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Design and synthesis of butynyloxyphenyl β-sulfone piperidine hydroxamates as TACE inhibitors

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Abstract—A series of butynyloxyphenyl β-sulfone piperidine hydroxamate TACE inhibitors was designed and synthesized. The resulting structure–activity relationship and MMP selectivity of the series were examined. Of the compounds investigated, **17s** has excellent in vitro potency against isolated TACE enzyme, shows good selectivity over MMP-1, -2, -7, -8, -9, -13, and -14, and oral activity in an in vivo mouse model of TNF-α production.

TACE (TNF-α converting enzyme), a member of the ADAM (a disintegrin and metalloprotease-containing enzyme) family of proteases, is responsible for cleaving 26 kDa membrane-bound TNF-α (tumor necrosis factor-α) to generate 17 kDa soluble TNF-α, a pro-inflammatory cytokine.[1] It has been reported that TNF-α plays a pivotal role in rheumatoid arthritis (RA)[2] and that elevated concentrations of soluble TNF-α are found in the synovial fluid of RA patients.[3] Agents such as etanercept (Enbrel®),[4] a soluble TNF-α receptor, and infliximab (Remicade®),[5] an anti-TNF-α antibody, have been used effectively to treat RA patients. However, these biologics have limitations including the need for administration by infusion or parenteral injection. Hence the development of orally active small molecule TACE inhibitors is a highly desirable goal for the treatment of RA.

Recently, a number of small molecule TACE inhibitors have been reported.[6] These include both selective inhibitors of TACE[6b,6e] and more broad spectrum TACE and MMP inhibitors.[6c,6f] While TACE inhibitors with significant activity against some MMPs may provide an advantage in treating RA, since various MMPs are over-expressed in RA synovial tissue and contribute to joint destruction,[7] many broad spectrum MMP inhibitors have suffered from dose-limiting toxicity in clinical trials.[8] Selective inhibitors of TACE are needed to explore the possibility of a greater safety margin on long-term dosing in clinical trials. The structure-based design of selective TACE inhibitors has been based both on homology models[9a] and an X-ray structure of a peptide-based hydroxamic acid inhibitor bound to the active site of TACE.[9b] These methods have revealed that the S1′ and S3′ pockets of TACE are connected, providing a subsite with a unique shape that sets it apart from the S1′ subsites of the MMPs. Structure-based design at Wyeth has led to the discovery of sulfonamide and sulfone hydroxamate TACE inhibitors bearing a novel butynyloxy P1′ group which fits well in the channel between the S1′ and S3′ pockets of TACE (Fig. 1). This P1′ moiety provides varying levels of selectivity for TACE, and cellular activity, depending on the scaffold that bears the hydroxamate. Thus, anthranilate sulfonamide hydroxamate inhibitor **1** shows excellent in vitro potency against TACE and excellent selectivity over MMP-1.[10] Sulfonamide hydroxamate inhibitor **2** has excellent TACE enzyme activity and cellular activity, good selectivity over MMP-1 and MMP-9, and oral activity in vivo.[11] α-Sulfone piperidine hydroxamate inhibitor **3** exhibits good in vitro potency against TACE and excellent selectivity for TACE over MMP-1, MMP-9, and MMP-13.[12] Thiomorpholine-carboxamides **4a**–**4b** are orally bioavailable dual TACE/MMP

Keywords: β-Sulfone piperidine hydroxamates; TACE inhibitors; Structure–activity relationship; MMP selectivity.
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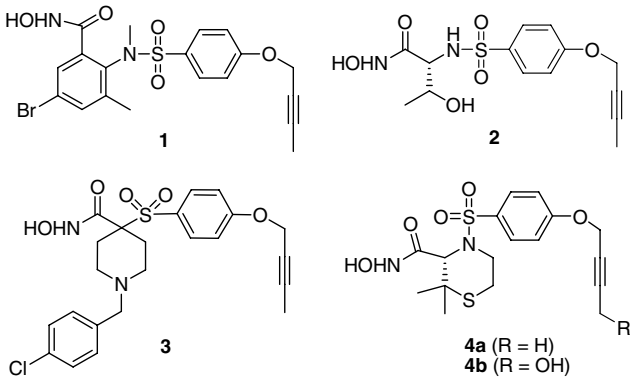


Figure 1. TACE inhibitors bearing the butynyloxy P1′ group.

