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Acetylenic TACE inhibitors. Part 2: SAR of six-membered cyclic sulfonamide hydroxamates

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Abstract—The SAR of a series of potent sulfonamide hydroxamate TACE inhibitors bearing a butynyloxy P1′ group was explored. In particular, compound **5k** has excellent in vitro potency against TACE enzyme and in cells, and oral activity in an in vivo model of TNF-α production and a collagen-induced arthritis model.

The ability of biologics that modulate levels of the pro-inflammatory cytokine TNF, including TNF-soluble receptors and TNF antibodies, to effectively treat rheumatoid arthritis (RA), has fueled the search for orally active mediators of TNF.[1] Small molecule inhibitors of TNF-α converting enzyme (TACE/ADAM-17), the metalloprotease responsible for the cleavage of the 26 kDa membrane-bound form of TNF, may offer an effective treatment for RA by limiting the release of 17 kDa soluble TNF.[2,3]

A variety of small molecule TACE inhibitors possessing excellent enzyme and cellular potency have been disclosed.[4,5] Some of these compounds inhibit TACE while sparing the structurally similar MMPs,[4] in an effort to avoid dose-related toxicities displayed by many MMP inhibitors in clinical trials.[6] Broad spectrum MMP/TACE inhibitors[5] are of interest, since a variety of MMPs have been found to be over-expressed in RA synovial tissue and have been implicated in the destruction of cartilage in RA joints.[7]

We,[8] and others,[9] have previously disclosed several series of sulfonamide and sulfone hydroxamic acid TACE inhibitors bearing novel propargylic P1′ groups, exemplified by compounds **1–4** (Fig. 1). These compounds are excellent inhibitors of TACE in a cell-free enzyme assay and many also potently inhibit the LPS-induced release of soluble TNF in THP-1 cells. Selectivity for TACE over MMP-1, oral activity in an in vivo mouse model of TNF-α production, and oral activity in a mouse collagen-induced arthritis (CIA) efficacy model has also been demonstrated. We were interested in extending the use of the butynyloxy P1′ group to a series of sulfonamide hydroxamates, **5**, derived from morpholine, thiomorpholine, and piperazine scaffolds (Fig. 2). The ability of sulfonamide hydroxamate derivatives of six-membered ring cyclic amino acids, bearing a variety of P1′ groups, to provide potent inhibitors of MMPs and cell-free TACE, including one that advanced to clinical trials, is well documented and made these scaffolds

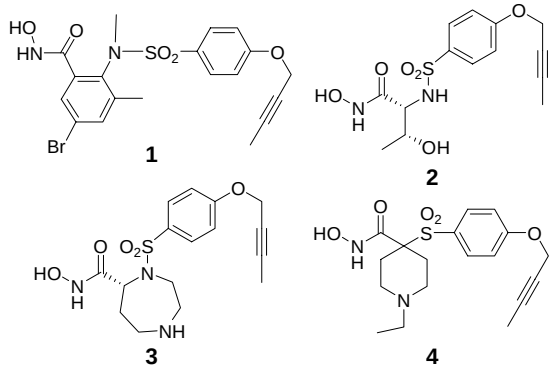

Figure 1. Wyeth butynyloxy P1′ TACE inhibitors.

Keywords: TACE; MMP; Hydroxamate; Rheumatoid arthritis.
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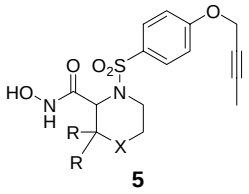
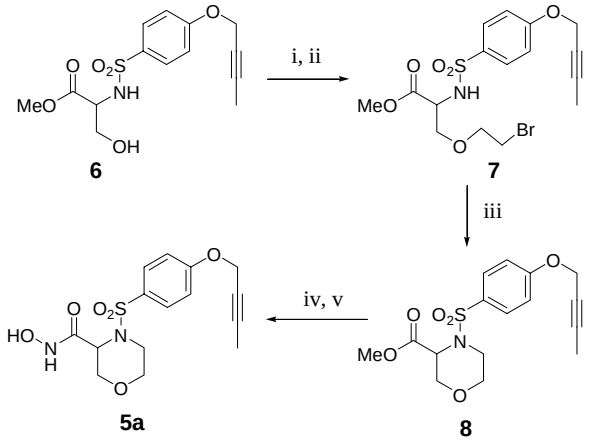


