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Design and synthesis of 3,3-piperidine hydroxamate analogs as selective TACE inhibitors

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Abstract—Structure-based methods were used to design β-sulfone 3,3-piperidine hydroxamates as TACE inhibitors with the aim of improving selectivity for TACE versus MMP-13. Several compounds in this series were synthesized and evaluated in enzymatic and cell-based assays. These analogs exhibit excellent in vitro potency against isolated TACE enzyme and show good selectivity for TACE over the related metalloproteases MMP-2, -13, and -14.

TACE (TNF-α converting enzyme, ADAM-17) is the zinc protease responsible for the release of soluble TNF-α (tumor necrosis factor-α) from parent membrane-bound pro-TNF-α.[1] TNF-α, a cytokine, is an important mediator of immuno-inflammatory responses of other pro-inflammatory cytokines. These cytokines have been linked to the pathogenesis of rheumatoid arthritis (RA)[2] and are involved in promoting inflammation as well as bone and cartilage destruction. The clinical success of TNF-α soluble receptor etanercept (Enbrel®)[3] and TNF-α monoclonal antibodies infliximab (Remicade®)[4] and adalimumab (Humira®)[5] has validated TNF as a target for the treatment of inflammatory diseases such as RA and psoriasis. While these biologics are effective, they are costly and must be administered via parenteral injection. The development of orally active small molecule TACE inhibitors is therefore a highly desirable goal for the treatment of RA and related diseases.

In the past few years, a number of selective small molecule inhibitors of TACE, as well as more broad spectrum inhibitors of TACE and related matrix metalloproteases (MMPs), have been reported in the literature.[6] Because various MMPs are overexpressed in RA synovial tissue and contribute to joint destruction,[7] it may be therapeutically advantageous to inhibit such MMPs in addition to TACE. However, since side effects from broad spectrum MMP inhibitors have been observed in clinical studies,[8] more selective inhibitors of TACE may demonstrate improved safety margins on long term dosing.

Earlier efforts at Wyeth led to the discovery of TACE inhibitors bearing a butynyloxy P1′ moiety that have shown excellent in vitro potency against TACE and good selectivity over some MMPs (e.g., MMP-1 and -9).[9–12] Structural analysis suggests that this particular P1′ moiety, on some inhibitor scaffolds, introduces a level of selectivity over various MMPs because of its tight fit in the channel between the S1′ and S3′ pockets of TACE, and the inability of some MMPs to accommodate its length and rigidity. The selectivity of these compounds over MMPs that possess deep S1′ pockets (e.g., MMP-13) generally remains low, but varies depending on the scaffold that bears the hydroxamic acid. Two such analogs, thiomorpholine–sulfonamides **1a** and **1b** (Fig. 1), are orally bioavailable dual TACE/MMP inhibitors with excellent potency in human whole blood.[10] Compound **1b** has entered clinical trials for the treat-

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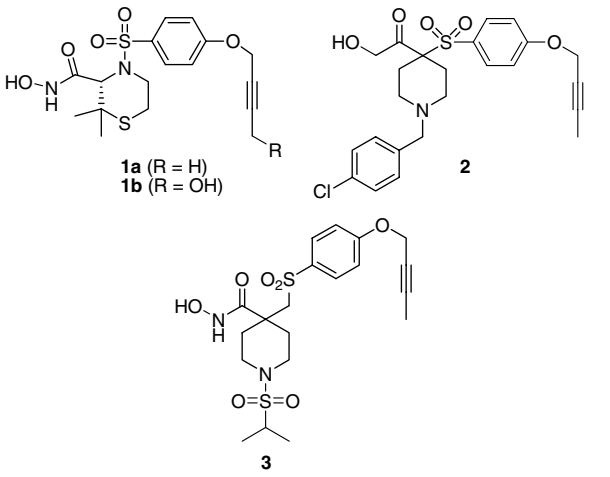


Figure 1. Thiomorpholine sulfonamide and piperidine sulfone TACE inhibitors.

ment of RA.[10c] While these thiomorpholines show little selectivity for TACE versus MMPs, we have found that a series of α-sulfone piperidines, exemplified by compound **2**, exhibit good in vitro potency against TACE and some selectivity for TACE over MMP-1, -9, and -13.[11] Similarly, 4,4-piperidine β-sulfone hydroxamic acid **3** (Fig. 1) has excellent TACE activity (IC_{50} = 1.5 nM) and greater than 150-fold selectivity over both MMP-2 and -13.[12]

The selectivity exhibited by some 4,4-piperidine β-sulfone TACE inhibitors is believed to reflect structural differences between the S1 pocket of TACE and those of the MMPs.[13] Modeling analysis has shown that the S1 pocket of TACE tolerates bulkier P1 substituents more than the S1 subsite of many MMPs. In MMP-13, the amino acids Ile 159 and Tyr 151 appear to constrict the S1 pocket, while in TACE the corresponding residues, Thr 347 and Lys 315, leave a relatively expanded S1 pocket (Fig. 2).

