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Structure-based design of TACE selective inhibitors: Manipulations in the S1′–S3′ pocket

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Abstract—A series of β-sulfonyl hydroxamate TACE inhibitors, bearing a butynylamino or a butynyloxy P1′ group, was designed and synthesized. Of the compounds investigated, **22** has excellent potency against isolated TACE enzyme, shows good selectivity over MMP-2 and MMP-13, and oral activity in an in vivo mouse model of TNF-α production.
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1. Introduction

Elevated concentrations of soluble tumor necrosis factor-α (TNF-α) have been linked to several diseases including rheumatoid arthritis (RA),[1] Crohn's disease,[2] and psoriasis.[3] That TNF-α is a validated therapeutic target is clearly demonstrated by the success in treating RA using the soluble TNF p75 receptor fusion protein Enbrel® (etanercept), and the monoclonal TNF-α antibody Remicade® (infliximab).[4] However, orally bioavailable small molecules that could achieve the same effect are still highly desirable.

TNF-α converting enzyme (TACE) is responsible for the cleavage of membrane anchored 26 kDa TNF-α, resulting in the release of soluble 17 kDa TNF-α.[5,6] TACE (ADAM-17) belongs to the adamalysin/reprolysin subfamily of the metzincin superfamily which also includes the matrix metalloproteinases (MMPs).[7,8] The active site of TACE shows significant similarity in shape to the active site of the MMPs, even though it has relatively low overall homology to MMPs.[9] As a result, the design of selective TACE inhibitors can be problematic. A variety of TACE inhibitors have been reported recently, including

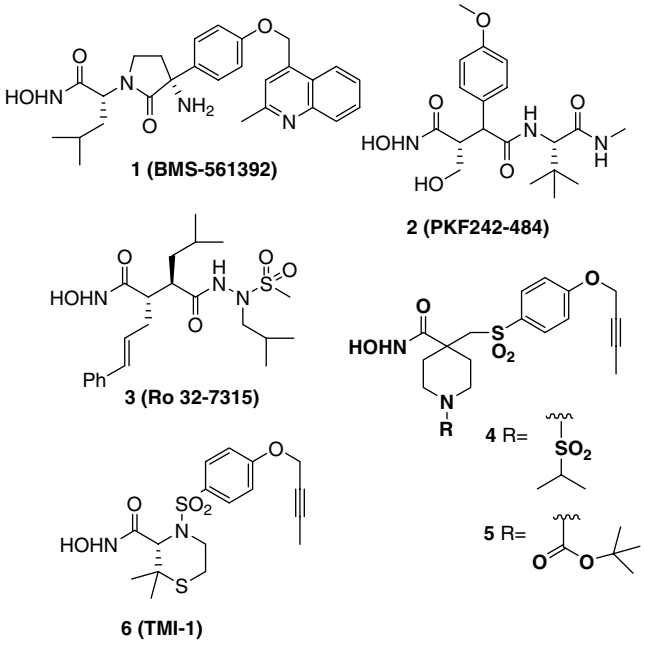

Figure 1. Reported TACE inhibitors.

Keywords: β-Sulfone hydroxamates; TACE inhibitors; MMP selectivity.
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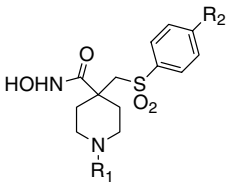
Table 1. In vitro potency[d] of β-piperidine sulfone hydroxamic acids



Compound	R_1	R_2	TACE[a]	MMP-2[a]	MMP-13[a]	MMP-14[a]	HWB[b]
4	SO_2-*i*-Pr	OCH_2CCCH_3	3 ± 1	280 ± 65	157 ± 43	3642 ± 1067	1.5 ± 1
5	Boc	OCH_2CCCH_3	2 ± 1	NT[c]	135 ± 10	NT	14 ± 1
7	Boc	$NHCH_2CCCH_3$	1.6 ± 0.4	120 ± 20	860 ± 20	2370 ± 300	16 ± 2
11	Boc	$N(CH_3)CH_2CCCH_3$	3.3 ± 0.3	NT	1600	NT	>50
12	Boc	$NHCH_2CCCH_2OH$	10 ± 3	334	1038 ± 10	NT	25 ± 3
16	H	$NHCH_2CCCH_3$	64.5	NT	NT	NT	NT
17	SO_2-*i*-Pr	$NHCH_2CCCH_3$	2 ± 0.2	97	2075	NT	5 ± 2
18	CH_2-4-pyridine	$NHCH_2CCCH_3$	6.4 ± 0.4	1530 ± 373	6882	4320 ± 1943	7.2 ± 0.8
19	$CONEt_2$	$NHCH_2CCCH_3$	<1	216 ± 31	772 ± 54	3619 ± 604	6.4 ± 1.6
20	CO-Ph-2′-CH_3	$NHCH_2CCCH_3$	2.5 ± 0.5	46 ± 1	584 ± 45	1000 ± 150	4.8 ± 2.0
21	$COCH(CH_3)Et$	$NHCH_2CCCH_3$	3.5 ± 0.5	1312 ± 38	2476 ± 372	7047 ± 2283	4.9 ± 0.2
22	$COCH(CH_3)_2$	$NHCH_2CCCH_3$	2.3 ± 0.3	513 ± 210	3199 ± 674	4891 ± 1412	3.6 ± 0.6
27	SO_2-*i*-Pr	$OCH(CH_3)CCCH_3$	4 ± 2	4181 ± 1681	2912 ± 712	NT	31 ± 10
28	SO_2-*i*-Pr	$OC(CH_3)_2CCCH_3$	27 ± 1	>1666	12,000 ± 2542	NT	>50

[a] IC_{50}, nM.
[b] Human whole blood, IC_{50}, μM.
[c] NT, not tested.
[d] Potency data are reported as average ± SD; for compounds tested only once, the TACE FRET assay data have a fluctuation of ±30%.

Table 2. In vitro potency[c] of thiomorpholine sulfone hydroxamic acids

Compound	TACE[a]	MMP-2[a]	MMP-13[a]	HWB[b]
6	8	4.7	2.4 ± 0.7	0.3 ± 0.1
26	2.3	56 ± 30	30	3.5 ± 0.9

[a] IC_{50}, nM.
[b] Human whole blood, IC_{50}, μM.
[c] Potency data are reported as average ± SD; for compounds tested only once, the TACE FRET data have a fluctuation of ±30%.

the TACE selective inhibitor BMS-561392 (**1**, Fig. 1)[10a,b] and more broad spectrum TACE/MMP inhibitors such as PKF242-484 (**2**, Fig. 1)[11] and Ro 32-7315 (**3**, Fig. 1).[12] TACE selective inhibitors may be desirable for the long term treatment of TNF-α mediated pathologies in order to avoid side effects that have plagued clinical trials of more broad spectrum MMP inhibitors.[13a,b]

Wyeth has previously reported several series of TACE inhibitors bearing the P1′ butynyloxy moiety. Among these are the piperidine hydroxamate series, exemplified by **4**[14] and **5**[15a,b]; and the thiomorpholine hydroxamate series, exemplified by **6** (TMI-1).[16a–d] Compounds **4**, **5**, and **6** are all potent inhibitors of TACE, but they are also active against many MMPs (Tables 1 and 2). We now report our efforts to further improve the TACE selectivity of these two series by focusing on the S1′ specificity pocket.

The distinctively bent shape of the TACE S1′/S3′ pockets, as compared to the MMPs, appeared to offer an opportunity for designing P1′ groups that would confer selectivity for TACE (Fig. 2). Thus, modeling[17a] of **5** bound to TACE indicated that the butynyloxy group must be 'bent' with a dihedral angle of −65° to fit in the TACE S1′–S3′ pocket, and that this 'bent' conformation is 0.12 kcal/mol lower in energy than the 'extended' geometry that is required for binding in the straight S1′ subsite of most MMPs.[18] We envisioned that replacement of the butynyloxy group with a butynylamino group might provide enhanced selectivity for TACE since a model[17a] of **7** bound to TACE shows that the 'bent' conformation required for binding this P1′ moiety in the TACE S1′–S3′ pocket is 0.68 kcal/mol lower in energy than 'extended' conformation needed to bind in the MMP-13 S1′ pocket. Thus, the relative cost for extending the tail is significantly higher for the

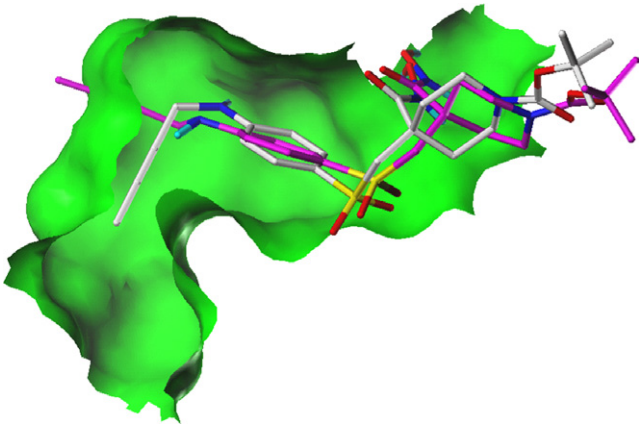


Figure 2. A surface in green depicts the TACE S1′–S3′ pocket. A model of **7** bound to TACE (colored by element with carbons in grey) is shown superimposed on the X-ray structure[17b] of **7** bound to MMP-13 (colored by element with carbons in magenta). Protein backbone atoms (not shown) only were used for the alignment.

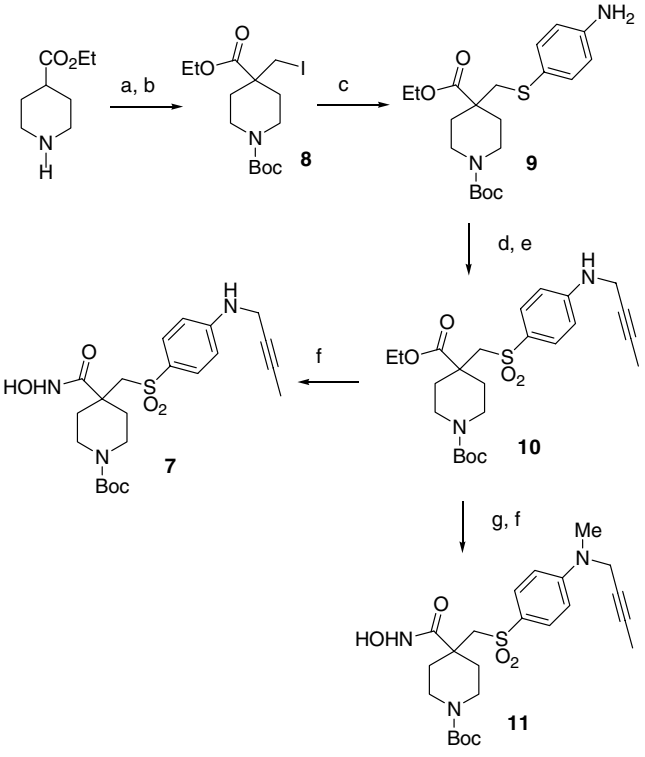
butynylamine analog than that for the butynyloxy analog and **7** would therefore be predicted to be more TACE selective than **5**.