Figure 2. Six-membered cyclic α-sulfonamide hydroxamates.

particularly interesting in our search for more potent, orally active inhibitors of TACE.[10]

Sulfonamide hydroxamic acids **5** (Table 1) were prepared as shown in Schemes 1–3. Thus, in Scheme 1, sulfonamide **6**[8f] reacted with triphenylphospine and DEAD to afford an intermediate aziridine that was then converted into bromide **7** with bromoethanol and BF_3-etherate.[11] Ring closure of **7** proceeded in the presence of potassium carbonate in DMF to give the desired morpholine scaffold **8**. Hydrolysis of ester **8** with lithium hydroxide followed by conversion into the acid chloride and subsequent reaction with hydroxylamine gave the racemic hydroxamic acid **5a**.

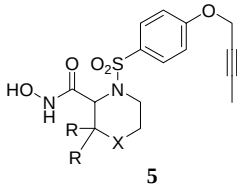
The thiomorpholine derivatives **5b**, **5k**, and **5l** resulted from initial S-alkylation of the thiol amino acid with bromoethanol followed by sulfonylation with 4-butynyloxybenzenesulfonyl chloride and formation of the *t*-butyl ester with *t*-butyl bromide to give alcohol **10** (Scheme 2). The alcohol was converted into the corresponding bromide and then cyclized with potassium carbonate to give **11**. Deprotection of the ester with TFA followed by hydroxamate formation then gave the thiomorpholines **5b**, **5k**, and **5l**. Of these, **5b** and **5l** were racemic while **5k**, derived from D-penicillamine was obtained in optically pure form.



Scheme 1. Reagents: (i) PPh_3, DEAD; (ii) $Br(CH_2)_2OH$, BF_3-Et_2O; (iii) K_2CO_3; (iv) LiOH; (v) (a) $(COCl)_2$, DMF; (b) NH_2OH.

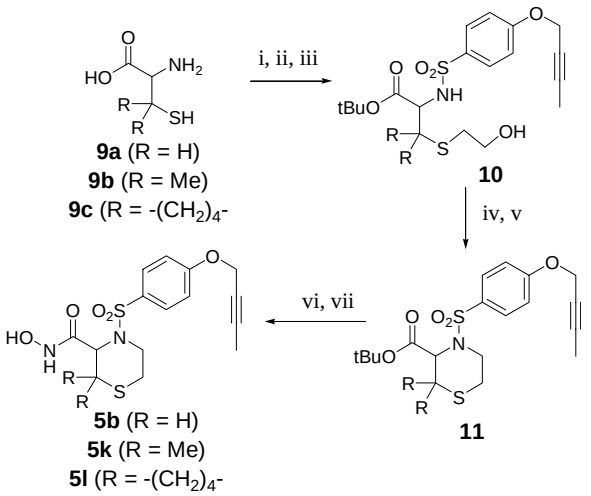
The piperazine sulfonamides were prepared from the mono-protected racemic piperazine ethyl ester **12** (Scheme 3). Sulfonylation with 4-butynyloxybenzenesulfonyl chloride afforded sulfonamide **13**. The NH-piperazine was prepared by ester hydrolysis of **13**, conversion of the resulting carboxylic acid into the corresponding hydroxamate, accomplished with hydroxylamine after activation with EDC/HOBT, and removal of the Boc protecting group with TFA to give **5c**. *N*-Substituted piperazines were available via removal of the Boc group of **13** followed by functionalization of the piperazine nitrogen to provide a tertiary amine, amides, ureas, and sulfonamides **14**. Hydrolysis of the ester with sodium or lithium hydroxide gave the carboxylates that were subsequently converted into the desired racemic hydroxamates, **5d**–**5j** with EDC/HOBT or oxalyl chloride, followed by hydroxylamine.