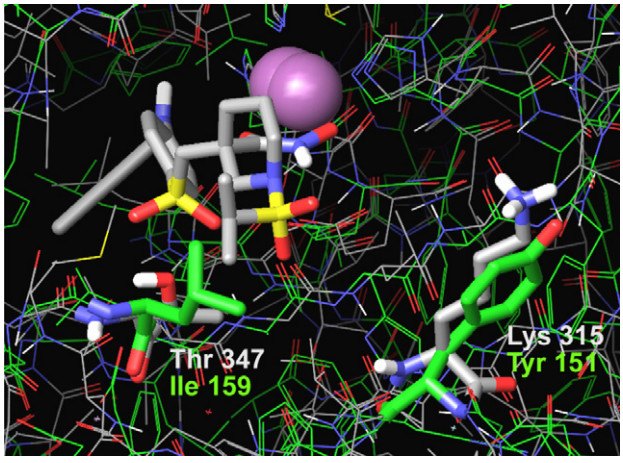


Figure 2. Model of a 3,3-piperidine sulfone **12l** bounced to TACE superimposed on MMP13 (green).

To apply these observations to the design of TACE inhibitors and exploit the differences in the TACE and MMP S1 pockets, we sought to introduce sterically demanding P1 groups at the piperidine nitrogen of a 3,3-piperidine scaffold in order to increase selectivity for TACE over MMP-13 (Figs. 2 and 3).

The desired 3,3-piperidine β-sulfone hydroxamates were prepared via the synthetic route shown in Scheme 1. Ethyl piperidine-3,3-carboxylate **4** was Boc protected and α-iodomethylation of **5** afforded ester **6**. Alkylation

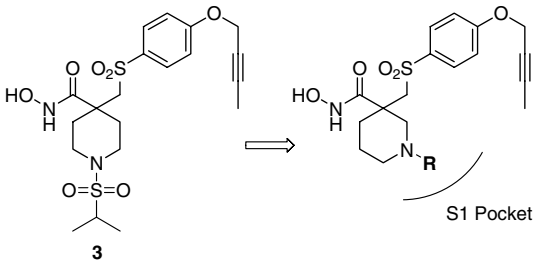
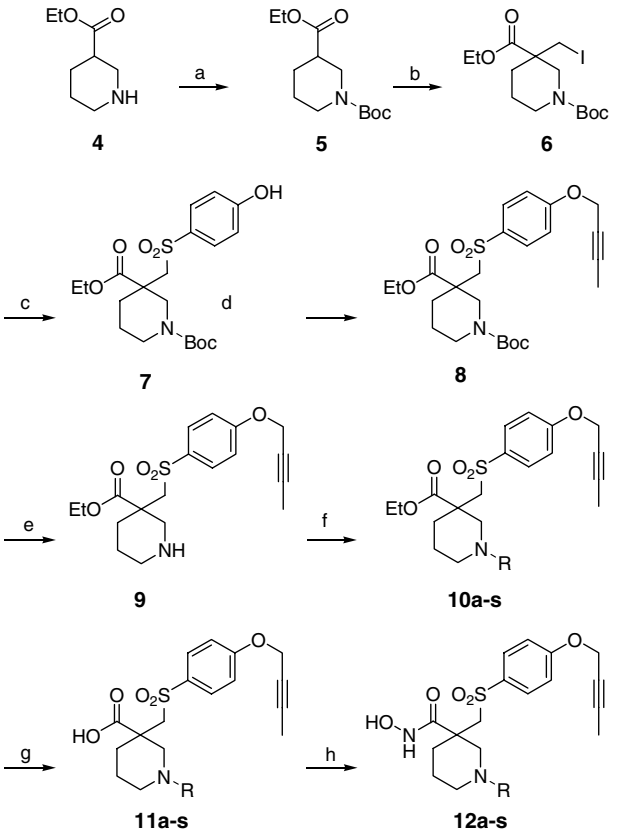


Figure 3. Design of 3,3-piperidine hydroxamic acid TACE inhibitors based on β-sulfone 4-piperidine analogs **3**.



Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, THF, rt, 2 h, 95%; (b) LDA, THF, −78 °C, 3 h, CH_2I_2, rt, 48 h, 35%; (c) i—4-hydroxythiophenol, K_2CO_3, DMF (degassed), rt, 3 h; ii—*m*CPBA, CH_2Cl_2, rt, 3 h, 70%; (d) 1-bromo-2-butyne, $CsCO_3$, DMF, rt, 1 h, 86%; (e) TFA, CH_2Cl_2, rt, 1 h, quant; (f) RCOCl or RSO_2Cl, TEA, CH_2Cl_2, rt, 12 h, or RCO_2H, TBTU/HOBT, TEA, DMF, rt, 12 h, 40–95%; (g) 2 N LiOH, THF–MeOH, microwave, 100 °C, 300 s, 60–95%; (h) NH_2OHHCl, BOP, DIEA, DMF, 0 °C to rt, 20 h, 60–80%.

of **6** with 4-hydroxythiophenol in the presence of K_2CO_3 gave the corresponding sulfide, which was directly oxidized to sulfone **7** using *m*CPBA. The butynyloxy P1′ moiety was introduced by reaction of hydroxysulfone **7** with 1-bromo-2-butyne in the presence of $CsCO_3$. The Boc group was subsequently removed with TFA to provide the key piperidine intermediate **9**. Reaction of **9** with a variety of electrophiles including acid chlorides, sulfonyl chlorides, acids, and carbamates gave a diverse set of β-sulfone 3,3-piperidine esters **10a–s**, which were converted to the corresponding hydroxamic acids[15] **12a–s** as illustrated in Scheme 1.

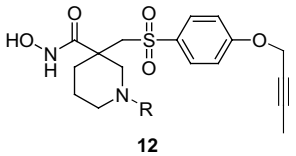
The analogs were tested in a FRET assay using the catalytic domain of TACE,[16] and a subset of analogs were then profiled for selectivity against MMP-2, -13, and -14 (Table 1). Past efforts from our laboratories indicate[9a,d,10b,14] that gaining selectivity over these enzymes can be challenging, and that selectivity over these MMPs would be indicative of further broad-spectrum selectivity. In addition, selected compounds were 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 **12a–o** have excellent TACE enzyme activity with low nanomolar IC_{50}s that parallel the activity of the corresponding 4,4-piperidine sulfone analogs related to **3**.[12] Only the N-unsubstituted piperidine analog **12p** has a TACE IC_{50} worse than 15 nM. Also, all of these analogs show greater than 100-fold selectivity for TACE over MMP-13 and -14. Selectivity over MMP-2 was somewhat lower, with a range of 40-fold for **12p** up to almost 500-fold for *o*-toluamide **12h**. Among the carbamates **12a–d**, compound **12c** is the most potent against TACE and the most selective, with greater than 300-fold selectivity over MMP-2, 380-fold over MMP-13, and 1100-fold over MMP-14. TACE potency and selectivity increased with increasing length of the alkyl chain of the carbamates. In the amide series, **12e–k**, both **12h** and **12k** show greater than 300-fold selectivity for TACE over MMP-2, and greater than 1000-fold over MMP-14, with **12k** demonstrating substantial selectivity over MMP-13 as well. The *o*-toluamide **12h** is slightly more active against TACE, and more selective, than the *m*- and *p*-toluamides, **12i** and **12j**. Sulfonamides **12l**, **12m**, and **12n**, and urea **12o** are also very active inhibitors of TACE, with selectivities >100-fold against all MMPs screened. Interestingly, the benzyl sulfonamide derivative **12m** has a significantly decreased selectivity for TACE over MMP-2 (less than 65-fold) than the pyridyl analog **12n** (175-fold). Isopropylamide **12e** and isopropylsulfonamides **12l** have similar selectivities of >100-fold against all MMPs screened.

When we compared these results with the selectivity profiles exhibited by the analogous 4,4-piperidine sulfone hydroxamates,[12] we were gratified to find that the 3,3-piperidine series is more selective over MMP-13, validating our structural analysis. For example, **12b** is 14-fold more selective over MMP-13 than the corresponding 4-piperidine ethyl carbamate (TACE IC_{50} = 1.4 nM; MMP-13 IC_{50} = 16 nM).[17] The introduction of bulky P1 substituents and the optimal placement of these moieties offered by the 3,3-piperidine scaffold have indeed had a positive effect on selectivity over several MMPs.

