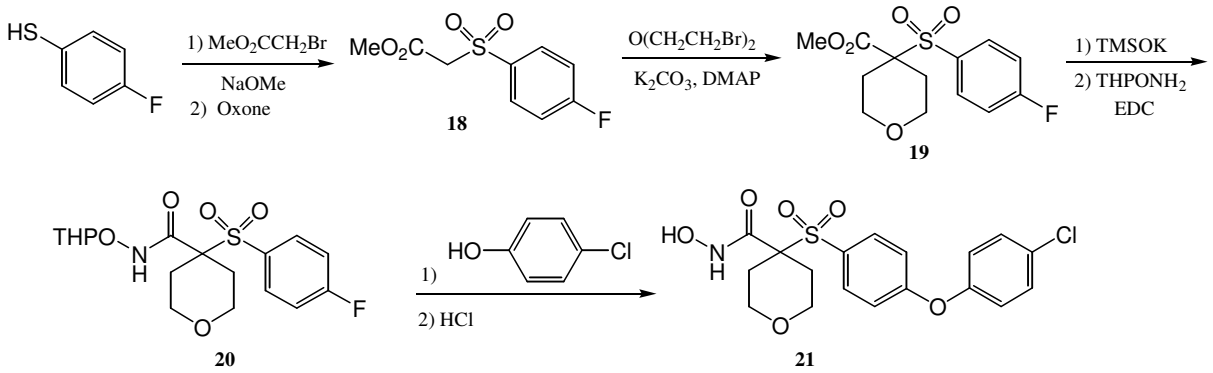
Scheme 2. Original Synthesis of α-sulphone **12**



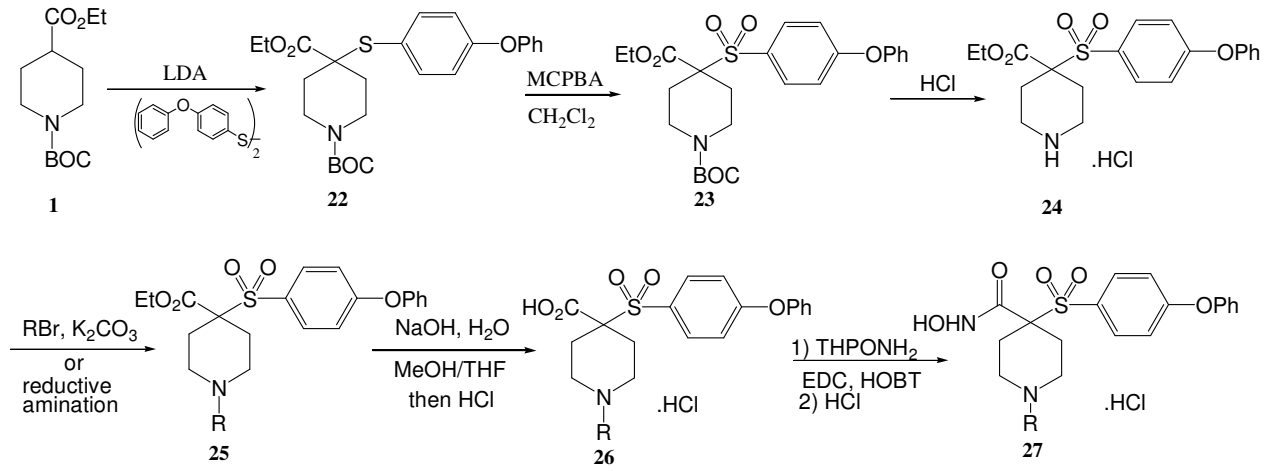
Scheme 3. Synthesis of α,α-dialkyl-α-sulphone **17**