Table 1. In vitro potency of cyclic sulfonamide hydroxamic acids

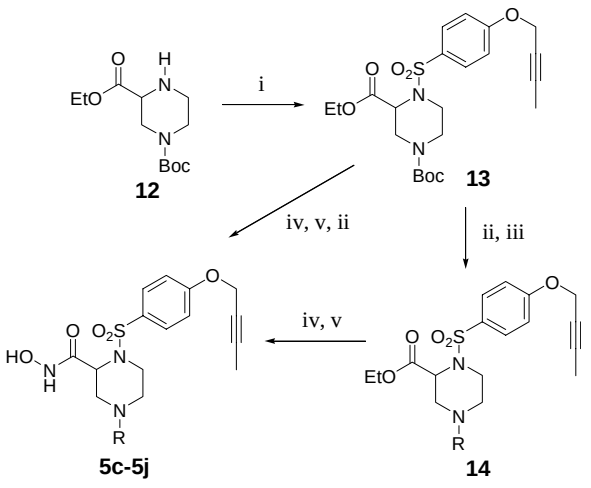


Comp	R	X	TACE[a]	THP[b]	MMP-1[a]	MMP-9[a]	MMP-13[a]
5a	H	O	5	80	162	170	26
5b	H	S	3	84	148	21	12
5c	H	NH	23	71	676	14	8
5d	H	NCH_2-3-Py	28	25	3197	108	49
5e	H	$NCOCH_3$	13	81	357	88	22
5f	H	NCO-2-C_4H_3S	12	86	498	251	119
5g	H	NCO_2CH_3	9	81	201	71	9
5h	H	NSO_2CH_3	7	81	96	51	6
5i	H	$NCON(CH_2CH_3)_2$	28	59	1752	221	97
5j	H	$NCOC_4H_8$	28	73	1248	209	83
5k (TMI-1)	CH_3	S	8	94	7	12	3
5l	$-(CH_2)_4-$	S	43	94	24	NT[c]	11

[a] IC_{50} (nM).
[b] % Inhibition at 3 μM.
[c] NT, not tested.



Scheme 2. Reagents: (i) $Br(CH_2)_2OH$, NaOH; (ii) 4-butynyloxybenzenesulfonyl chloride, Na_2CO_3; (iii) tBuBr, K_2CO_3; (iv) PPh_3, CBr_4; (v) K_2CO_3; (vi) TFA; (vii) (a) $(COCl)_2$, DMF or EDC, HOBT; (b) NH_2OH.



Scheme 3. Reagents: (i) 4-Butynyloxybenzenesulfonyl chloride, Na_2CO_3; (ii) TFA; (iii) R^1Cl, or R^1COCl, or CH_3SO_2Cl, or R^1R^2NCOCl; (iv) NaOH or LiOH; (v) (a) $(COCl)_2$, DMF; (b) NH_2OH.

All of the sulfonamide hydroxamic acids were tested in vitro[12] for their ability to inhibit MMP-1, MMP-9, MMP-13, and TACE.[13] The inhibition of these enzymes may help to prevent cartilage degradation in RA, and therefore may be therapeutically desirable.[8] However, inhibitors of TACE with various MMP inhibition profiles were also sought in order to gain insight into the possible source of musculoskeletal side effects seen in clinical trials of many broad-spectrum MMP inhibitors.[6]

The in vitro potencies for the cyclic sulfonamide hydroxamic acid analogs bearing a butynyloxy P1′ group are shown in Table 1.