The desired compound **7** was prepared as described in Scheme 1. Protection of the nitrogen of ethyl 4-piperidinecarboxylate with a Boc group, followed by deprotonation α to the ester, and subsequent alkylation with diiodomethane provided compound **8** in good yield. Displacement of the iodide of **8** with 4-aminothiophenol in the presence of potassium carbonate gave **9**. Oxidation of the sulfide to the sulfone with *m*CPBA and alkylation of **9** with butynyl bromide then afforded **10**, which was next converted into the corresponding hydroxamic acid **7** via base hydrolysis followed by reaction with hydroxylamine under peptide coupling conditions.

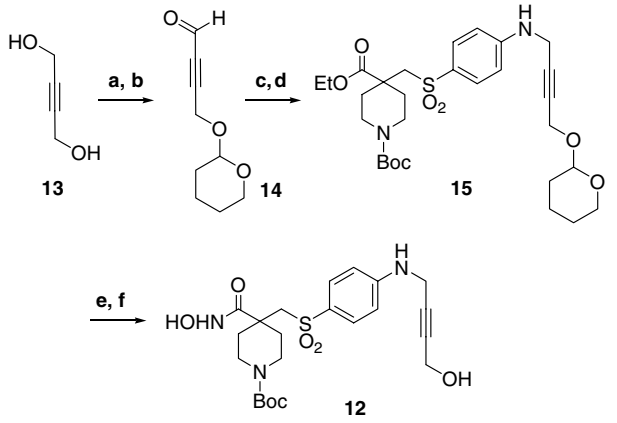
The enzyme activity[19] and human whole blood (HWB)[19] data for **7** are shown in Table 1.

The butynylamino analog **7** is essentially equipotent to butynyloxy analog **5** against TACE enzyme and in human whole blood. However, to our delight, compound **7** has greatly improved selectivity for TACE over MMP-13 (>400-fold), validating our design strategy.

Encouraged by the results for **7**, a series of related derivatives was prepared to further explore the effect of nitrogen-containing P1′ groups on TACE potency and selectivity. The desired *N*-methyl butynylamine **11** and



Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, THF, 87%; (b) LDA, THF, −78 °C, 1 h, CH_2I_2, 78%; (c) 4-amino thiophenol, K_2CO_3, DMF, 87%; (d) *m*CPBA; (e) 1-bromo-2-butyne, K_2CO_3, DMF, microwave, 100 °C, 50 min, 80%; (f) NaOH, MeOH, H_2O; BOP, NH_2OH, DMF, 50%; (g) MeI, Ag_2O, 80%.

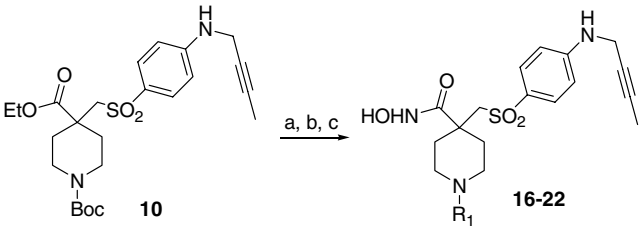


Scheme 2. Reagents and conditions: (a) THP, *p*-TsOH, Et_2O, 40%; (b) DMSO, $Cl(CO)_2Cl$, Et_3N, CH_2Cl_2; (c) **9**, $NaCNBH_3$, EtOH, HOAc; (d) oxone·NBu_4, 13%, three steps; (e) PPTS, MeOH, 100%; (f) NaOH, MeOH, H_2O; BOP, NH_2OH, DMF, 50%.

propargylic alcohol **12** were prepared as shown in Schemes 1 and 2, respectively. Methylation of **10** with neat MeI in the presence of Ag_2O, followed by ester cleavage and hydroxamate formation, gave **11**. Alcohol **12** was prepared from 2-butynyne-1,4-diol, **13**. Monoprotection of **13** with THP followed by Swern oxidation gave aldehyde **14**. Treatment of **14** with **9** under reductive amination conditions, and subsequent oxidation of the sulfide, afforded **15**. Removal of the THP group, ester cleavage, and hydroxamate formation then provided **12**.

As shown in Table 1, **11**, with a methyl group on the P1′ nitrogen of **7**, retains activity against TACE enzyme and selectivity over MMP-13, but has poor HWB activity. Compound **12**, with a terminal P1′ hydroxyl group, has slightly reduced activity against TACE and selectivity over MMP-2 (30-fold) and MMP-13 (90-fold) relative to the parent compound, **7**.

In an effort to identify analogs in the series with improved activity in human whole blood, we also explored the effect of variations on the P1 4-piperidine nitrogen in combination with the butynylamino P1′ group. Thus, while keeping the butynylamino P1′ group constant, we examined seven different P1 groups, as shown in Table 1. These compounds were prepared from *N*-Boc piperidine **10** as shown in Scheme 3. Removal of the *N*-Boc with TFA, and reaction with R_1–Cl or R_1–Br

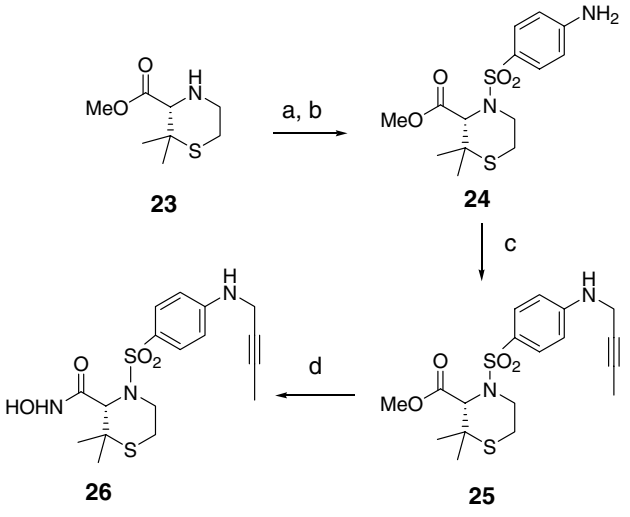


Scheme 3. Reagents and conditions: (a) TFA, CH_2Cl_2; (b) R_1Cl, CH_2Cl_2, H_2O, Na_2CO_3; or R_1Br, K_2CO_3; (c) NaOH, MeOH, H_2O; BOP, NH_2OH, DMF, 50%.

under basic conditions, provided the N-R_1 piperidines, which were converted to the corresponding hydroxamic acid **16**–**22** via base hydrolysis followed by reaction with hydroxylamine under peptide coupling conditions.

The –NH analog **16** is much less active against TACE than parent compound **7**. Isopropyl sulfonamide **17**, the butynylamine analog of **4**, led to a 17-fold improvement in selectivity over MMP-13, but lost HWB potency when compared to **4**. Compound **18**, with two basic nitrogens, maintains good activity against TACE and good selectivity over MMP-2 and MMP-13, but is still only weakly active in HWB. The best TACE enzyme activity and selectivity was achieved by the **19**, which has an $IC_{50} < 1$ nM against TACE enzyme and is over 750-fold selective over MMP-13. Unfortunately this analog does not have greatly improved activity in human whole blood. Amide **20** is 499-fold selective over MMP-13 and has slightly better HWB activity than **17** and **18**. The branched alkyl amide **21** greatly increased the selectivity for TACE over MMP-2, MMP-13, and MMP-14 relative to aryl amide **20**. Removal of one carbon from the amide side chain of **21** gave **22**, which has the best HWB ($IC_{50} = 3.6$ μM) activity of this series while retaining superior selectivity over the MMPs screened. Overall, except for **16**, all of these P1 analogs have increased, though still very modest, HWB potency relative to the parent compound, **7**, while retaining comparable TACE enzyme potency and selectivity.

Efforts were also made to explore whether the enhanced selectivity for TACE afforded by the butynyl amine P1′ group could be extended to the thiomorpholine sulfonamide series that had previously provided potent but non-selective TACE/MMP inhibitors. The butynylamine analog of TMI-1 (**6**) was prepared as shown in Scheme 4. Thiomorpholine **23**[20] was converted to aniline **24** via sulfonamide formation and zinc reduction. Aniline **24** reacted with 1-bromo-2-butyne to give ester **25**,



Scheme 4. Reagents and conditions: (a) 4-NO_2PhSO_2Cl, N-methylmorpholine, CH_2Cl_2, 44%; (b) Zn, MeOH, HOAc, 100%; (c) 1-bromo-2-butyne, K_2CO_3, DMF, microwave, 100 °C, 40 min, 80%; (d) NaOH, MeOH, H_2O; BOP, NH_2OH, DMF, 50%.

which was then transformed to the desired hydroxamate **26** via base hydrolysis and hydroxamate formation.

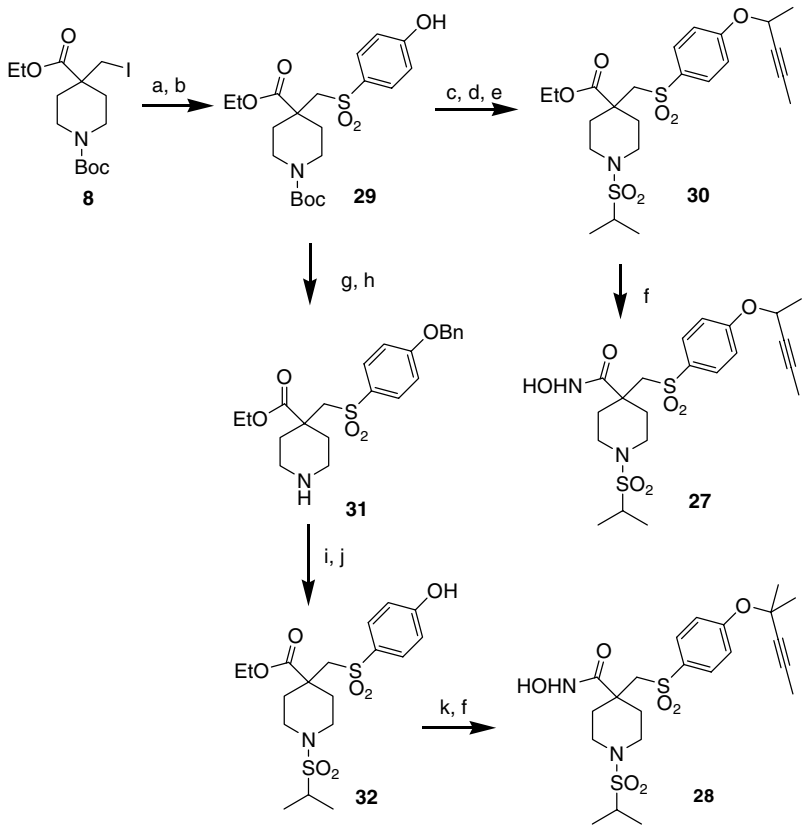
The in vitro and HWB activity of compound **26** is listed in Table 2. This butynylamine analog was slightly more active than butynyloxy analog **6** against TACE and 10-fold less potent in human whole blood. However, compound **26** was substantially more selective than **6** for TACE over MMP-2 and MMP-13.

