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Acetylenic TACE inhibitors. Part 3: Thiomorpholine sulfonamide hydroxamates

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Abstract—A series of thiomorpholine sulfonamide hydroxamate TACE inhibitors, all bearing propargylic ether P1′ groups, was explored. In particular, compound **5h** has excellent in vitro potency against isolated TACE enzyme and in cells, oral activity in a model of TNF-α production and a collagen-induced arthritis model, was selected as a clinical candidate for the treatment of RA.

The commercial success of biologics, including Enbrel® and Remicade®, that modulate levels of both membrane-bound 26 kDa TNF and the soluble 17 kDa form of this pro-inflammatory cytokine has led to an intensive search for orally active small molecules that might be similarly effective in the treatment of rheumatoid arthritis (RA).[1]

One attractive approach for affecting TNF levels is the inhibition of TNF-α converting enzyme (TACE/ADAM-17), the metalloprotease responsible for the shedding of membrane-bound TNF, thereby reducing circulating levels of soluble TNF.[2] Among the compounds directed at this mechanism of action are selective inhibitors of TACE, including the clinical candidate BMS-561392 (**1**, Fig. 1),[3a,b] and those that inhibit enzymes from the related family of matrix metalloproteinases (MMPs) in addition to TACE, like PKF242-484 (**2**, Fig. 1)[3c] and clinical candidate Ro 32-7315 (**3**, Fig. 1).[3d] The issue of whether broad spectrum inhibition of TACE and MMPs, or more selective inhibition of TACE, would be optimal remains to be settled by RA clinical trials. Many broad spectrum MMP inhibitors have displayed dose-limiting toxicity in oncology and osteoarthritis clinical trials,[4] but the inhibition of MMPs that are overexpressed in synovial tissue and degrade cartilage in RA joints may provide a more effective therapeutic.[5]

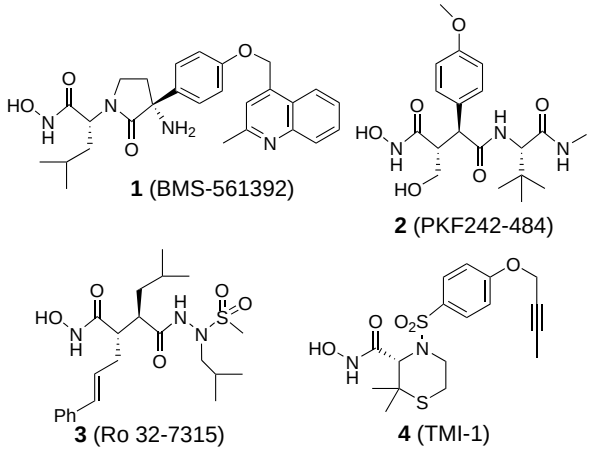

Figure 1. Literature TACE inhibitors.

We, and others, have previously disclosed several series of sulfonamide hydroxamic acid TACE inhibitors bearing novel propargylic P1′ groups, exemplified by TMI-1 (**4**, Fig. 1).[6] Compound **4** is an excellent

Keywords: TACE inhibitor; Thiomorpholine; Sulfonamide: hydroxamate; Rheumatoid arthritis.
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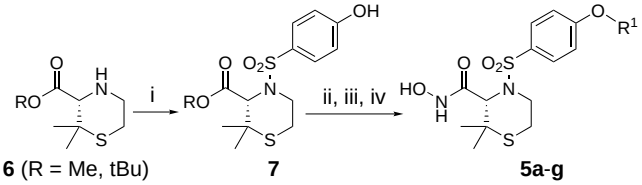
inhibitor of TACE and many MMPs, with good potency in human whole blood and potent oral activity in an animal model of RA.[6b] Unfortunately, poor solubility and poor bioavailability in rat and dog precluded the development of compound **4** as a clinical candidate. We now report our efforts to optimize the potency, physical properties, and bioavailability of the thiomorpholine sulfonamides by varying the P1′ terminus of these inhibitors and appending substituents on the thiomorpholine ring (**5a**–**y**, Table 1), resulting in a clinical candidate for the treatment of RA.