inhibitors with excellent potency in human whole blood.[13] Compound **4b** has entered clinical trials for the treatment of RA.[13c]

In order to ascertain whether the butynyloxy P1′ group could be applied to additional scaffolds, with increased levels of selectivity over the MMPs, we were interested in exploring a series of β-sulfone hydroxamate analogs of compound **3**. The β-sulfone hydroxamate scaffold has previously been used to provide potent MMP inhibitors investigated for the treatment of osteoarthritis (Fig. 2: **5 RS–130,830**)[14] and for oncology.[15] We had prepared β-sulfone piperidine hydroxamic acid **6** (Fig. 2) and found that it has excellent TACE activity (IC_{50} = 1.4 nM) and greater than 1000-fold selectivity over both MMP-2 and MMP-13. Unfortunately compound **6** is only weakly active at inhibiting LPS-stimulated TNF production in THP-1 cells[16] (IC_{50} > 3 μM). We now report on the enzyme and cellular activity of a series of analogs of **6**, substituted on the piperidine nitrogen, prepared in an effort to increase selectivity by taking advantage of differences between the TACE and MMP S1 subsites. For example, in MMP-13 Y150 and L151 appear to constrict its S1 subsite, presenting the possibility that bulky P1 groups will provide enhanced selectivity for TACE over this enzyme.

The desired analogs, **17**, were prepared via two synthetic routes as described in Schemes 1 and 2. In the first route (Scheme 1), ethyl piperidine-4-carboxylate **7** was Boc-protected followed by α-iodomethylation to afford ester **9**. Benzene thiol **11**, prepared from the reaction of readily available 4-butynyloxybenzene sulfonyl chloride **10**[11] with PPh_3, was then reacted with **9** in the presence of K_2CO_3 to give sulfide **12**. Sulfide **12** was next oxidized

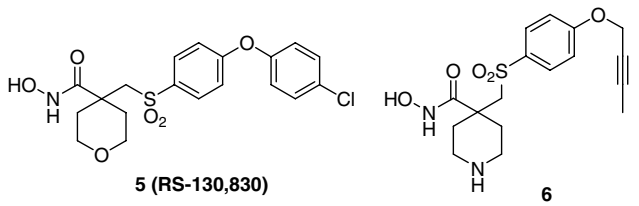
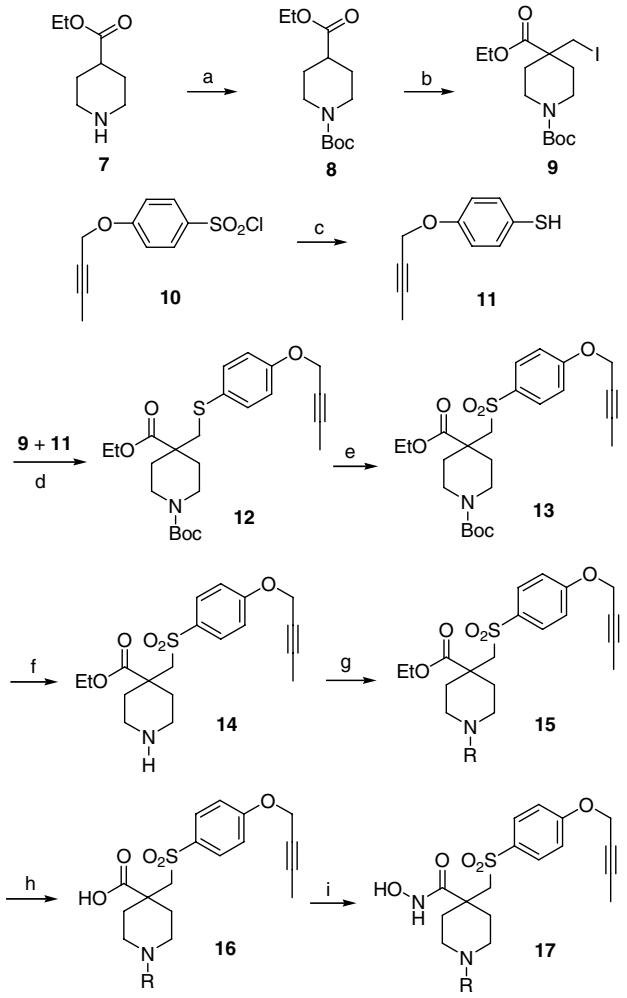