A second design strategy for increasing TACE selectivity through P1′ group variations involved replacement of the butynyloxy group in **4** with a more sterically demanding P1′ group. This was suggested by the structural difference between TACE and MMPs, wherein a tyrosine residue located on one side of the MMP S1′ pockets is replaced by a much smaller alanine in the TACE S1′ subsite.[18] The syntheses of the desired compounds **27** and **28** are shown in Scheme 5. Displacement of the iodide in **8** with 4-hydroxythiophenol, followed by oxidation of the sulfide to the sulfone with mCPBA, gave **29**. Mitsunobu alkylation of **29** with 3-pentyn-2-ol, removal of the Boc moiety with TFA, and sulfonamide formation under Schotten–Baumann conditions next provided **30**. Finally, ester **30** was converted to the corresponding hydroxamic acid **27** via base hydrolysis followed by reaction with hydroxylamine under peptide coupling conditions. On the other hand, protection of phenol **29** with a benzyl group, followed by removal of the Boc group, gave **31**. Sulfonamide formation, and subsequent removal of the benzyl moiety, provided **32**, which was converted to **28** via Mitsunobu alkylation and hydroxamate formation.

As shown in Table 1, compound **27**, with a bulkier P1′ moiety relative to butynyloxy analog **4**, has approximately 10-fold increased selectivity for TACE over both MMP-2 and MMP-13. In particular, **27** is now 1000- and 720-fold selective for TACE over MMP-2 and MMP-13, respectively. Unfortunately this compound suffers from poor activity in human whole blood. Introduction of a second methyl group on the butynyl P1′ tail (compound **28**) decreased affinity for TACE by 7-fold and further diminished activity in human whole blood, but still provided a very selective inhibitor.

Of the analogs prepared for this study, compound **22** has the best combination of potency against TACE enzyme, desirable selectivity profile, and moderate activity in HWB, and it was therefore selected for in vivo testing. In a preliminary in vivo model to measure its ability to inhibit the LPS-induced production of TNF in a mouse[19] a 25 mg/kg oral dose of this compound provided 72% inhibition of TNF production 90 min after administration of LPS.

In conclusion, we have succeeded in utilizing structure-based design to optimize the P1 and P1′ groups of a series of β-sulfonyl hydroxamate TACE inhibitors resulting in a series of potent TACE inhibitors with excellent selectivity over MMP-2, -13, and -14. We believe these inhibitors may offer useful leads for the development of drugs for the treatment of rheumatoid arthritis.



Scheme 5. Reagents and conditions: (a) 4-hydroxythiophenol, K_2CO_3, DMF; (b) *m*CPBA, 89% for two steps; (c) 3-pentyn-2-ol, Ph_3P, DIAD, CH_2Cl_2, 100%; (d) TFA, CH_2Cl_2; (e) isopropylsulfonyl chloride, CH_2Cl_2, H_2O, Na_2CO_3, 77% for two steps; (f) NaOH, MeOH, H_2O; BOP, NH_2OH, DMF, 50%; (g) BnBr, K_2CO_3, DMF, 100%; (h) TFA, CH_2Cl_2, 84%; (i) isopropylsulfonyl chloride, DIEA, CH_2Cl_2; (j) H_2, Pd/C, 97%; (k) 2-methyl-3-pentyn-2-ol, Ph_3P, DIAD, CH_2Cl_2, 10%.

2. Experimental

Reactions were run using commercially available starting materials and anhydrous solvents, without further purification. Proton NMR spectra were recorded on a 400 MHz Bruker AV-400 spectrometer using TMS (δ 0.0) as an internal reference. High resolution mass spectra were obtained using a Bruker APEXIII Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with an actively shielded 7 T superconducting magnet (Magnex Scientific Ltd, UK) and an external Bruker APOLLO electrospray ionization (ESI) source. Preparative HPLC was run using Waters reverse phase prep HPLC with Xterra C18 5 μM, 30 × 100 mm column (water/CH_3CN/0.1% formic acid). Purity in two solvent systems was determined using Agilent 1100 reverse phase HPLC with Agilent Zorbax SB-C18 5 μm, 4.6 × 30 mm column at 254 nm [Gradient: 5–95% in 7 min at 0.8 mL/min, H_2O/CH_3CN (method 1) and H_2O/MeOH (method 2)].

2.1. 4-(4-Amino-phenylsulfanylmethyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (9)

A mixture of 1-(*tert*-butyl) 4-ethyl-4-(iodomethyl)piperidine-1,4-dicarboxylate (compound **8**, 3.1 g, 7.8 mmol, prepared according to US Patent 6,358,980, Example 30), 4-aminothiophenol (1.1 g, 8.8 mmol), and potassium carbonate (1.5 g, 10.8 mmol) in 15 mL of DMF was stirred at 25 °C for 16 h. The resulting mixture was diluted with ethyl acetate, washed with water, brine, and concentrated to give a yellow oily residue. Flash column chromatography of the residue (silica gel, 4:1 *n*-hexane/ethyl acetate) afforded compound **9** (2.6 g, 85%) as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.21 (t, J = 7.07 Hz, 3H), 1.47 (s, 9H), 1.40–1.50 (m, 2H), 2.07–2.19 (m, 2H), 2.91–3.01 (m, 2H), 3.02 (s, 2H), 3.66–3.85 (m, 2H), 4.04 (q, J = 7.07 Hz, 2H), 6.59 (d, J = 8.84 Hz, 2H), 7.23 (d, J = 8.84 Hz, 2H).

2.2. 4-(4-But-2-ynylamino-benzenesulfonylmethyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (10)

To a solution of compound **9** (1.34 g, 2.40 mmol) in 30 mL dichloromethane at −40 °C was added 77% 3-chloroperoxybenzoic acid (1.66 g, 6.75 mmol). The mixture was slowly warmed to 25 °C and stirred for 16 h. The solid was filtered and the filtrate was concentrated to give a yellow oily residue. Flash column chromatography of the residue (silica gel, 2:1 *n*-hexane/ethyl acetate) afforded 4-(4-amino-benzenesulfonylmethyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (1.1 g, 75%) as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.28 (t, J = 7.16 Hz, 3H), 1.44 (s, 9H), 1.56–1.73 (m, 2H), 2.07–2.27 (m, 2H), 3.07–3.28 (m, 2H), 3.40 (s, 2H), 3.57–3.77 (m, 2H), 4.15 (q, J = 7.16 Hz, 2H), 6.68 (d, J = 8.84 Hz, 2H), 7.60 (d, J = 8.84 Hz, 2H).

To a microwave reaction vessel with a stir bar were added the above compound (0.50 g, 1.17 mmol), 1-bromo-2-butyne (0.11 mL, 1.18 mmol), potassium carbonate (0.32 g, 2.31 mmol), and 3 mL of *N*,*N*-dimethylacetamide. The reaction vessel was sealed with a cap and heated to 100 °C for 50 min in a microwave reactor. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was concentrated to give a light yellow oily residue. Flash column chromatography of the residue (silica gel, 5:1 *n*-hexane/ethyl acetate) afforded compound **10** (0.35 g, 63%) as a clear oil and the starting material 4-(4-amino-benzenesulfonylmethyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (0.18 g, 36%).

^{1}H NMR ($CDCl_3$) δ ppm 1.29 (t, J = 7.16 Hz, 3H), 1.44 (s, 9H), 1.59–1.70 (m, 2H), 1.81 (t, J = 2.27 Hz, 3H), 2.10–2.27 (m, 2H), 3.10–3.27 (m, 2H), 3.41 (s, 2H), 3.60–3.75 (m, 2H), 3.93 (q, J = 2.27 Hz, 2H), 4.16 (q, J = 7.16 Hz, 2H), 4.48 (t, J = 5.56 Hz, 1H), 6.67 (d, J = 8.84 Hz, 2H), 7.66 (d, J = 8.84 Hz, 2H).

2.3. General procedure A for preparation of hydroxamic acids

2.3.1. *tert*-Butyl 4-({[4-(but-2-ynylamino)phenyl]sulfonyl}methyl)-4-[(hydroxyamino)-carbonyl]piperidine-1-carboxylate (7). To a solution of ester **10** (0.12 g, 0.25 mmol) in 2 mL of THF and 2 mL methanol was added 5 N NaOH (0.5 mL, 2.5 mmol). The reaction mixture was stirred at 25 °C for 16 h. The solvents were removed in vacuo. To the resulting light yellow oily residue were added 1 N NaH_2PO_4 (2.6 mL, 2.6 mmol) and 5 mL of ethyl acetate. The organic layer was washed with 3 mL brine, dried over $MgSO_4$, filtered, and concentrated to provide the acid as a white solid.

To the above acid in 2 mL of DMF at 0 °C were added hydroxylamine hydrochloride (38 mg, 0.55 mmol), benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (0.166 g, 0.375 mmol), and *N*,*N*-diisopropylethylamine (0.19 mL, 1.1 mmol). The reaction mixture was warmed to 25 °C and stirred for 16 h. Preparative HPLC of the mixture provided the desired hydroxamic acid **7** (58 mg, 50%) as a white solid.

^{1}H NMR (CD_3CN) δ ppm 1.32 (s, 9H), 1.58–1.75 (m, 2H), 1.81–1.87 (m, 2H), 2.01 (t, J = 2.27 Hz, 3H), 3.14–3.26 (m, 2H), 3.30–3.42 (m, 2H), 3.35 (s, 2H), 3.82 (q, J = 2.27 Hz, 2H), 6.67 (d, J = 8.84 Hz, 2H), 7.51 (d, J = 8.84 Hz, 2H). HRMS (ESI+) Calcd for $C_{22}H_{31}N_3O_6S + NH_4^+$ ($[M+NH_4]^+$) 483.22718. Found: ($[M+NH_4]^{1+}$) 483.2277; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 4.36 min; 96.8%; H_2O/CH_3OH/0.1% formic acid: 5.74 min; 97.9%.