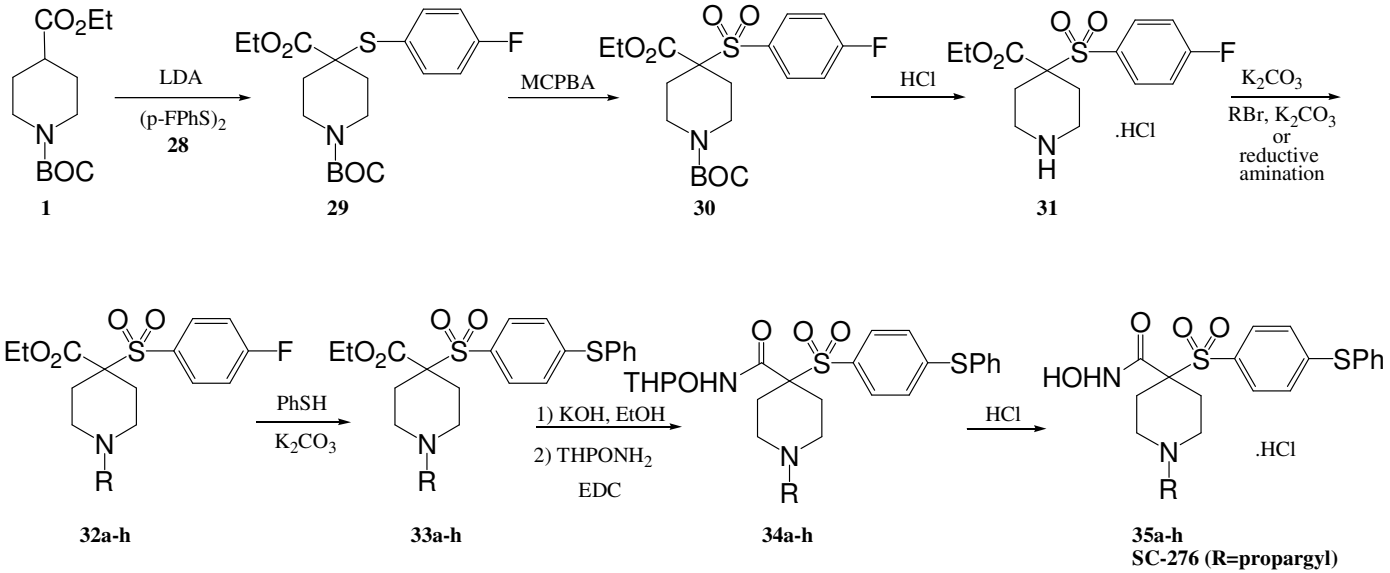
Scheme 4: Preparation of a-tetrahydropyran-α-sulphone **21**



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**

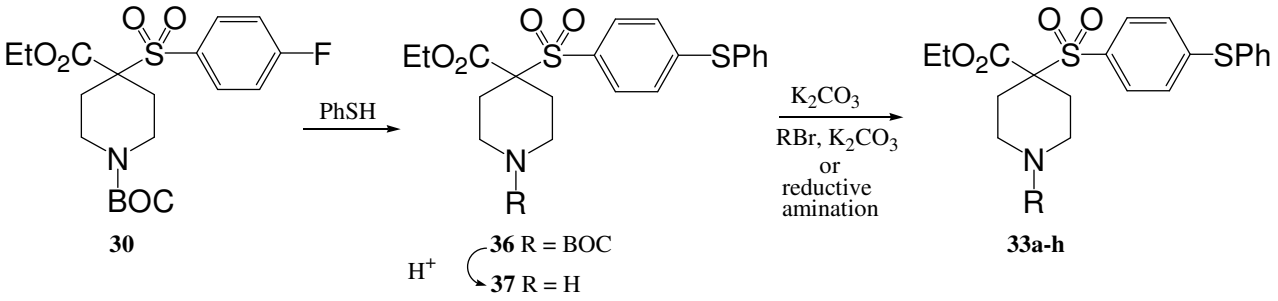
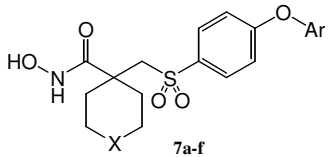


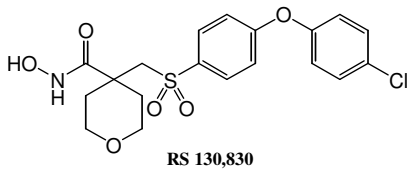
Table 1. In Vitro MMP Inhibitory Data [IC_{50} Values (nM)] and Oral Rat PK Data [C_{max} and C6h (μg/mL)] of β-sulphones **7**



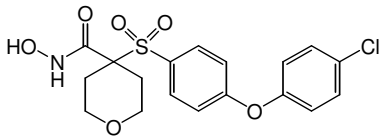
7a-f

Cmpd	X	Ar	MMP-1	MMP-2	MMP-3	MMP-8	MMP-9	MMP-13	C_{max}	C6h
RS-130830	O	p-ClPh	800	0.4	17.5	1.8	1.0	0.6	1372	537
7a	NBOC	Ph	475	0.2	-	-	-	0.2	-	-
7b	NH	Ph	2400	2.8	158	2.4	30.0	8.0	1095	12
7c	N-3-MeOBn	Ph	330	0.2	18.1	0.40	1.1	0.4	22	5
7d	NCH2CH2Ph	Ph	700	0.3	42.5	3.0	9.0	1.1	452	105
7e	N-propargyl	Ph	485	0.3	35.0	0.60	4.5	0.6	8038	49
7f	N-propargyl	3,4-diMePh	7700	0.9	18.1	0.70	7.0	0.8	1455	11