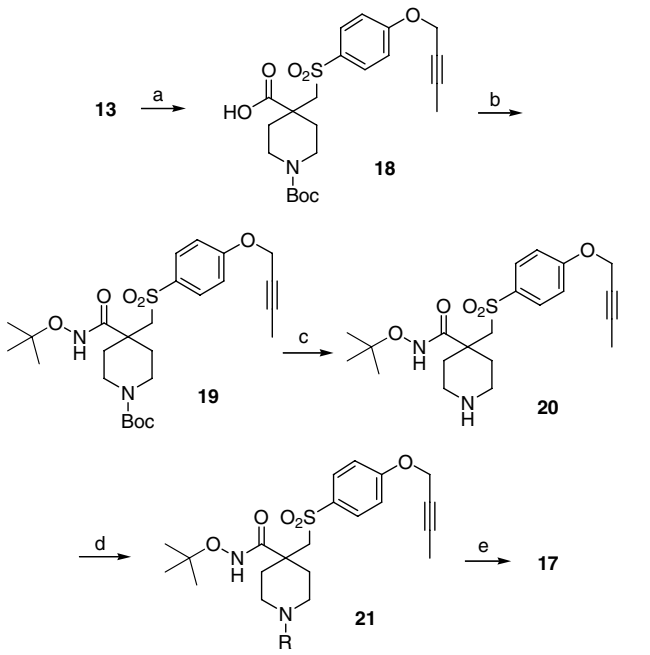
Figure 2. β-Sulfone piperidine hydroxamic acid MMP and TACE inhibitors.



Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, THF, rt, 2 h, 97%; (b) LDA, THF, −50 °C, 1 h, CH_2I_2, rt, 10 h, 95%; (c) PPh_3, cat. DMF, CH_2Cl_2, rt, 60%; (d) K_2CO_3, DMF, rt, 18 h, 99%; (e) Bu_4N oxone, CH_2Cl_2, rt, 20 h, 95%; (f) 4 M HCl in dioxane, CH_2Cl_2–MeOH, rt, 1 h, 80%; (g) R′-Br or R′COCl or R′SO_2Cl or R′NCO, TEA, DMAP, CH_2Cl_2, rt, 12 h, 85–95%; (h) 1 N NaOH, THF–MeOH, reflux, 3 h, 90%; (i) HOBT, EDC, 50% NH_2OH, DMF, rt, 18 h, 41%; or i. $(COCl)_2$, cat. DMF, CH_2Cl_2, rt; ii. 50% NH_2OH, THF, rt, 50%.

to sulfone **13** using tetrabutylammonium oxone and the Boc group was subsequently removed with HCl to provide key intermediate **14**. Reaction of **14** with a variety of electrophiles including alkyl halides, acid chlorides, sulfonyl chlorides, and isocyanates, gave a diverse set of β-sulfone piperidine esters, **15**. Hydrolysis of **15** was followed by the conversion of the resulting acids **16** into the desired β-sulfone piperidine hydroxamic acids **17**.

An alternative synthetic route to derivatives **17** is shown in Scheme 2. Thus, ester **13** was hydrolyzed to afford acid **18**, and **18** was then reacted with *O*-(*tert*-butyl)hydroxylamine under peptide coupling conditions to provide protected hydroxamic acid **19**. The Boc-protected piperidine nitrogen of **19** was selectively removed with TMSOTf/2,6-lutidine to give piperidine **20**. Reaction of **20** with various electrophiles afforded substituted piperidines **21** which were deprotected with TFA/CH_2Cl_2 to give the final products **17**.

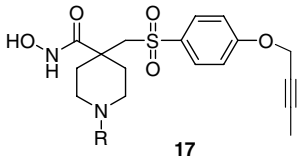


Scheme 2. Reagents and conditions: (a) 1 N NaOH, THF–MeOH, reflux, 3 h, 90%; (b) NH_2O-*t*-Bu, HOBT, EDC, DMF, rt, 20 h, 48%; (c) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 3 h, 100%; (d) R′-Br or R′COCl or R′SO_2Cl or R′NCO, TEA, DMAP, CH_2Cl_2, rt, 12 h, 85–95%; (e) TFA, CH_2Cl_2, rt, 5 h, 95%.