2.3.2. *tert*-Butyl 4-[({4-[but-2-ynyl(methyl)amino]phenyl}sulfonyl)methyl]-4-[(hydroxyamino)carbonyl]piperidine-1-carboxylate (11). A mixture of compound **10** (0.15 g, 0.31 mmol), silver (I) oxide (80 mg, 0.34 mmol), and iodomethane (3 mL, excess) was stirred at 25 °C for 16 h. Filtration and concentration of the filtrate gave a light yellow residue. Flash column chromatography of the residue (silica gel, 5:1 *n*-hexane/ethyl acetate) afforded 4-[4-(but-2-ynyl-methyl-amino)-benzenesulfonylmethyl]-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (0.11 g, 72%) as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.29 (t, J = 7.07 Hz, 3H), 1.44 (s, 9H), 1.57–1.70 (m, 2H), 1.79 (t, J = 2.27 Hz, 3H), 2.08–2.29 (m, 2H), 3.07 (s, 3H), 3.12–3.27 (m, 2H), 3.41 (s, 2H), 3.63–3.74 (m, 2H), 4.06 (q, J = 2.27 Hz, 2H), 4.15 (q, J = 7.07 Hz, 2H), 6.80 (d, J = 9.09 Hz, 2H), 7.69 (d, J = 8.84 Hz, 2H).

Compound **11** was synthesized by following the procedure in Section 2.3. 4-[4-(But-2-ynyl-methyl-amino)-benzenesulfonylmethyl]-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (0.11 g, 3.45 mmol) was converted to the desired product (59.5 mg, 40%), obtained as a white solid.

^{1}H NMR (CD_3OD) δ ppm 1.41–1.47 (s, 9H), 1.75 (t, J = 2.27 Hz, 3H), 1.77–1.90 (m, 2H), 1.94–2.09 (m, 2H), 3.06 (s, 3H), 3.29–3.40 (m, 2H), 3.45–3.61 (m, 2H), 3.54 (s, 2H), 4.14 (q, J = 2.27 Hz, 2H), 6.91 (d, J = 9.09 Hz, 2H), 7.70 (d, J = 9.09 Hz, 2H). HRMS (ESI+) Calcd for $C_{23}H_{33}N_3O_6S$ ($[M+H]^+$) 480.21628. Found: ($[M+H]^+$) 480.21602; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 5.02 min; 96.5%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 6.48 min; 97.0%.

2.3.3. 4-(Tetrahydro-pyran-2-yloxy)-but-2-ynal (14). To a solution of 2-butyne-1,4-diol (1.4 g, 16.2 mmol) in 100 mL of dichloromethane was added 3,4-tetrahydropyran (1.48 mL, 16.2 mmol) along with *p*-toluenesulfonic acid (62 mg, 0.32 mmol). The mixture was stirred at 25 °C for 0.5 h and then concentrated to give a light yellow oily residue. Flash column chromatography of the residue (silica gel, 5:1 *n*-hexane/ethyl acetate) afforded 4-(tetrahydro-pyran-2-yloxy)-but-2-yn-1-ol (1.1 g, 40%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ ppm 1.61–1.90 (m, 6H), 3.50–3.59 (m, 1H), 3.84 (ddd, J = 11.43, 8.65, 3.16 Hz, 1H), 4.30–4.35 (m, 4H), 4.81 (dd, J = 3.28, 3.27 Hz, 1H).

Oxalyl chloride (1.17 mL, 13.5 mmol) was added to a solution of dimethylsulfoxide (1.92 mL, 27.0 mmol) in 120 mL dry dichloromethane at −78 °C under nitrogen. After the mixture was stirred for 15 min, a solution of 4-(tetrahydro-pyran-2-yloxy)-but-2-yn-1-ol (1.15 g, 6.76 mmol) in 15 mL dry dichloromethane was added dropwise. The reaction mixture was stirred for 45 min and was then quenched with triethylamine (4.7 mL, 33.8 mmol) and warmed to 25 °C. The reaction mixture was washed with water, brine, dried over $MgSO_4$, and concentrated to provide the desired compound **14** (1 g, 90%) as a light yellow oil, which was used for the next step without further purification.

^{1}H NMR ($CDCl_3$) δ ppm 1.62–1.88 (m, 6H), 3.52–3.61 (m, 1H), 3.83 (m, 1H), 4.44–4.48 (m, 2H), 4.81 (dd, J = 3.28, 3.27 Hz, 1H), 9.24 (s, 1H).

2.3.4. 4-{4-[4-(Tetrahydro-pyran-2-yloxy)-but-2-ynylamino]-benzenesulfonylmethyl}-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (15). A mixture of aldehyde **14** (0.79 g, 4.7 mmol), compound **9** (2 g, 4.7 mmol), and sodium cyanborohydride (0.44 g, 7.1 mmol) in 50 mL of ethanol and 2 mL of acetic acid was stirred at 25 °C for 16 h. Concentration of reaction mixture gave a light yellow oily residue. Dichloromethane (30 mL) and 1 N potassium sodium tartrate (30 mL) were added, and the resulting mixture was stirred vigorously for 2 h. The aqueous layer was extracted with dichloromethane, and the combined organic layers were concentrated to give an oily residue. Flash column chromatography of the residue (silica gel, 5:1 *n*-hexane/ethyl acetate) afforded 4-{4-[4-(tetrahydro-pyran-2-yloxy)-but-2-ynylamino]-phenylsulfanylmethyl}-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (0.81 g) as a slightly impure colorless oil, that was carried on to the next step.

A mixture of above ester (0.81 g, 1.48 mmol), oxone·N-Bu_4 (5 g, 5.9 mmol), and 50 mL dichloromethane was stirred at 25 °C for 16 h. The mixture was washed with water, brine, and concentrated to give an oily residue. Flash column chromatography of the residue (silica gel, 3:1 *n*-hexane/ethyl acetate) afforded compound **15** (0.11 g, 13%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ ppm 1.30 (t, J = 7.07 Hz, 3H), 1.44 (s, 9H), 1.48–1.76 (m, 8H), 2.08–2.30 (m, 2H), 3.10–3.31 (m, 2H), 3.40 (s, 2H), 3.46–3.55 (m, 1H), 3.62–3.74 (m, 2H), 3.75–3.87 (m, 1H), 4.00–4.07 (m, 2H), 4.17 (q, J = 7.07 Hz, 2H), 4.55 (t, J = 5.56 Hz, 1H), 4.75 (t, J = 3.28 Hz, 2H), 6.68 (d, J = 8.84 Hz, 2H), 7.67 (d, J = 8.84 Hz, 2H).

2.3.5. 4-[4-(4-Hydroxy-but-2-ynylamino)-benzenesulfonylmethyl]-4-hydroxycarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (12). A mixture of compound **15** (0.11 g, 0.19 mmol), pyridinium *p*-toluenesulfonate (7.7 mg, 0.05 mmol), and 10 mL methanol was stirred at 50 °C for 2 h. Concentration of the reaction mixture gave 4-[4-(4-hydroxy-but-2-ynylamino)-benzenesulfonylmethyl]-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (0.1 g, 100%) as a light yellow oily residue, which was used in the next step without further purification. ^{1}H NMR (CD_3OD) δ ppm 1.29 (t, J = 7.20 Hz, 3H), 1.44 (s, 9H), 1.59–1.72 (m, 2H), 2.05–2.17 (m, 2H), 3.10–3.26 (m, 2H), 3.53 (s, 2H), 3.58–3.70 (m, 2H), 3.99–4.06 (s, 2H), 4.13 (q, J = 7.20 Hz, 2H), 4.22 (s, 2H), 6.78 (d, J = 8.84 Hz, 2H), 7.61 (d, J = 8.84 Hz, 2H).

Compound **12** was synthesized by following the procedure in Section 2.3. The above ester (0.1 g, 0.19 mmol) was converted into compound **12** (50 mg, 55%), obtained as a white solid.

^{1}H NMR (CD_3OD) δ ppm 1.45 (s, 9H), 1.77–1.88 (m, 2H), 2.05–2.14 (m, 2H), 3.33–3.41 (m, 2H), 3.48 (s, 2H), 3.51–3.62 (m, 2H), 4.01 (s, 2H), 4.19 (s, 2H), 6.75 (d, J = 8.84 Hz, 2H), 7.63 (d, J = 8.84 Hz, 2H). HRMS (ESI+) Calcd for $C_{22}H_{31}N_3O_7S$ ($[M-H]^-$) 480.18100. Found: ($[M-H]^{1-}$) 480.1814; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 3.74 min; 100%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 5.17 min; 100%.

2.3.6. 4-(4-But-2-ynylamino-benzenesulfonylmethyl)-piperidine-4-carboxylic acid hydroxyamide (16). To a solution of compound **10** (81 mg, 0.17 mmol) in 3 mL dichloromethane was added 0.3 mL trifluoroacetic acid dropwise. The mixture was stirred at 25 °C for 2 h. Concentration of the reaction mixture gave 4-(4-but-2-ynylamino-benzenesulfonyl-methyl)-piperidine-4-carboxylic acid ethyl ester trifluoroacetic acid salt as a light yellow oil.

^{1}H NMR (CD_3OD) δ ppm 1.30 (t, J = 7.07 Hz, 3H), 1.77 (t, J = 2.27 Hz, 3H), 1.90–2.04 (m, 2H), 2.34–2.46 (m, 2H), 3.07–3.20 (m, 2H), 3.29–3.36 (m, 2H), 3.59 (s, 2H), 3.91 (q, J = 2.27 Hz, 2H), 4.15 (q, J = 7.07 Hz, 2H), 6.76 (d, J = 8.84 Hz, 2H), 7.60 (d, J = 8.84 Hz, 2H).

Compound **16** was synthesized by following the procedure in Section 2.3. The above ester (84 mg, 0.17 mmol) was converted into the desired product (27.5 mg, 44%), obtained as a white solid.

^{1}H NMR (CD_3OD) δ ppm 1.76 (t, J = 2.27 Hz, 3H), 2.03–2.16 (m, 2H), 2.31–2.43 (m, 2H), 3.08–3.20 (m, 2H), 3.32–3.38 (m, 2H), 3.52 (s, 2H), 3.90 (q, J = 2.27 Hz, 2H), 6.75 (d, J = 8.84 Hz, 2H), 7.63 (d, J = 8.84 Hz, 2H). HRMS (ESI+) Calcd for $C_{17}H_{23}N_3O_4S$ ($[M+H]^+$) 366.14820. Found: ($[M+H]^+$) 366.1479; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 2.93 min; 95.6%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 2.56 min; 95.0%.