A comparison of the potency and selectivity of the three heterocyclic sulfonamide hydroxamate scaffolds, **5a**–**5c** (Table 1), shows that morpholine **5a** and thiomorpholine **5b** are potent inhibitors of TACE enzyme in a cell-free assay. An X-ray crystal structure of **5b** was obtained (Fig. 3) and shows that the butynyloxy P1′ moiety is positioned in the center of the uniquely shaped channel connecting the S1′ and S3′ subsites of TACE.[14] Both **5a** and **5b** are also moderately selective, 30- and 50-fold, respectively, for TACE over MMP-1, and less than 5-fold selective over MMP-13. In addition, morpholine **5a** is more than 30-fold selective over MMP-9. In contrast, piperazine **5c**, a 23 nM inhibitor of TACE with 30-fold selectivity over MMP-1, is most potent against MMP-13 (IC_{50} = 8 nM) and MMP-9 (IC_{50} = 14 nM). The ability of compounds **5a**–**5c** to inhibit TNF production in LPS-stimulated THP-1 cells[15] parallels their potency in the cell-free TACE assay. Thus, morpholine **5a** and thiomorpholine **5b** provide 80% and 84% inhibition at 3 μM, respectively, while piperazine **5c** is slightly less potent, providing 71% inhibition (IC_{50}s were not determined). Although piperazine sulfonamide **5c** is less potent in cells than the morpholine and thiomorpholine, this scaffold was the most amenable to analog synthesis in pursuit of increased cellular potency.

The selected *N*-substituted piperazines **5d**–**5j** are all highly active inhibitors of cell-free TACE enzyme with only a 4-fold range in potency despite a wide variation in shape and size. However, differences are apparent in the selectivity profiles and cellular potencies of these analogs. Thus, picolyl derivative **5d**, a 28 nM inhibitor of TACE, is over 100-fold selective for TACE over MMP-1, but is unfortunately only weakly active in THP-1 cells. Acetamide **5e**, lacking a basic nitrogen in the piperazine ring, is somewhat more potent against TACE than **5d**, but is several times less selective than **5d** over MMP-1. Thienyl amide **5f** is equipotent to **5e** against TACE, with slightly improved selectivity over MMP-1, -9, and -13. Carbamate **5g** and sulfonamide **5h** are the most potent piperazine analogs against cell-free TACE, retaining excellent potency against MMP-13 as well, but lacking substantial selectivity over MMP-1. Compounds **5e**–**5h** are also equivalent in potency to the morpholine and thiomorpholine analogs, **5a** and **5b**, in THP-1 cells, and more active at 3 μM than analogs **5c** and **5d**, bearing a basic nitrogen. Urea derivatives **5i** and **5j** are less potent against TACE and in cells

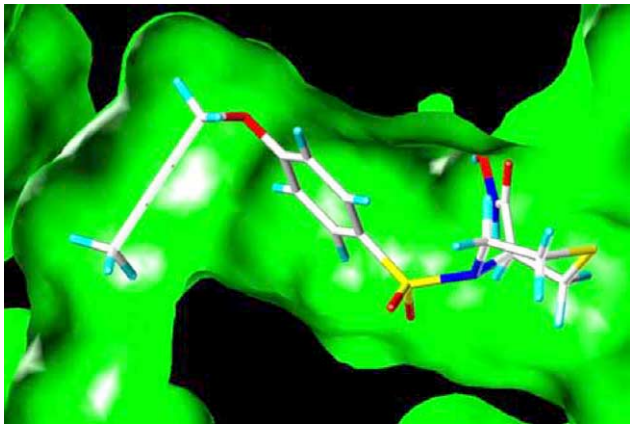


Figure 3. X-ray structure of compound **5b** bound to TACE.