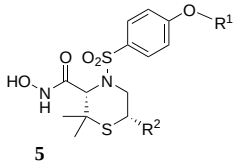
Initial attempts at increasing the potency and selectivity of **4** focused on the size of the alkynyl ether P1′ moiety and the position of the carbon–carbon triple bond (Scheme 1), which had previously been optimized on an anthranilate-derived scaffold.[6a] Sulfonylation of thiomorpholine methyl or *t*-butyl ester **6**[7] with in situ silylated 4-hydroxybenzenesulfonyl chloride provided phenol **7** after work-up with methanol.[8] The phenol next underwent Mitsunobu alkylation with the selected alcohol, followed by cleavage of the ester and conversion of the resulting carboxylate into the desired hydroxamic acids **5a**–**5g**.



Scheme 1. Reagents: (i) a—4-HOPhSO$_2$Cl, BTSA; b—MeOH; (ii) R^{1}OH, PPh$_3$, DEAD; (iii) HCl (g) or LiI; (iv) a—(COCl)$_2$, DMF; b—NH$_2$OH.

In an effort to achieve additional interactions between the protein and the inhibitor, we also examined alcohol, amine, and carbamate derivatives of the butynyl P1′ moiety that could potentially contact the glutamate and valine residues in the TACE S3′ subsite. The alcohols were prepared as shown in Scheme 2. The one carbon tether was prepared by direct Mitsunobu alkylation of **7** with 2-butyn-1,4-diol. Acetylation of the resulting alcohol gave **8**. Ester cleavage of **8** with TFA, and conversion of the unmasked carboxylic acid to the hydroxamic acid, provided **5h**. The two-, three-, and four-carbon tethers were prepared starting from THP-protected 3-butyn-1-ol, 4-pentyn-1-ol, and 5-hexyn-1-ol. These alkynes were metallated with *n*BuLi and the resulting anion

Table 1. In vitro potency of cyclic sulfonamide hydroxamic acids



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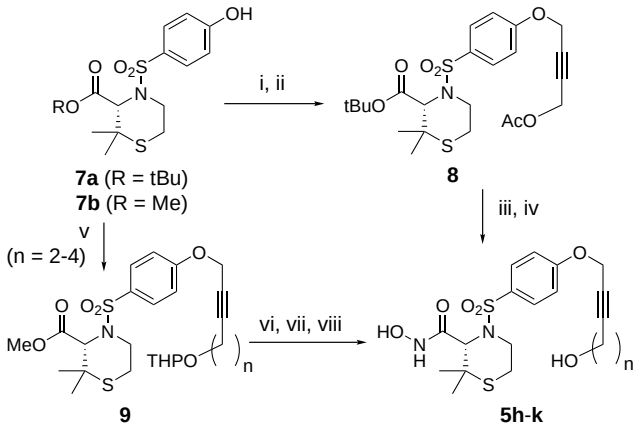
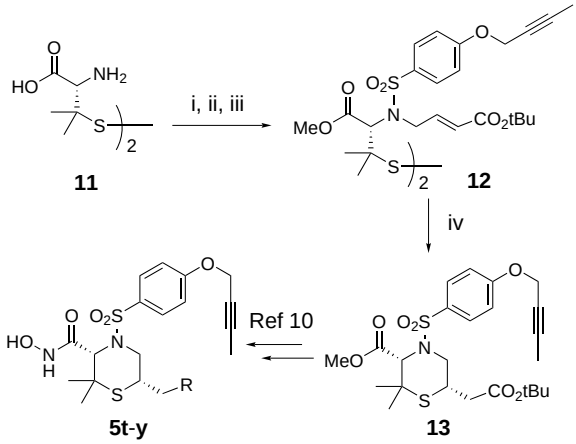
Compound	R^1	R^2	TACE[a]	THP[b]	MMP-l[a]	MMP-13[a]
4 (TMI-1)	CH_2CCCH_3	H	8	94/87	7	3
5a	CH_2CCH	H	19	91/76	1	1
5b	$(CH_2)_2CCH$	H	32	64/36	2	1
5c	$(CH_2)_3CCH$	H	40	38/16	11	8
5d	$CH_2CHCHCH_3$	H	35	80/50	7	2
5e	$(CH_2)_3CH_3$	H	42	38/11	7	9
5f	$CH_2CC(CH_2)_3CH_3$	H	23	82/48	29	7
5g	CH_2CCCCH	H	42	88/62	6	11
5h	CH_2CCCH_2OH	H	20	95/89	33	8
5i	$CH_2CC(CH_2)_2OH$	H	62	57/25	35	14
5j	$CH_2CC(CH_2)_3OH$	H	40	51/19	159	86
5k	$CH_2CC(CH_2)_4OH$	H	53	77/52	101	17
51	CH_2CCCH_2NHBoc	H	74	79/53	26	4
5m	$CH_2CC(CH_2)_2NHBoc$	H	112	37/14	300	7
5n	$CH_2CC(CH_2)_3NHBoc$	H	153	27/5	42	2
5o	$CH_2CC(CH_2)_4NHBoc$	H	199	70/40	87	4
5p	$CH_2CCCH_2NH_2$	H	67	40/10	97	8
5q	$CH_2CC(CH_2)_2NH_2$	H	138	4/0	1052	27
5r	$CH_2CC(CH_2)_3NH_2$	H	28	22/0	226	9
5s	$CH_2CC(CH_2)_4NH_2$	H	40	37/13	92	7
5t	CH_2CCCH_3	CH_2CO_2H	20	89/73	17	7
5u	CH_2CCCH_3	CH_2CONH_2	42	91/76	35	29
5v	CH_2CCCH_3	CH_2NH_2	57	94/78	21	24
5w	CH_2CCCH_3	$CH_2NHSO_2CH_3$	11	91/81	19	14
5x	CH_2CCCH_3	$(CH_2)_2OH$	15	90/74	21	23
5y	CH_2CCCH_3	$(CH_2)_2NH(CH_2CH_3)_2$	143	87/67	33	48