2.3.7. 4-(4-But-2-ynylamino-benzenesulfonylmethyl)-1-(propane-2-sulfonyl)-piperidine-4-carboxylic acid hydroxyamide (17). To a solution of compound **10** (0.23 g, 0.48 mmol) in 5 mL dichloromethane was added 0.5 mL trifluoroacetic acid dropwise. The mixture was stirred at 25 °C for 2 h. Concentration of the reaction mixture gave a light yellow oil. At 0 °C, the oily residue was mixed with 2 mL dichloromethane, 2 mL saturated sodium bicarbonate (aq), and isopropylsulfonyl chloride (84 μL, 0.72 mmol). The resulting mixture was stirred at 25 °C for 16 h. The organic layer was separated and concentrated to give a yellow oily residue. Flash column chromatography of the residue (silica gel, 5:1 *n*-hexane/ethyl acetate) afforded compound 4-(4-but-2-ynylamino-benzenesulfonylmethyl)-1-(propane-2-sulfonyl)-piperidine-4-carboxylic acid ethyl ester (0.197 g, 85%) as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.28–1.35 (m, 9H), 1.68–1.78 (m, 2H), 1.81 (t, J = 2.40 Hz, 3H), 2.24–2.33 (m, 2H), 3.09–3.26 (m, 3H), 3.39 (s, 2H), 3.53–3.63 (m, 2H), 3.90–3.96 (q, J = 2.40 Hz, 2H), 4.19 (q, J = 7.16 Hz, 2H), 4.51 (t, J = 5.68 Hz, 1H), 6.67 (d, J = 8.84 Hz, 2H), 7.65 (d, J = 8.84 Hz, 2H).

Compound **17** was synthesized by following the procedure in Section 2.3. The above ester (0.26 g, 0.54 mmol)

was converted into the desired product (0.115 g, 45%), obtained as a white solid.

^{1}H NMR (CD_3OD) δ ppm 1.28 (d, J = 6.82 Hz, 6H), 1.76 (t, J = 2.27 Hz, 3H), 1.82–1.97 (m, 2H), 2.09–2.21 (m, 2H), 3.20–3.31 (m, 3H), 3.39–3.50 (m, 2H), 3.53 (s, 2H), 3.90 (q, J = 2.27 Hz, 2H), 6.74 (d, J = 8.84 Hz, 2H), 7.63 (d, J = 8.84 Hz, 2H). HRMS (ESI+) Calcd for $C_{20}H_{29}N_3O_6S_2 + H^+$ ($[M+H]^+$) 472.15705. Found: ($[M+H]^+$) 472.1566; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 4.26 min; 100%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 4.92 min; 96.4%.

2.3.8. 4-(4-But-2-ynylamino-benzenesulfonylmethyl)-1-pyridin-4-ylmethyl-piperidine-4-carboxylic acid hydroxyamide (18). To a solution of compound **10** (0.48 g, 1.0 mmol) in 10 mL dichloromethane was added 1.0 mL trifluoroacetic acid dropwise. The mixture was stirred at 25 °C for 2 h. Concentration of the reaction mixture gave a light yellow oil. At 0 °C, the oily residue was mixed with 2 mL dichloromethane, 4-(bromomethyl)pyridine hydrobromide (0.38 g, 1.5 mmol), and *N*,*N*-diisopropylethylamine (2 mL, excess). The resulting mixture was stirred at 25 °C for 16 h. Preparative HPLC of the mixture provided 4-(4-but-2-ynylamino-benzenesulfonylmethyl)-1-pyridin-4-ylmethyl-piperidine-4-carboxylic acid ethyl ester (0.10 g, 21%) as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.28 (t, J = 7.20 Hz, 3H), 1.76 (m, 2H), 1.80 (t, J = 2.53 Hz, 3H), 2.19–2.28 (m, 2H), 2.28–2.40 (m, 2H), 2.49–2.61 (m, 2H), 3.43 (s, 2H), 3.46 (s, 2H), 3.88–3.96 (q, J = 2.53, 2H), 4.13 (q, J = 7.20 Hz, 2H), 4.59 (s, 1H), 6.67 (d, J = 8.08 Hz, 2H), 7.23 (d, J = 5.05 Hz, 2H), 7.66 (d, J = 8.08 Hz, 2H), 8.51 (d, J = 5.05 Hz, 2H).

Compound **18** was synthesized by following the procedure in Section 2.3. The above ester (0.10 g, 0.21 mmol) was converted into the desired product (49.5 mg, 40%), obtained as a white solid.

^{1}H NMR (CD_3OD) δ ppm 1.76 (t, J = 2.27 Hz, 3H), 1.84–1.96 (m, 2H), 2.07–2.19 (m, 2H), 2.36–2.46 (m, 2H), 2.47–2.59 (m, 2H), 3.50 (s, 2H), 3.55 (s, 2H), 3.90 (q, J = 2.27 Hz, 2H), 6.74 (d, J = 8.84 Hz, 2H), 7.40 (d, J = 6.06 Hz, 2H), 7.62 (d, J = 8.84 Hz, 2H), 8.46 (d, J = 6.06 Hz, 2H).

HRMS (ESI+) Calcd for $C_{23}H_{28}N_4O_4S$ ($[M+H]^+$) 457.19040. Found: ($[M+H]^+$) 457.191; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 2.36 min; 100%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 2.35 min; 100%.

2.3.9. 4-(4-But-2-ynylamino-benzenesulfonylmethyl)-piperidine-1,4-dicarboxylic acid 1-diethylamide 4-hydroxyamide (19). To a solution of compound **10** (0.12 g, 0.25 mmol) in 3 mL dichloromethane was added 0.25 mL trifluoroacetic acid dropwise. The mixture was stirred at 25 °C for 2 h. Concentration of the reaction mixture gave a light yellow oil. At 0 °C, the oily residue was mixed with 2 mL dichloromethane, 2 mL saturated sodium bicarbonate, and diethylcarbamyl chloride (35 μL, 0.27 mmol). The resulting mixture was stirred at 25 °C for 16 h. The organic layer was separated and concentrated to give a yellow oily residue. Flash column chromatography of the residue (silica gel, 5:1 *n*-hexane/ethyl acetate) afforded 4-(4-but-2-ynylamino-benzenesulfonylmethyl)-1-diethylcarbamoyl-piperidine-4-carboxylic acid ethyl ester (50 mg, 42%) as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.10 (t, J = 7.07 Hz, 6H), 1.29 (t, J = 7.07 Hz, 3H), 1.68–1.78 (m, 2H), 1.81 (t, J = 2.27 Hz, 3H), 2.16–2.26 (m, 2H), 3.03–3.13 (m, 2H), 3.18 (q, J = 7.07 Hz, 4H), 3.31–3.40 (m, 2H), 3.41 (s, 2H), 3.92 (q, J = 2.27, Hz, 2H), 4.15 (q, J = 7.07 Hz, 2H), 4.61 (s, 1H), 6.67 (d, J = 8.84 Hz, 2H), 7.65 (d, J = 8.84 Hz, 2H).

Compound **19** was synthesized by following the procedure in Section 2.3. The above ester (50 mg, 0.10 mmol) was converted into the desired product (31 mg, 67%), obtained as a white solid.

^{1}H NMR (CD_3OD) δ ppm 1.11 (t, J = 7.07 Hz, 6H), 1.76 (t, J = 2.27 Hz, 3H), 1.80–1.91 (m, 2H), 2.02–2.14 (m, 2H), 3.11–3.20 (m, 2H), 3.19 (q, J = 7.07 Hz, 4H), 3.25–3.35 (m, 2H), 3.53 (s, 2H), 3.90 (q, J = 2.27 Hz, 2H), 6.74 (d, J = 8.84 Hz, 2H), 7.63 (d, J = 8.84 Hz, 2H).

HRMS (ESI+) Calcd for $C_{22}H_{32}N_4O_5S$ ($[M+H]^+$) 465.21662. Found: ($[M+H]^+$) 465.2171; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 4.00 min; 95.5%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 5.46 min; 95.0%.

2.3.10. 4-(4-But-2-ynylamino-benzenesulfonylmethyl)-1-(2-methyl-benzoyl)-piperidine-4-carboxylic acid hydroxyamide (20). To a solution of compound **10** (0.16 g, 0.33 mmol) in 5 mL dichloromethane was added 0.20 mL trifluoroacetic acid dropwise. The mixture was stirred at 25 °C for 2 h. Concentration of the reaction mixture gave light yellow oil. The oily residue was mixed with 2 mL dichloromethane, 2 mL saturated sodium bicarbonate, and 2-methylbenzoyl chloride (76 mg, 0.49 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 16 h. The organic layer was separated and concentrated to give a yellow oily residue. Flash column chromatography of the residue (silica gel, 4:1 *n*-hexane/ethyl acetate) afforded 4-(4-but-2-ynylamino-benzenesulfonylmethyl)-1-(2-methyl-benzoyl)-piperidine-4-carboxylic acid ethyl ester (68 mg, 42%) as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.31 (t, J = 7.20 Hz, 3H), 1.63–1.75 (m, 2H), 1.80 (t, J = 2.27 Hz, 3H), 2.15–2.34 (m, 2H), 2.37 (s, 3H), 3.16–3.69 (m, 6H), 3.92 (q, J = 2.27 Hz, 2H), 4.19 (q, J = 7.20 Hz, 2H), 4.60 (t, J = 5.68 Hz, 1H), 6.67 (d, J = 8.84 Hz, 2H), 7.09–7.33 (m, 4H), 7.65 (d, J = 8.84 Hz, 2H).

Compound **20** was synthesized by following the procedure in Section 2.3. The above ester (0.12 g, 0.24 mmol) was converted into the desired product (65.6 mg, 56%), obtained as a white solid.

^{1}H NMR (CD_3OD) δ ppm 1.75 (t, J = 2.27 Hz, 3H), 1.77–1.98 (m, 2H), 1.99–2.24 (m, 2H), 2.37 (s, 3H), 3.33–3.43 (m, 1H), 3.44–3.54 (m, 2H), 3.56 (s, 2H)

3.87–4.01 (m, 1H), 3.90 (q, J = 2.27 Hz, 2H), 6.74 (d, J = 8.84 Hz, 2H), 7.13–7.18 (m, 2H), 7.20 (m, 2H), 7.25–7.37 (d, J = 8.84 Hz, 2H). HRMS (ESI+) Calcd for $C_{25}H_{29}N_3O_5S$ ($[M+H]^+$) 484.19007. Found: ($[M+H]^+$) 484.1889; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 4.72 min; 95.5%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 5.85 min; 96.0%.