Table 2. In Vitro MMP Inhibitory Data (IC_{50} Values, nM) and Oral Rat PK of **RS 130,830** and the corresponding α-sulphone **21**



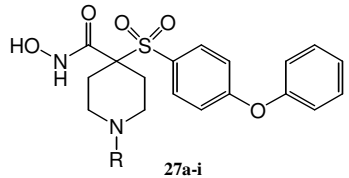
RS 130,830



21

Cmpd	MMP-1	MMP-2	MMP-3	MMP-9	MMP-13	C_{max}	C6h	$t_{1/2}$ (h)	BA (%)
RS-130830	800	0.4	17.5	1.0	0.60	1372	537	1.5	22.1
21	435	<0.1	18.1	0.3	0.15	3119	506	1.5	45.8

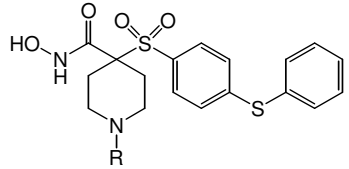
Table 3. In Vitro MMP Inhibitory Data [IC_{50} Values (nM)] and Oral Rat PK Data [C_{max} and C6h (μg/mL)] of Phenyloxyphenyl α-sulphones **27a-i**



27a-i

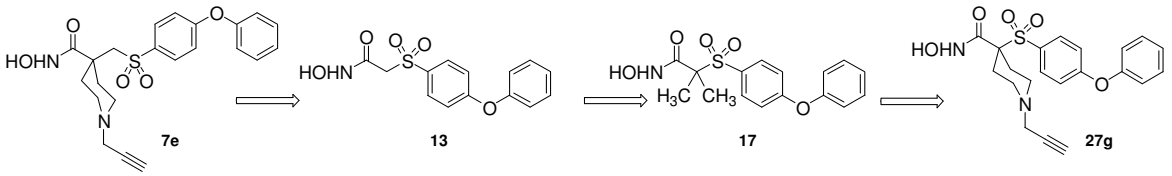
Cmpd	R	MMP-1	MMP-2	MMP-3	MMP-8	MMP-9	MMP-13	C_{max} (ng/mL)	C6h (ng/mL)	$t_{1/2}$ (h)	BA (%)
27a	BOC	1140	0.2	-	-	-	0.3	-	-	-	
27b	H	880	0.2	59	3.5	5.0	0.04	1839	254	1.8	16
27c	CH_3	464	<0.1	-	-	0.29	0.1	4130	102	1.25	59
27d	Methoxyethyl	350	0.1	0.3	9.4	0.7	0.1	3111	97	-	-
27e	Cyclopropyl	400	0.2	0.3	12.1	0.6	0.3	15,720	135	0.74	36
27f	Cyclopropylmethyl										
27g	Propargyl	268	0.1	11.4	1.3	0.5	0.25	22,882	345	1.19	35.5
27h	Acetyl	464	<0.1	-	-	-	<0.1	998	121	0.86	11.1
27i	Mesyl	800	0.3	-	-	1.0	0.5	-	-	-	-

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**



Cmpd	R	MMP-1	MMP-2	MMP-3	MMP-8	MMP-9	MMP-13	C_{max} (ng/mL)	C6h (ng/mL)	$t_{1/2}$ (h)	BA (%)
35a	CH_3	>10,000	0.5	39.3	11.4	9.4	0.55	3330	543	1.91	27.5
35b	Et	>10,000	0.8	-	-	-	0.8	-	-	-	-
35c	Methoxyethyl	>10,000	0.3	20.0	4.0	3.0	0.5	12,589	1,237	-	-
35d	Cyclopropyl	>10,000	0.1	23.5	3.5	2.5	0.2	7647	529	1.03	34.6
35e	Allyl	>10,000	0.15	-	-	-	0.3	10,015	537	-	-
SC-276	Propargyl	9000	0.2	13.0	1.8	1.5	0.3	13,630	281	1.1	28
35f	Acetyl	7300	0.4	23.0	5.0	8.0	0.6	162	72	0.65	12.7
35g	Mesyl	>10,000	2.0	32.0	4.0	14.7	2.6	-	-	-	-