[a] IC_{50} (nM).
[b] % Inhibition at 3/1 μM.



Scheme 2. Reagents: (i) $HOCH_2CCCH_2OH$, PPh_3, DEAD; (ii) Ac_2O; (iii) HCl (g); (iv) a—$(COCl)_2$, DMF; b—NH_2OH; (v) $HOCH_2CC(CH_2)_nOTHP$, PPh_3, DEAD; (vi) LiI, EtOAc; (vii) a—$(COCl)_2$, DMF or EDC, HOBT; b—NH_2OH; (viii) PPTS.

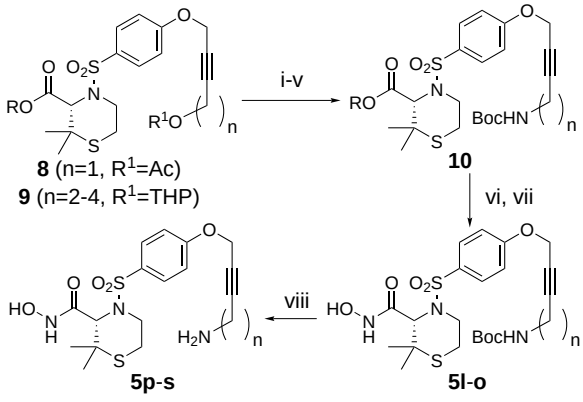


Scheme 4. Reagents: (i) a—HCl (g); b—$SOCl_2$, MeOH; (ii) 4-butynyloxybenzene sulfonyl chloride, TEA; (iii) $BrCH_2CH{=}CHCO_2t$-Bu, K_2CO_3; (iv) Bu_3P, THF, H_2O.

was quenched with formaldehyde. Mitsunobu alkylation of **7b** then gave **9**, followed by ester cleavage and hydroxamate formation, and subsequent removal of the THP moiety to give **5i**–**5k**.

The Boc carbamates **5l**–**5o** and the primary amine derivatives **5p**–**5s** were prepared from the protected alcohol intermediates **8** and **9** according to Scheme 3. Thus, after deprotection of **8** and **9** the alcohols were converted into the propargylic bromides, followed by displacement with sodium azide, reduction of the resulting azide to the primary amine, and Boc protection to give **10**. The ester moiety was next converted into the desired hydroxamate in two steps to give carbamates **5l**–**5o**. Removal of the Boc group then afforded the primary amines **5p**–**5s** as TFA or HCl salts.