2.3.11. 4-(4-But-2-ynylamino-benzenesulfonylmethyl)-1-(2-methyl-butyryl)-piperidine-4-carboxylic acid hydroxyamide (21). To a solution of compound **10** (0.15 g, 0.32 mmol) in 5 mL of dichloromethane was added 0.20 mL of trifluoroacetic acid dropwise. The mixture was stirred at 25 °C for 2 h. Concentration of the reaction mixture gave light yellow oil. The oily residue was mixed with 2 mL of dichloromethane, 2 mL saturated sodium bicarbonate, and 2-methyl-butyryl chloride (42 mg, 0.35 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 16 h. The organic layer was separated and concentrated to give a yellow oily residue. Flash column chromatography of the residue (silica gel, 5:1 *n*-hexane/ethyl acetate) afforded 4-(4-but-2-ynylamino-benzenesulfonylmethyl)-1-(2-methyl-butyryl)-piperidine-4-carboxylic acid ethyl ester (30 mg, 20%) as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 0.83–0.93 (two sets of triplets, J = 6.82 Hz, 3H), 1.05–1.12 (two sets of doublets, J = 6.32 Hz, 3H), 1.31 (t, J = 7.07 Hz, 3H), 1.34–1.46 (m, 1H), 1.63–1.80 (m, 1H), 1.81 (t, J = 2.27 Hz, 3H), 2.04–2.13 (m, 1H), 2.40–2.51 (m, 1H), 2.53–2.66 (m, 1H), 3.02–3.10 (m, 1H), 3.28 (d, J = 16.0 Hz, 1H), 3.43–3.51 (m, 2H), 3.52 (d, J = 16.0 Hz, 1H), 3.65–3.77 (m, 1H), 3.93 (q, J = 2.27 Hz, 2H), 4.06–4.15 (m, 2H), 4.18 (q, J = 7.07 Hz, 2H), 4.48 (t, J = 5.0 Hz, 1H), 6.68 (d, J = 8.59 Hz, 2H), 7.66 (d, J = 8.59 Hz, 2H).

Compound **21** was synthesized by following the procedure in Section 2.3. The above ester (30 mg, 0.065 mmol) was converted into the desired product (20 mg, 65%), obtained as a white solid.

^{1}H NMR (CD_3OD) δ ppm 0.87 (two sets of triplets, J = 7.41 Hz, 3H), 1.06 (two sets of doublets, J = 6.57, 3H), 1.32–1.50 (m, 1H), 1.55–1.73 (m, 1H), 1.76 (t, J = 2.27 Hz, 3H), 1.77–1.93 (m, 2H), 1.96–2.08 (m, 1H), 2.09–2.23 (m, 1H), 2.71–2.82 (m, 1H), 3.36–3.56 (m, 2H), 3.55 (s, 2H), 3.66–3.87 (m, 2H), 3.90 (q, J = 2.27 Hz, 2H), 6.74 (d, J = 8.84 Hz, 2H), 7.63 (d, J = 8.84 Hz, 2H).

HRMS (ESI+) Calcd for $C_{22}H_{31}N_3O_5S$ ($[M+H]^+$) 450.20572. Found: ($[M+H]^+$) 450.2058; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 4.24 min; 95.5%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 5.29 min; 95.0%.

2.3.12. 4-(4-But-2-ynylamino-benzenesulfonylmethyl)-1-isobutyryl-piperidine-4-carboxylic acid hydroxyamide (22). To a solution of compound **10** (0.15 g, 0.32 mmol) in 5 mL dichloromethane was added 0.20 mL trifluoroacetic acid dropwise. The mixture was stirred at 25 °C for 2 h. Concentration of the reaction mixture gave a light yellow oil. The oily residue was mixed with 2 mL of dichloromethane, 2 mL saturated sodium bicarbonate, and isobutyryl chloride (37 mg, 0.35 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 16 h. The organic layer was separated and concentrated to give a yellow oily residue. Flash column chromatography of the residue (silica gel, 5:1 *n*-hexane/ethyl acetate) afforded 4-(4-but-2-ynylamino-benzenesulfonylmethyl)-1-isobutyryl-piperidine-4-carboxylic acid ethyl ester (28 mg, 20%) as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.11 (d, J = 6.06 Hz, 6H), 1.31 (t, J = 7.20 Hz, 3H), 1.49–1.57 (m, 1H), 1.71–1.81 (m, 1H), 1.81 (t, J = 2.27 Hz, 3H), 2.04–2.12 (m, 1H), 2.38–2.51 (m, 1H), 2.71–2.83 (m, 1H), 2.98–3.12 (m, 1H), 3.28–3.26 (m, 1H), 3.43–3.50 (m, 2H), 3.62–3.76 (m, 1H), 3.93 (q, J = 2.27 Hz, 2H), 4.03–4.14 (m, 1H), 4.18 (q, J = 7.20 Hz, 2H), 4.48 (t, J = 5.31 Hz, 1H), 6.67 (d, J = 8.84 Hz, 2H), 7.66 (d, J = 8.84 Hz, 2H).

Compound **22** was synthesized by following the procedure in Section 2.3. The above ester (32 mg, 0.071 mmol) was converted into the desired product (20 mg, 65%), obtained as a white solid.

^{1}H NMR (CD_3OD) δ ppm 1.07 (two sets of doublets, J = 6.69, 3.41 Hz, 6H), 1.76 (t, J = 2.27 Hz, 3H), 1.78–1.92 (m, 2H), 1.99–2.08 (m, 1H), 2.11–2.20 (m, 1H), 2.86–2.97 (m, 1H), 3.34–3.53 (m, 2H), 3.55 (s, 2H), 3.66–3.84 (m, 2H), 3.90 (q, J = 2.27 Hz, 2H), 6.74 (d, J = 8.84 Hz, 2H), 7.63 (d, J = 8.84 Hz, 2H). HRMS (ESI+) Calcd for $C_{21}H_{29}N_3O_5S$ ($[M+H]^+$) 436.19007. Found: ($[M+H]^+$) 436.1898; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 3.68 min; 95.5%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 5.25 min; 100%.

2.3.13. 4-(4-Amino-benzenesulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid methyl ester (24). 4-Nitrobenzenesulfonyl chloride (1.77 g, 13.4 mmol) was added to a solution of compound **23** (prepared according to the method described in PCT Application WO9720824; 0.65 g, 6.7 mmol) in 30 mL of dichloromethane and *N*-methylmorpholine (1.5 mL, 13.4 mmol) at 0 °C. The reaction mixture was warmed to 25 °C and stirred overnight. The mixture was washed with water. The organic layer was concentrated to give a light yellow oily residue. Flash column chromatography of the residue (silica gel, 9:1 *n*-hexane/ethyl acetate) afforded 2,2-dimethyl-4-(4-nitro-benzenesulfonyl)-thiomorpholine-3-carboxylic acid methyl ester (0.57 g, 44%) as a clear oil.

^{1}H NMR ($CDCl_3$) δ ppm 1.32 (s, 3H), 1.64 (s, 3H), 2.48 (d, J = 13.45 Hz, 1H), 3.16 (ddd, J = 13.45, 13.45, 3.66 Hz, 1H), 3.44 (s, 3H) 3.77 (ddd, J = 12.69, 12.69, 2.65 Hz, 1H), 4.05–4.16 (m, 1H), 4.48 (s, 1H), 7.89 (d, J = 8.59 Hz, 2H), 8.34 (d, J = 8.59 Hz, 2H).

To a solution of the above ester (0.52 g, 1.39 mmol) in 11 mL of methanol and 0.6 mL acetic acid was added zinc dust (<10 μm, 740 mg). After stirring at 25 °C for 1 h, the reaction mixture was filtered through a thin layer of silica gel. Concentration of the filtrate afforded compound **24** (0.47 g, 100%) as a light yellow oil, which was used for the next step without further purification.

^{1}H NMR ($CDCl_3$) δ ppm 1.26 (s, 3H), 1.61 (s, 3H), 2.45 (dd, J = 13.14, 3.79 Hz, 1H), 3.11 (ddd, J = 13.14, 13.14, 3.79 Hz, 1H), 3.44 (s, 3H), 3.75 (ddd, J = 12.63, 12.63, 2.78 Hz, 1H), 4.03 (ddd, J = 12.63, 3.28, 3.16 Hz, 1H), 4.39 (s, 1H), 6.64 (d, J = 8.59 Hz, 2H), 7.47 (d, J = 8.59 Hz, 2H).

2.3.14. 4-(4-But-2-ynylamino-benzenesulfonyl)-2,2-dimethyl-thiomorpholine-3-carboxylic acid methyl ester (25). 1-Bromo-2-butyne (0.14 mL, 1.55 mmol), compound **24** (0.52 g, 1.51 mmol), potassium carbonate (0.36 mg, 2.6 mmol), 3 mL *N*,*N*-dimethylacetamide, and a stir bar were placed in a microwave reaction vessel. The reaction vessel was sealed with a cap, and then heated to 100 °C for 50 min in a microwave reactor. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was concentrated to give a light yellow oily residue. Flash column chromatography of the residue (silica gel, 5:1 *n*-hexane/ethyl acetate) afforded **25** (0.22 g, 37%) as a clear oil and the starting material **24** (0.32 g, 62%).

^{1}H NMR ($CDCl_3$) δ ppm 1.29 (s, 3H), 1.63 (s, 3H), 1.80 (t, J = 2.27 Hz, 3H), 2.45 (dd, J = 13.14, 4.00 Hz, 1H), 3.12 (ddd, J = 13.14, 13.14, 3.79 Hz, 1H), 3.42 (s, 3H), 3.75 (ddd, J = 12.63, 12.63, 3.03 Hz, 1H), 3.91 (q, J = 2.27 Hz, 2H), 4.05 (dd, J = 12.25, 3.16 Hz, 1H), 4.36 (t, J = 4.00 Hz, 1H), 4.40 (s, 1H), 6.62 (d, J = 8.84 Hz, 2H), 7.52 (d, J = 8.84 Hz, 2H).

2.3.15. (3*S*)-4-{[4-(But-2-ynylamino)phenyl]sulfonyl}-*N*-hydroxy-2,2-dimethylthio-morpholine-3-carboxamide (26). Compound **26** was synthesized by following the procedure in Section 2.3. The above ester **25** (40 mg, 0.1 mmol) was converted into the desired product (10 mg, 25%), obtained as a white solid.