The activity of compounds **12a–c** and **12k** was next assessed in raw cells, and moderate potency was observed, with the most potent being amide **12k** (IC_{50} = 0.3 μM). However, HWB activity was problematic for the 3,3-

Table 1. In vitro potency of butynyloxyphenyl β-sulfone piperidine hydroxamic acids **12**

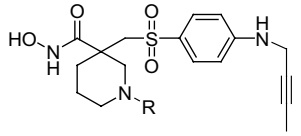


12

Compound	R	TACE[a]	MMP-2[a]	MMP-13[a]	MMP-14[a]	Raw Cells[b]	HWB[c]
12a	CO_2CH_3	14	870	1200	3440	0.87	34
12b	$CO_2CH_2CH_3$	8.0	1630	1100	7440	0.75	26
12c	$CO_2CH_2CH(CH_3)_2$	3.2	960	1170	3410	1.55	—
12d	$CO_2C(CH_3)_3$	15	2230	2860	4160	—	—
12e	$COCH(CH_3)_2$	6.3	840	1200	5640	—	19
12f	$COCH(CH_3)CH_2CH_3$	6.0	520	1110	1460	—	34
12g	CO-Ph	5.8	1140	840	5650	—	17
12h	CO-(2-CH_3Ph)	1.7	840	—	1860	—	27
12i	CO-(3-CH_3Ph)	5.0	1620	1010	3020	—	56
12j	CO-(4-CH_3Ph)	8.8	760	1370	—	—	28
12k	CO-(4-$CH_2OCH_2CH_3$-Ph)	3.0	940	470	3290	0.30	13
12l	$SO_2CH(CH_3)_2$	5.4	700	1190	5640	—	39
12m	SO_2CH_2Ph	4.1	260	—	1250	—	37
12n	SO_2CH_2-(4-Pyridyl)	5.9	1030	950	1650	—	24
12o	$CON(CH_2CH_3)_2$	9.6	—	1740	—	—	29
12p	H	62	2570	—	1020	—	—

[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).

Table 2. In vitro potency of butynylaminophenyl β-sulfone piperidine hydroxamic acids **13**



13

Compound	R	TACE[a]	MMP -2[a]	MMP -13[a]	HWB[b]
13b	$CO_2CH_2CH_3$	21	1230	>16,666	38
13i	CO-(3-CH_3Ph)	8.0	1450	>16,666	35
13l	$SO_2CH(CH_3)_2$	18	1000	>16,666	36

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

piperidine sulfone hydroxamate series of analogs. Thus, in contrast to the 4,4-piperidine analogs, many of which have low micromolar IC_{50}s in HWB, the 3,3-piperidine analogs tested are dramatically less active. For example, compound **12k** is the most potent member of the series in HWB with an IC_{50} of 13 μM, and sulfonamide **12l** has an IC_{50} of 39 μM in HWB, while the corresponding isopropyl sulfonamide **3** has an IC_{50} of 1.5 μM.[12]

In a final effort to achieve increased potency and selectivity along with acceptable HWB activity a series of three 3,3-piperidine sulfone hydroxamates bearing a butynylamine P1′ group were also prepared. Recent studies have shown that compounds with this P1′ moiety have excellent selectivity over MMP-2 and -13.[18] Butynylaminophenyl β-sulfone 3,3-piperidine hydroxamic acids **13b**, **13i**, and **13l** were prepared by the reaction of **6** with 4-aminothiophenol and subsequently following the synthetic route described in Scheme 1. The in vitro and HWB activities of compounds **13** are listed in Table 2. All of the butynylamine analogs were slightly less active in the FRET assay than the corresponding oxygen analogs (**12b**, **12i**, and **12l**), and were somewhat less selective over MMP-2. However, replacement of the oxygen atom with a nitrogen atom did significantly improve the selectivity for TACE over MMP-13 in all cases, to greater than 800-fold for **13b**, and to greater than 2000-fold for **13i**. Unfortunately, the HWB activity of these compounds was poor.

In summary, using structure-based methods focused on capitalizing on the shape difference between the S1 pockets of TACE and structurally related MMPs, we have designed and synthesized a series of β-sulfone 3,3-piperidine hydroxamate TACE inhibitors. All of these analogs show excellent, low nanomolar IC_{50} enzyme activity in a FRET assay and good selectivity over MMPs (up to 1100-fold).

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