than the less sterically bulky amide, carbamate, and sulfonamide analogs. But, this steric bulk may account for their relatively good selectivity, greater than 40-fold, for TACE over MMP-1. The dramatic differences in cellular activity seen in the piperazine series among compounds with similar levels of enzyme activity does not appear to correlate with any particular physical property. For example, the *c*Log *P* values for **5d**, **5i**, and **5j** are 2.1, 2.9, and 2.6, respectively, and their topological polar surface areas are virtually identical. Properties that have been postulated by others to impact activity in human whole blood are cell permeability and protein binding. However, there is less than 1% protein in the THP assay and we have not seen any correlation between permeability or protein binding, and cell activity.[16]

Although some of the analogs **5a**–**5j** demonstrate good cellular activity, increased potency in THP-1 cells was still desirable. Interestingly, appending two methyl groups on the thiomorpholine ring of **5b**, as in penicillamine derivative **5k** (TACE $IC_{50} = 8$ nM), abolishes selectivity for TACE over MMP-1 and improves activity in THP-1 cells, providing 94% inhibition of LPS-stimulated TNF production at 3 μM and an IC_{50} of 0.2 μM. Compound **5k** also potently inhibits LPS-stimulated TNF-α production in human whole blood with an IC_{50} of 0.3 μM. The loss of TACE selectivity over MMP-1 for **5k** is due to a 20-fold increase in potency against MMP-1, rather than a loss of TACE activity, indicative of beneficial interactions with the S2′ pocket of this enzyme. This is consistent with the SAR we have described for *N*-methyl sulfonamide hydroxamates derived from acyclic amino acids, wherein amino acids with lipophilic side chains afforded increased potency against MMP-1.[8c] To explore whether bulkier substituents were tolerated at this position on the thiomorpholine, particularly in terms of cellular potency, the spiro-fused cyclopentyl analog **5l** was also prepared. This compound was in fact more potent against both MMP-1 and MMP-13 than against TACE, although the excellent cellular potency of **5k** was retained.

The in vivo activity of most of the compounds in Table 1 was initially measured by their ability to inhibit the LPS-stimulated production of TNF-α after oral dosing in a mouse.[15] Analogs **5a**, **5b**, and **5h**, dosed at 50 mg/kg po, provided 88%, 75%, and 62% inhibition, respectively, of TNF-α levels 1 h after administration of LPS. The most potent analog in this model was penicillamine derivative **5k** (also designated TMI-1) with an ED_{50} of 5 mg/kg po. Compound **5k** is reproducibly active at reducing clinical severity scores in a mouse prophylactic collagen-induced arthritis (CIA) efficacy model at 10 mg/kg po bid.[15] Unfortunately, while **5k** has excellent bioavailability at 10 mg/kg in the DBA mouse (71%), it is poorly bioavailable at 10 mg/kg po in the rat (5%), and the dog (0%). Although this analog is permeable in Caco-2 cells and is not highly protein bound (~40%), its moderate solubility in simulated gastric and intestinal fluids (<75 μg/mL) and multiple metabolites (in vitro liver microsomes), including loss of the butynyl P1′ group, are issues that may contribute to its poor PK properties and present problems for its development as a therapeutic agent for RA.

In summary, we have synthesized a series of sulfonamide hydroxamate derivatives of six-membered cyclic amino acids bearing a butynyloxy P1′ group as inhibitors of MMPs and TACE. All of these compounds are potent inhibitors of TACE in an isolated enzyme assay, most are potent in THP-1 cells, and **5d** possesses greater than 100-fold selectivity for TACE over MMP-1. Oral activity has been demonstrated for several of these compounds in a mouse model of LPS-stimulated TNF-α production. Thiomorpholine (**5k**, TMI-1) is among the most potent sulfonamide hydroxamates described to date at inhibiting LPS-stimulated TNF production in cells, whole blood, and in vivo, and shows excellent oral potency in a standard model of human RA. Additional SAR information on the structural series exemplified by **5k**, and improvements of that lead, will be presented in due course.

Acknowledgments

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