The prepared compounds **17** were tested in a FRET assay using the catalytic domain of TACE[16] and selected analogs were then profiled for selectivity against MMP-1, MMP-2, MMP-9, MMP-13 and MMP-14 (Table 1). Compounds were also evaluated for their ability to inhibit LPS-stimulated TNF production in Raw cells and in human whole blood (HWB).[16]

As shown in Table 1, compounds **17a**–**17x** all have excellent TACE enzyme activity with low nanomolar IC_{50}s. Also, most of these analogs show greater than 1000-fold selectivity for TACE over MMP-1, presumably due to the butynyloxy P1′ group, in contrast to cyclic sulfonamide hydroxamate analogs (e.g., **4**) bearing the same tail. Among the compounds tested in the MMP-1 assay, only benzyl sulfonamide **17r**, for reasons that are unclear, is less than 500-fold selective for TACE. In addition, most of compounds screened against MMP-14 show greater than 240-fold selectivity for TACE over MMP-14, with the exception of **17n** (57-fold) and **17r** (12-fold). Compound **17a** has good activity in Raw cells and moderate activity in human whole blood, but shows only moderate TACE selectivity against MMP-2 (37-fold) and MMP-13 (54-fold). Butynyl derivative **17b** shows a level of selectivity similar to **17a**, but with reduced cell and HWB activity. Of the alkyl amides, **17c**–**17j**, none had greater than 100-fold selectivity over MMP-13, but the acetyl and hexyl

Table 1. In vitro potency of butynyloxy β-sulfone piperidine hydroxamic acid



17

Compound	R	TACE[a]	MMP-1[a]	MMP-2[a]	MMP-9[a]	MMP-13[a]	MMP-14[a]	Raw cells[b]	HWB[c]
17a	CH_2-4-pyridyl	2.1	7250	77	—	114	784	0.11	2.7
17b	CH_2CCCH_3	4.8	—	249	—	327	—	0.62	11
17c	$COCH_3$	2.1	4670	341	591	155	963	0.49	6.5
17d	$CO(CH_2)_2CH_3$	2.2	4150	49	—	24	725	0.06	28
17e	$CO(CH_2)_2OCH_3$	6.0	4700	24	—	13	891	0.51	12
17f	$CO(CH_2)_4CH_3$	1.8	5460	553	1070	—	4850	1.5	24
17g	COC_6H_{11}	2.3	—	—	—	—	—	—	14
17h	$COCH_2N[(CH_2)_2]_2O$	3.4	6270	113	879	69	2080	1.2	3.4
17i	$CO(CH_2)_3N(CH_3)_2$	4.9	7970	302	2120	177	2740	1.8	5.2
17j	$COC(CH_3)[CH_2OH]_2$	2.2	3320	54	972	54	889	0.15	2.4
17k	COPh	1.0	3040	62	454	69	489	0.40	2.5
17l	CO–(2-CH_3Ph)	2.0	1850	15	68	14	488	0.24	2.4
17m	CO–4-pyridyl	2.1	3010	46	191	21	553	0.03	1.3
17n	CO–(2-NH_2Ph)	1.7	—	16	—	39	97	0.19	2.9
17o	CO–(4-CH_3Ph)	1.4	6980	111	907	79	1515	0.57	4.8
17p	CO–2-thiophene	<1.0	2700	19	—	10	257	0.07	24
17q	SO_2CH_3	2.3	—	518	—	—	5910	0.18	4.7
17r	SO_2CH_2Ph	<1.0	65	3.1	19	—	12	1.3	9.8
17s	$SO_2CH(CH_3)_2$	1.5	8780	355	1670	230	4710	1.0	1.5
17t	$SO_2(CH_2)_3CH_3$	2.2	—	44	19	—	1380	—	10
17u	SO_2Ph	2.5	—	—	—	—	—	0.44	13
17v	$CONH(CH_2)_4CH_3$	4.0	—	—	—	—	—	3.7	>50
17w	$CON(CH_3)Ph$	1.0	—	—	—	—	—	0.45	14
17x	$CON(CH_2CH_3)_2$	1.4	6600	345	—	74	1900	0.17	3.3

[a] IC_{50}, nM.
[b] Inhibition of LPS-stimulated TNF-α production in Raw cells, IC_{50}, μM.
[c] Inhibition of LPS-stimulated TNF-α production in human whole blood, IC_{50}, μM.