^{1}H NMR (CD_3OD) δ ppm 1.22 (s, 3H), 1.53 (s, 3H), 1.76 (t, J = 2.27 Hz, 3H), 2.45 (dd, J = 13.14, 4.00 Hz, 1H), 3.02 (ddd, J = 13.14, 13.14, 3.79 Hz, 1H), 3.76–3.92 (m, 2H), 3.87 (q, J = 2.27 Hz, 2H), 4.11 (s, 1H), 6.68 (d, J = 8.84 Hz, 2H), 7.51 (d, J = 8.84 Hz, 2H). HRMS (ESI+) Calcd for $C_{17}H_{23}N_3O_4S_2$ ($[M+H]^+$) 398.12027. Found: ($[M+H]^+$) 398.1191; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 4.62 min; 95.3%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 5.10 min; 97.1%.

2.3.16. 4-(4-Hydroxy-benzenesulfonylmethyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (29). A mixture of compound **8** (18.51 g, 46.6 mmol), 4-mercaptophenol (7.06 g, 55.91 mmol), and potassium carbonate (7.08 g, 51.26 mmol) in 80 mL DMF was stirred at 25 °C for 5 h. The resulting mixture was diluted with ethyl acetate, washed with water, brine, and concentrated to give a light yellow solid residue (19.52 g), which was used for the next step without further purification.

^{1}H NMR ($CDCl_3$) δ ppm 1.20 (t, J = 7.91 Hz, 3H), 1.45 (s, 9H), 1.40–1.52 (m, 2H), 2.09–2.20 (m, 2H), 2.89–3.03 (m, 2H), 3.06 (s, 2H), 3.67–3.89 (m, 2H), 4.00 (q, J = 7.91 Hz, 2H), 5.71 (s, 1H), 6.75 (d, J = 9.22 Hz, 2H), 7.28 (d, J = 9.22 Hz, 2H).

To a solution of above solid in 30 mL dichloromethane at 0 °C was added 77% 3-chloroperoxybenzoic acid (25.3 g 113 mmol). The mixture was slowly warmed to 25 °C and stirred for 16 h. The solid was filtered and the filtrate was concentrated to give a yellow oily residue. Flash column chromatography of the residue (silica gel, 1:1 *n*-hexane/ethyl acetate) afforded the desired product **29** (17.87 g, 89% for two steps) as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.31 (t, J = 7.37 Hz, 3H), 1.45 (s, 9H), 1.52–1.76 (m, 2H), 2.05–2.38 (m, 2H), 3.06–3.29 (m, 2H), 3.43 (s, 2H), 3.63–3.74 (m, 2H), 4.20 (q, J = 7.37 Hz, 2H), 6.95 (d, J = 8.72 Hz, 2H), 7.72 (d, J = 8.72 Hz, 2H).

2.3.17. 4-[4-(1-Methyl-but-2-ynyloxy)-benzenesulfonylmethyl]-1-(propane-2-sulfonyl)-piperidine-4-carboxylic acid ethyl ester (30). A mixture of compound **29** (300 mg, 0.69 mmol), 3-pentyn-2-ol (87.5 mg, 1.04 mmol), triphenylphosphine (362 mg, 1.38 mmol), and diisopropyl azodicarboxylate (279 mg, 1.38 mmol) in dichloromethane (15 mL) was stirred at 0 °C for 1 day and then concentrated. Chromatography (silica, 3:1 *n*-hexane/ethyl acetate) afforded 4-[4-(1-methyl-but-2-ynyloxy)-benzenesulfonylmethyl]-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester as a colorless oil (344 mg, 100%).

^{1}H NMR ($CDCl_3$) δ ppm 1.27–1.36 (m, 2H), 1.36–1.53 (m, 9H), 1.56–1.71 (m, 5H), 1.82 (d, J = 2.02 Hz, 3H), 2.08–2.31 (m, 2H), 3.20 (s, 2H), 3.44 (s, 2H), 3.69 (d, J = 13.39 Hz, 2H), 4.06–4.23 (m, 2H), 4.83–5.06 (m, 2H), 7.03–7.15 (m, 2H), 7.72–7.87 (m, 2H).

The above product (344 mg, 0.69 mmol) was stirred in dichloromethane (5 mL) and 1 mL of trifluoroacetic acid at room temperature for 30 min. The reaction mixture was then concentrated to give 4-[4-(1-methyl-but-2-ynyloxy)-benzenesulfonylmethyl]-piperidine-4-carboxylic acid ethyl ester that was precipitated from ethyl ether as a trifluoroacetate salt.

^{1}H NMR (DMSO-d_6) δ ppm 1.20 (t, J = 7.07 Hz, 3H), 1.56 (d, J = 6.57 Hz, 3H), 1.80 (d, J = 2.02 Hz, 3H), 1.91 (t, 2H), 2.14 (t, J = 14.91 Hz, 2H), 3.00 (m, 2H), 3.22 (m, 2H), 3.78 (s, 2H), 4.03 (q, J = 7.16 Hz, 2H), 5.16–5.27 (m, 1H), 7.17–7.25 (m, 2H), 7.74–7.84 (m, 2H), 8.51 (s, 2H).

The above trifluoroacetate salt (0.34 g, 0.67 mmol) was stirred with isopropylsulfonyl chloride (0.19 g, 1.34 mmol) in dichloromethane (10 mL) and saturated sodium bicarbonate (5 mL) at room temperature overnight. The organic layer was separated and concentrated to give a yellow oily residue. Flash column chromatography of the residue (silica gel, 5:1 *n*-hexane/ethyl acetate) afforded compound **30** (0.26 g, 77%) as a white powder. ^{1}H NMR ($CDCl_3$) δ ppm 1.28–1.40 (m, 10H), 1.60–1.69 (m, 3H), 1.70–1.80 (m, 2H), 1.82 (d, J = 2.02 Hz, 3H), 2.29 (d, J = 14.65 Hz, 2H), 3.11–3.29 (m, 2H), 3.42 (s, 2H), 3.59 (d, J = 13.64 Hz, 2H), 4.20 (q, J = 7.07 Hz, 2H), 4.79–4.97 (m, 1H), 7.05–7.15 (m, 2H), 7.67–7.85 (m, 2H).

2.3.18. *N*-Hydroxy-1-(isopropylsulfonyl)-4-[({4-[(1-methylbut-2-yn-1-yl)oxy]phenyl}sulfonyl)-methyl]piperidine-4-carboxamide (27). Compound **27** was synthesized by following the procedure in Section 2.3. The above ester **30** (0.25 g, 0.49 mmol) was converted into the desired product (0.12 g, 61%), obtained as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.30 (d, J = 6.82 Hz, 6H), 1.64 (d, J = 6.42 Hz, 3H), 1.82 (d, J = 2.02 Hz, 3H), 1.87–1.98 (m, 2H), 2.30 (m, 2H), 3.11–3.20 (m, 1H), 3.32 (t, J = 8.34 Hz, 2H), 3.42 (s, 2H), 3.54 (t, J = 13.39 Hz, 2H), 4.84–4.94 (m, 1H), 7.10 (d, J = 8.84 Hz, 2H), 7.80 (d, J = 8.08 Hz, 2H), 9.52 (s, 1H). HRMS (ESI+) Calcd for $C_{21}H_{30}N_2O_7S_2$ ($[M+H]^+$) 487.15672. Found: ($[M+H]^+$) 487.1567; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 4.56 min; 97.0%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 5.68 min; 100.0%.

2.3.19. 4-(4-Benzyloxy-benzenesulfonylmethyl)-piperidine-4-carboxylic acid ethyl ester (31). To a solution of compound **29** (1.1 g, 2.6 mmol) in DMF (20 mL) were added benzyl bromide (0.49 g, 2.9 mmol) and potassium carbonate (1.8 g, 13 mmol) at 0 °C. The mixture was stirred for 30 min. The reaction mixture was taken up in ethyl acetate (100 mL) and washed with water (50 mL). The organic layer was separated and concentrated to afford 4-(4-benzyloxy-benzenesulfonylmethyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (1.35 g, 100%) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ ppm 1.29 (t, J = 7.30 Hz, 3H), 1.44 (s, 9H), 1.58–1.72 (m, 2H), 2.06–2.32 (m, 2H), 3.06–3.31 (m, 2H), 3.42 (s, 2H), 3.67 (m, 2H), 4.15 (q, J = 7.30 Hz, 2H), 5.15 (s, 2H), 7.08 (d, J = 9.51 Hz, 2H), 7.40–7.43 (m, 5H), 7.80 (d, J = 8.65 Hz, 2H).

The above compound (1.35 g, 2.6 mmol) was stirred in dichloromethane (20 mL) and 2 mL of trifluoroacetic acid at room temperature for 4 h. The reaction mixture was concentrated to afford the trifluoroacetate salt of **31** (1.16 g, 84%) as a white solid.

^{1}H NMR (DMSO-d_6) δ ppm 1.19 (t, J = 7.07 Hz, 3H), 1.83–1.95 (m, 2H), 2.06–2.18 (m, 2H), 2.91–3.06 (m, 2H), 3.15–3.27 (m, 2H), 3.77 (s, 2H), 4.00 (q, J = 7.07 Hz, 2H), 5.25 (s, 2H), 7.24–7.30 (m, 2H), 7.32–7.51 (m, 5H), 7.76–7.83 (m, 2H), 8.51 (d, 2H).

2.3.20. 4-(4-Hydroxy-benzenesulfonylmethyl)-1-(propane-2-sulfonyl)-piperidine-4-carboxylic acid ethyl ester (32). To a solution of the above TFA salt (1.06 g, 2.0 mmol) in dichloromethane (20 mL) were added isopropylsulfonyl chloride (0.34 mL, 3.1 mmol) and *N*,*N*-diisopropylethylamine (1.4 mL, 8.1 mmol). The reaction mixture was stirred at 25 °C for 16 h and concentrated. Chromatography (silica gel, 4:1 *n*-hexane/ethyl acetate) afforded 4-(4-benzyloxy-benzenesulfonylmethyl)-1-(propane-2-sulfonyl)-piperidine-4-carboxylic acid ethyl ester (0.52 g, 49%) as an off-white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.29–1.33 (m, 9H), 1.69–1.76 (m, 2H), 2.26–2.29 (m, 2H), 3.11–3.23 (m, 3H), 3.41 (s, 2H), 3.54–3.63 (m, 2H), 4.19 (q, J = 7.16 Hz, 2H), 5.15 (s, 2H), 7.01–7.14 (m, 2H), 7.32–7.48 (m, 5H), 7.73–7.87 (m, 2H).

The above compound (0.5 g, 0.96 mmol) was suspended in methanol (20 mL) and hydrogenated using a hydrogen balloon in the presence of 10% of palladium over carbon (65 mg). The mixture was stirred for 20 h, filtered through Celite, and concentrated to afford **32** (0.4 g, 97%) as an off-white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.29–1.37 (m, 9H), 1.65–1.80 (m, 2H), 2.27 (d, J = 13.89 Hz, 2H), 3.13–3.26 (m, 3H), 3.42 (s, 2H), 3.54–3.64 (m, 2H), 4.22 (q, J = 7.07 Hz, 2H), 6.92–6.99 (m, 2H), 7.68–7.76 (m, 2H).