Finally, analysis of computer models of compound **4** bound to the active site of TACE indicated that the 6-position (see R^2 in **5**, Table 1) of the thiomorpholine is solvent exposed, and that substituents affecting the physical properties of the molecule might be placed there with minimal loss of enzyme inhibitory activity. A similar strategy has been used on a series of pipecolic



Scheme 3. Reagents: (i) MeOH, K_2CO_3 (for **8**), PPTS (for **9**) (ii) PPh_3, CBr_4; (iii) NaN_3; (iv) Bu_3P, THF, H_2O; (v) Boc_2O; (vi) LiI; (vii) a—HOBt, EDC; b—NH_2OH; (viii) HCl (g) or TFA.

acid-based TACE inhibitors.[9] The preparation of these compounds, **5t**–**5y**, from D-penicillamine disulfide (**11**) utilizing a key diastereoselective intra-molecular Michael reaction to construct the thiomorpholine ring of **13** from **12**, has been reported elsewhere and is summarized briefly in Scheme 4.[10]

All of the sulfonamide hydroxamic acids were tested in vitro[11] for their ability to inhibit MMP-1, MMP-13, and TACE.[12] Activity against MMP-1 was assessed since the inhibition of this enzyme had been postulated to contribute to musculoskeletal side effects seen for MMP inhibitors.[4] The inhibition of MMP-13 was measured since this may help prevent the degradation of cartilage in RA.[5] The ability of compounds to inhibit TNF production in LPS-stimulated THP-1 cells was also assessed, although IC_{50}s were determined for only the most active analogs.[13] The in vitro potencies for the cyclic sulfonamide hydroxamic acid analogs bearing a variety of P1′ groups are shown in Table 1.

As for the analogs of anthranilate-based TACE inhibitors,[6a] the shorter propargyl ether P1′ analog **5a** is substantially more active than butynyl ether derivative **4** against MMP-1, while slightly less active against TACE. Increasing the length of the linker between the alkyne and the P1′ ether oxygen (**5b**–**5c**) progressively decreased MMP-1 and TACE activity, and activity against LPS-stimulated TNF production in THP-1 cells. The *trans*-olefin analog **5d** is 4-fold less potent than **4** against cell-free TACE and also slightly less active than **4** in THP-1 cells. This trend continues with the fully saturated butyl ether P1′ derivative **5e**, which has dramatically less cellular activity than **4** and **5d**, though it is essentially equipotent to **5d** against cell-free TACE. Lengthening of the butynyl ether to the heptynyl ether **5f** or the rigid diyne **5g** results in a slight loss of activity against both cell-free TACE and in cells. That analogs **5f** and **5g** do not increase selectivity for TACE over MMP-1, though the P1′ groups of both can clearly extend past the arginine side chain that normally forms the base of the shallow MMP-1 S1′ pocket, confirms that this residue

is mobile and can move to accommodate larger P1′ substituents on the ligand.[14] All of compounds **5a**–**5g** remain potent inhibitors of MMP-13.

The alcohols **5h**–**5k** were all less active than the butynyl analog **4** in the TACE FRET assay, with the shortest analog, **5h**, being the most potent. TACE activity does not fall off substantially with increasing length, but activity in THP cells decreases dramatically in going from **5h** (89% inhibition at 1 μM, IC_{50} = 140 nM) to the pentynyl and hexynyl alcohols **5i** and **5j** (<25% inhibition at 1 μM). Interestingly, the heptynyl alcohol **5k** recovers substantial cell activity (52% inhibition at 1 μM), relative to **5i**–**j**. The same general trend is seen for carbamates **5l**–**5o**. Despite their unimpressive activity against TACE enzyme, at least 80-fold less potent than **4**, both **5l** and **5o** display modest cellular activity (⩾40%) at 1 μM, while **5m** and **5n** are only weakly active even at 3 μM. The amines **5p** and **5q** are essentially equivalent in activity to their corresponding carbamates, **5l** and **5m**, against TACE, but are far less potent in the THP cellular assay. Furthermore, the hexynyl and heptynyl amines, **5r** and **5s**, are both approximately 5-fold more active in the TACE FRET assay than the analogous carbamates, **5n** and **5o**, but are less active in cells. Although all of the amines are only weakly active in cells, the butynyl and heptynyl analogs are again the most potent, as in the alcohol and carbamate series. All of the alcohols, carbamates, and amines, **5h**–**5s**, maintain excellent activity against MMP-13, with little or no selectivity for TACE over MMP-1.

An X-ray crystal structure has been obtained for **5p** bound to the active site of TACE (Fig. 2).[15] It is interesting to note that the amine moiety of **5p** is within hydrogen bonding distance to both a valine residue and a glutamate residue in the S3′ pocket of TACE, yet it is less active against the enzyme than **4**, which makes neither of these contacts.