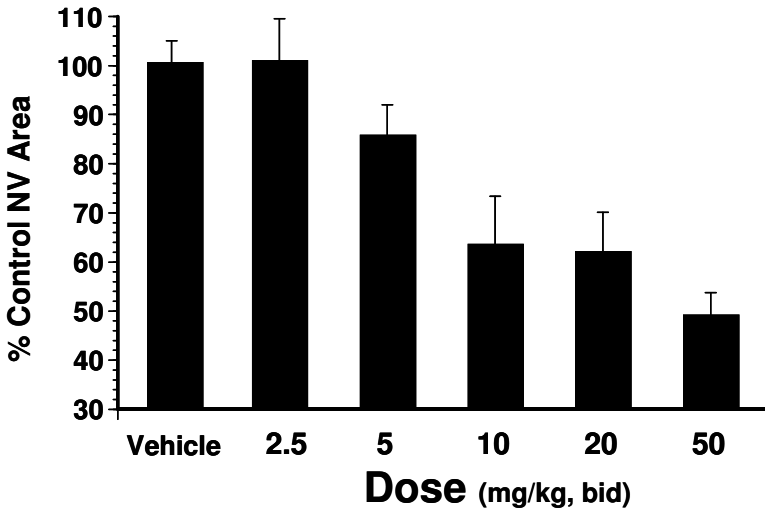
Figure 3: β-sulphone versus α-sulphones (MMP IC_{50} values, nM; rat PK 20 mpk suspension, μg/mL)



7e		13		17		27g	
MMP-13	0.6 nM	MMP-13	5.1 nM	MMP-13	0.25 nM	MMP-13	0.25 nM
MMP-2	0.3 nM	MMP-2	2.6 nM	MMP-2	0.1 nM	MMP-2	0.1 nM
MMP-1	485 nM	MMP-1	6600 nM	MMP-1	220 nM	MMP-1	268 nM
Cmax	8038 ug/mL					Cmax	22,882 ug/mL
C6h	49 ug/mL					C6h	345 ug/mL

Figure 5:

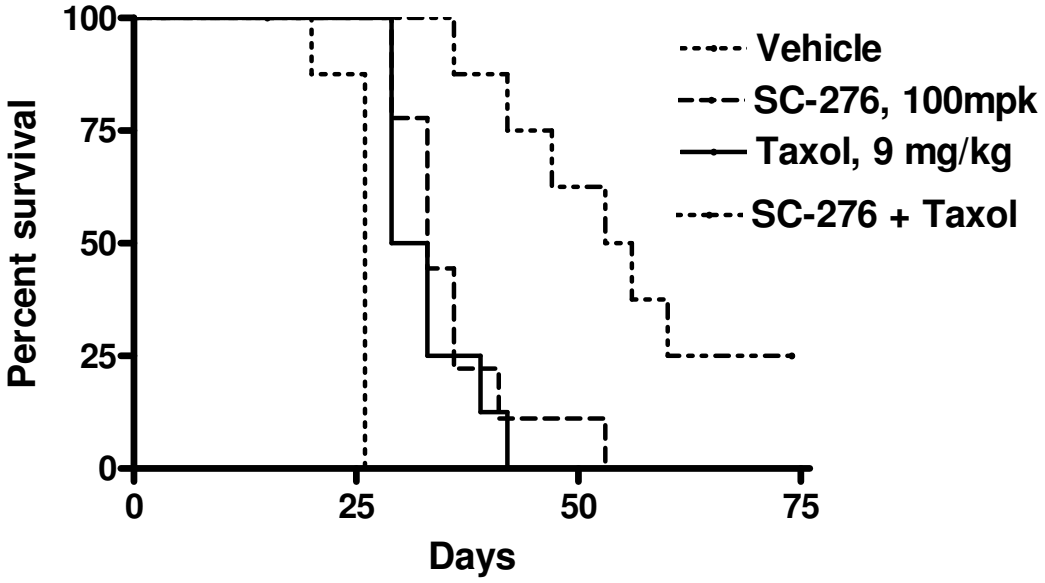
Figure 6.



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% methylcellose/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-1tumor 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

Drug 1	Drug 2	MDS	P value
Vehicle	-	26.0	-
Taxol	-	31.0	*p=0.0001
-	SC-276	33.0	**p<0.0001
Taxol	SC-276	54.5	***p=0.0004

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