2.3.21. 4-[({4-[(1,1-Dimethylbut-2-yn-1-yl)oxy]phenyl}sulfonyl)methyl]-*N*-hydroxy-1-(isopropylsulfonyl)piperidine-4-carboxamide (28). To a solution of compound **32** (0.4 g, 0.93 mmol) in dichloromethane (15 mL) were added 2-methyl-3-pentyn-2-ol (0.14 g, 1.4 mmol, prepared according to *Syn. Commun.*, **1992**, *22*, 2997–3002), triphenylphosphine (0.49 g, 1.86 mmol), and diisopropyl azodicarboxylate (0.38 g, 1.86 mmol). The reaction mixture was stirred at 0 °C for 16 h and concentrated. Chromatography (silica gel, 3:1 *n*-hexane/ethyl acetate) afforded the impure product, which was further purified via HPLC (CH_3CN/H_2O/0.1% formic acid) to afford 4-[4-(1,1-dimethyl-but-2-ynyloxy)-benzenesulfonylmethyl]-1-(propane-2-sulfonyl)-piperidine-4-carboxylic acid ethyl ester (0.1 g, 20%) as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.28–1.35 (m, 9H), 1.67 (s, 6H), 1.71–1.81 (m, 2H), 1.85 (s, 3H), 2.30 (d, J = 13.89 Hz, 2H), 3.11–3.27 (m, 3H), 3.42 (s, 2H), 3.55–3.63 (m, 2H), 4.20 (q, J = 7.07 Hz, 2H), 7.30–7.36 (m, 2H), 7.73–7.79 (m, 2H).

Compound **28** was synthesized by following the procedure in Section 2.3. The above ester (100 mg, 0.19 mmol) was converted into the desired product (31 mg, 34%), obtained as a white solid.

^{1}H NMR ($CDCl_3$) δ ppm 1.31 (d, J = 6.82 Hz, 6H), 1.67 (s, 6H), 1.85 (s, 3H), 1.88–1.99 (m, 2H), 2.27–2.37 (m, 2H), 3.11–3.20 (m, 1H), 3.32 (t, J = 10.2 Hz, 2H), 3.43 (s, 2H), 3.54 (d, J = 14.1 Hz, 2H), 7.34 (d, J = 8.34 Hz, 2H), 7.77 (d, J = 8.34 Hz, 2H), 9.25–9.70 (m, 1H). HRMS (ESI+) Calcd for $C_{22}H_{32}N_2O_7S_2$ ($[M+H]^+$), 501.17237. Found: ($[M+H]^+$) 501.173; HPLC-1: H_2O/CH_3CN/0.1% formic acid: 4.74 min; 95.7%; HPLC-2: H_2O/CH_3OH/0.1% formic acid: 6.00 min; 95.0%.

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References and notes

1. Feldmann, M.; Brennan, F. M.; Williams, R. O.; Cope, A. P.; Gibbons, D. L.; Katsikis, P. D.; Maini, R. N. *Prog. Growth Factor Res.* **1992**, *4*, 247.
2. Van Assche, G.; Rutgeerts, P. *Expert Opin. Invest. Drugs* **2000**, *9*, 103.
3. Kristensen, M.; Chu, C. Q.; Eedy, D. J.; Feldmann, M.; Brennan, F. M.; Breathnach, S. M. *Clin. Exp. Immunol.* **1993**, *94*, 354.
4. Feldmann, M.; Ravinder, N. M. *Annu. Rev. Immunol.* **2001**, *19*, 163.
5. Black, R. A.; Rauch, C. T.; Kozlosky, C. J.; Peschon, J. J.; Slack, J. L.; Wolfson, M. F.; Castner, B. J.; Stocking, K. L.; Reddy, P.; Srinivasan, S.; Nelson, N.; Boiani, N.; Schooley, K. A.; Gerhart, M.; Davis, R.; Fitzner, J. N.; Johnson, R. S.; Paxton, R. J.; March, C. J.; Cerretti, D. P. *Nature* **1997**, *385*, 729.
6. Moss, M. L.; Jin, S.-L. C.; Milla, M. E.; Burkhart, W.; Carter, H. L.; Chen, W.-J.; Clay, W. C.; Didsbury, J. R.; Hassler, D.; Hoffman, C. R.; Kost, T. A.; Lambert, M. H.; Leesnitzer, M. A.; McCauley, P.; McGeehan, G.; Mitchell, J.; Moyer, M.; Pahel, G.; Rocque, W.; Overton, L. K.; Schoenen, F.; Seaton, T.; Su, J.-L.; Warner, J.; Willard, D.; Becherer, J. D. *Nature* **1997**, *385*, 733.
7. Stocker, W.; Grams, F.; Baumann, U.; Reinemer, P.; Gomis-Ruth, F.-X.; Mckay, D. B.; Bode, W. *Protein Sci.* **1995**, *4*, 823.
8. Hooper, N. M. *FEBS Lett.* **1994**, *354*, 1.
9. Maskos, K.; Fernandez-Catalan, C.; Huber, R.; Bourenkov, G.; Bartunik, H.; Ellestad, G.; Reddy, P.; Wolfson, M.; Rauch, C.; Castner, B.; Davis, R.; Clarke, H.; Petersen, M.; Fitzner, J.; Cerretti, D.; March, C.; Paxton, R.; Black, R.; Bode, W. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3408.
10. (a) Grootveld, M.; McDermott, M. F. *Curr. Opin. Invest. Drugs* **2003**, *4*, 598; (b) Duan, J. J.-W.; Lu, Z.; Xue, C.-B.; He, X.; Seng, J. L.; Roderick, J. J.; Wasserman, Z. R.; Liu, R.-Q.; Covington, M. B.; Magolda, R. L.; Newton, R. C.; Trzaskos, J. M.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2035.
11. Trifilieff, A.; Walker, C.; Keller, T.; Kottirsch, G.; Neumann, U. *Br. J. Pharmacol.* **2002**, *135*, 1655.
12. Beck, G.; Bottomley, G.; Bradshaw, D.; Brewster, M.; Broadhurst, M.; Devos, R.; Hill, C.; Johnson, W.; Kim, H.-J.; Kirtland, S.; Kneer, J.; Lad, N.; Mackenzie, R.; Martin, R.; Nixon, J.; Price, G.; Rodwell, A.; Rose, F.; Tang, J.-P.; Walter, D. S.; Wilson, K.; Worth, E. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 390.
13. (a) Peterson, J. T. *Heart Fail. Rev.* **2004**, *9*, 63; (b) Renkiewicz, R.; Qiu, L.; Lesch, C.; Sun, X.; Devalaraja, R.; Cody, T.; Kaldjian, E.; Welgus, H.; Baragi, V. *Arthritis Rheum.* **2003**, *48*, 1742.
14. Park, K.; Aplasca, A.; Du, M.; Sun, L.; Zhu, Y.; Zhang, Y.; Levin, J. I. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3927.
15. (a) Levin, J. I.; Venkatesan, A. M.; Chen, J. M.; Zask, A.; Sandanayaka, V. P.; Du, M. T.; Baker, J. L. U.S. 6358980, 2002; (b) Huang, A.; Condon, J.; Joseph-McCarthy, D.; Lombart, H.; Lovering, F.; Park, K.; Rao, V.; Sun, L.; Wang, Q.; Wang, W.; Xu, W.; Zeng, C.; Zhang, Y.; Zhu, Z.; Levin, J. I. Poster, AAPS Conference: Critical Issues in Discovering Quality Clinical Candidates, Philadelphia, PA, April 24–26, 2006.
16. (a) Zask, A.; Kaplan, J.; Du, X.; MacEwan, G.; Sandanayaka, V.; Eudy, N.; Levin, J.; Jin, G.; Xu, J.; Cummons, T.; Barone, D.; Ayral-Kaloustian, S.; Skotnicki, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1641; (b) Levin, J. I.; Chen, J. M.; Laakso, L. M.; Du, M.; Du, X.; Venkatesan, A. M.; Sandanayaka, V.; Zask, A.; Xu, J.; Xu, W.; Zhang, Y.; Skotnicki, J. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4345; (c) Tsukida, T.; Moriyama, H.; Inoue, Y.; Kondo, H.; Yoshino, K.; Nishimura, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1569; (d) Moriyama, H.; Tsukida, T.; Inoue, Y.; Yokota, K.; Yoshino, K.; Kondo, H.; Miura, N.; Nishimura, S.-I. *J. Med. Chem.* **2004**, *47*, 1930.
17. (a) Initial models for compounds **5** and **7** bound to TACE, respectively, were generated via Monte Carlo docking using the program FLO (McMartin, C.; Bohacek, R. S. *J. Comput.-Aided Mol. Design*, **1997**, *11*, 333–344). A scan of the linker dihedral (the dihedral about the O–CH_2 bond) was carried out starting with the modeled bound conformation of compound **5** with TACE. A similar scan of the linker dihedral (about the NH–CH_2 bond) was carried out starting with **7** in the identical conformation. For both ligand structures, the quantum mechanical energy of ligand was calculated while varying the linker dihedral in 5° increments from −180° to +180°. The program Jaguar 6.0 (Schrödinger, LLC, Portland, OR, 2005) was used to perform a relaxed coordinate scan of the specified dihedral angles at the B3LYP/6-31G** level of theory, including a Poisson–Boltzmann self-consistent reaction field model to account for the effects of aqueous solvation; (b) The RCSB PDB ID code of the X-ray structure of **7** bound to MMP-13 is 2PJT.
18. Duan, J. J.-W.; Chen, L.; Wasserman, Z. R.; Lu, Z.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Hardman, K. D.; Magolda, R. L.; Newton, R. C.; Christ, D. D.; Wexler, R. R.; Decicco, C. P. *J. Med. Chem.* **2002**, *45*, 4954–4957.
19. For descriptions of all the in vitro and in vivo assays used herein, see: Zhang, Y.; Xu, J.; Levin, J.; Hegen, M.; Li, G.; Robertshaw, H.; Brennan, F.; Cummons, T.; Clarke, D.; Vansell, N.; Nickerson-Nutter, C.; Barone, D.; Mohler, K.; Black, R.; Skotnicki, J.; Gibbons, J.; Feldmann, M.; Frost, P.; Larsen, G.; Lin, L. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 348–355.
20. Bender, S. L.; Melnick, M. J. U.S. Patent 5,753,653, 1998; *Chem. Abstr.*, **1998**, *129*, 16140.