The in vitro activity of the 6-substituted thiomorpholines **5t**–**5y** demonstrates that a variety of functionality is tolerated at this position, as was expected. Thus, the carboxylic acid **5t** is only 2-fold less active than **4** against cell-free TACE and slightly less active than **4** in THP cells at 1 μM. The corresponding primary amide **5u** and the primary amine **5v** are at least 5-fold less active than **4** in the FRET assay, but still sub-micromolar in cells. Sulfonamide **5w** and alcohol **5x** are the most potent of the 6-substituted thiomorpholines in the TACE FRET assay, similar in potency to **4**, and both are sub-micromolar inhibitors in THP cells. Diethylamine **5y**, like the other analog bearing a basic amine at the thiomorpholine 6-position (**5v**), loses significant enzyme activity in the FRET assay, 18-fold compared to **4**, but is still reasonably potent in THP cells, affording 67% inhibition of LPS-stimulated TNF production at 1 μM. We have previously noted that discrepancies between the level of enzyme activity in the TACE FRET assay and in THP cells are frequently not attributable to cell permeability and protein binding issues.[16]

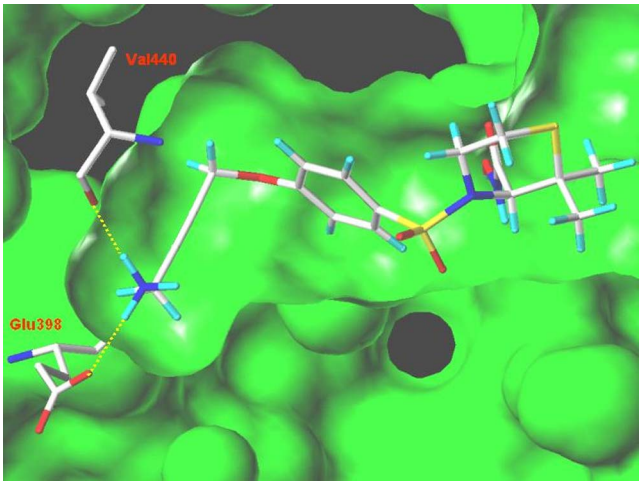


Figure 2. X-ray structure of compound **5p** bound to TACE.

The in vivo activity of the compounds in Table 1 with the greatest activity in the THP assay was initially measured by their ability to inhibit the LPS-stimulated production of TNF-α after oral dosing in a mouse.[13] Of compounds **5a**–**5y**, several compounds equaled or exceeded the level of activity of **4** in this model at a 50 mg/kg po dose. When dosed orally at 50 mg/kg, **5h**, **5v**, **5x**, and **5y** each provide ⩾95% inhibition of TNF-α levels one hour after administration of LPS. The most potent analog in this model is propargylic alcohol derivative **5h** with an ED_{50} of 5 mg/kg po. Analogs **5h** and **5v** were also examined in a mouse prophylactic collagen-induced arthritis (CIA) efficacy model,[13] using an LPS boost, and both gave statistically significant ($p \leqslant 0.05$) reductions in clinical severity scores at 10 mg/kg bid po. In fact, in this model a 10 mg/kg po dose of **5h** provides a > 50% reduction in clinical severity score ($p \leqslant 0.05$, $n = 15$), comparable to a 30 μg qd dose of Enbrel®. Also, in human whole blood **5h** inhibits LPS-stimulated TNF production with an IC_{50} of 300 nM. Analysis of in vitro stability of **5h** in liver microsomes from rat, dog, monkey, and human shows diminished levels of metabolites resulting from loss of the P1′ moiety, as compared to **4**. In addition, **5h** is permeable in Caco-2 cells (Mean $P_{app} = 2.2 \times 10^{-6}$ cm/s), is not highly protein bound (~50%), and has vastly improved solubility in simulated gastric and intestinal fluids (>1.5 mg/mL) as compared to **4** (<0.08 mg/mL). Perhaps as a result of these properties, bioavailability of **5h** at 10 mg/kg (mouse: 24%, rat: 8%, and dog: 36%) is in general better than that of **4** (mouse: 71%, rat: 5%, and dog: 0%), particularly in dogs.

In summary, we have expanded a series of thiomorpholine sulfonamide hydroxamates bearing a propargylic P1′ group as inhibitors of MMPs and TACE. One of these compounds, **5h**, has activity equivalent to that of compound **4** in an animal model of RA, but with improved solubility and PK properties, and has been advanced to clinical trials. The complete pharmacological profile of propargylic alcohol **5h** (TMI-005) will be reported in due course.[17]

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