amides, **17c** and **17f**, provided excellent selectivity over both MMP-2 and MMP-9, while amide **17e** bearing an ether tail was far less selective. Amides **17h**–**17j**, bearing amine and alcohol tails, were less than 100-fold selective over MMP-2 but retained significant selectivity over MMP-9. Compound **17d** is the most potent alkyl amide analog in Raw cells (IC_{50} = 60 nM) but only diol **17j** had moderate potency in both Raw cells and HWB. Aryl and heteroaryl amides, **17k**–**17p**, are in general more potent in the TACE FRET assay than the alkyl amides. The unsubstituted benzamide **17k** and 4-methylbenzamide derivative **17o** are both 50-fold selective for TACE over MMP-2 and MMP-13, with greater than 400-fold selectivity over MMP-9. In contrast, the ortho-substituted benzamides **17l** and **17n** are less than 20-fold selective over MMP-2 and MMP-13. Pyridyl amide **17m** is slightly less potent than **17k** against TACE and slightly more potent than **17k** against MMPs-2, -9, and -13. Amides **17m** and **17p** show excellent activity in Raw cells, with IC_{50}s of 30 and 70 nM, respectively. In the case of pyridyl amide **17m** the potent cellular activity carries over to activity in HWB, providing the most active analog of this series in this assay, 2-fold better than the more basic picolyl analog **17a**. However, as for butyl amide **17d**, thienyl amide **17p** is dramatically less active in HWB than in Raw cells. Analysis of differences in clog *P*, permeability, and protein binding does not provide an adequate explanation for the discrepancy between activity in Raw cells and HWB for most analogs.

As expected, the piperidine sulfonamides, **17q**–**17u**, are also all potent inhibitors of cell-free TACE enzyme. Methanesulfonamide **17q** shows good selectivity over MMP-2, but the benzyl and *n*-butyl sulfonamides, **17r** and **17t**, are both minimally selective over MMP-2 and MMP-9. However, surprisingly, isopropyl sulfonamide **17s** shows greater than 100-fold selectivity over all five MMPs screened, with greater than 1000-fold selectivity over MMP-1, MMP-9 and MMP-14. This favorable selectivity profile may be due to a combination of both the steric bulk of isopropyl P1 moiety and an electronic effect of the P1 sulfonamide functionality. Coincidentally, this compound is also among the most potent of the β-piperidine sulfone hydroxamates in human whole blood, with an IC_{50} of 1.5 μM, although its activity in Raw cells is only moderate. Among the ureas prepared, **17v**–**17x**, the bulky diethyl urea **17x** is greater than 200-fold selective over MMP-2, but only approximately 50-fold selective over MMP-13. Of the ureas, compound **17x** also has the best activity in Raw cells and moderate activity in HWB. Clearly the isopropyl sulfonamide P1 group of **17s** provides the best combination of activity against TACE, selectivity over a variety of MMPs, and activity in human whole blood.

Due to its excellent potency and selectivity, **17s** was tested for its ability to inhibit LPS-stimulated production of TNF-α in a mouse after oral dosing.[16] At 25 mg/kg po, compound **17s** provided greater than 72% inhibition of TNF-α production 1 h after administration of LPS. In a rat pharmacokinetic study, compound **17s**, dosed at 5 mg/kg iv, had a short half-life (0.5 h), and moderate clearance (26 mL/min/kg), AUC_{0-inf} (3343 ng h/mL), and volume of distribution (0.7 L/kg).

In summary, we have explored the effect of variations in the P1 moiety on the potency, selectivity, and cell activity of a series of butynyloxyphenyl β-sulfone piperidine hydroxamic acid TACE inhibitors. All of these compounds were found to be potent inhibitors of TACE in an isolated enzyme assay and several performed well in cell-based assays in Raw cells and in human whole blood (HWB). In particular, compound **17s** is a 1.5 nM inhibitor of TACE that possesses greater than 100-fold selectivity over MMP-1, -2, -7, -8, -9, -13, and -14, as well as good activity (IC_{50} = 1.5 μM) in HWB. Furthermore, in vivo oral activity of **17s** was demonstrated in a mouse model of LPS-stimulated TNF-α production. This validates the strategy of focusing on structural changes of the P1 group on this scaffold to dramatically improve selectivity while retaining sufficient cell activity. Compound **17s** is an excellent lead for the further optimization of this scaffold through variation of the P1 moiety.

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16. For descriptions of all the in vitro and in vivo assays used herein, see Ref. 13a.