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Novel thiol-based TACE inhibitors. Part 2: Rational design, synthesis, and SAR of thiol-containing aryl sulfones

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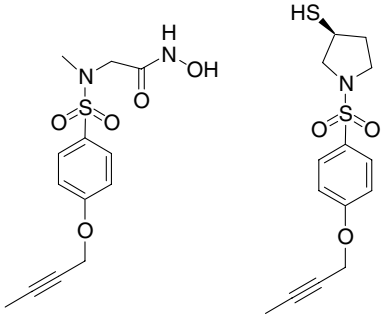
Abstract—A series of potent thiol-containing aryl sulfone TACE inhibitors were designed and synthesized. The SAR and MMP selectivity of the series were investigated. In particular, compound **8b** showed excellent in vitro potency against the isolated enzyme and good selectivity over MMP-2, -7, -8, -9, and -13. The X-ray structure of **8b** in complex with TACE was also obtained.

Rheumatoid arthritis (RA) is an autoimmune disease which affects over 2 million people in the United States alone.[1] The disease is currently treated with non-steroidal anti-inflammatory drugs (NSAIDs),[1] disease-modifying anti-rheumatoid drugs (DMARD),[1] and, recently, COX-2 selective inhibitors.[2] Due to limited effectiveness and/or side effects of these drug classes, development of active small molecule TACE (TNF-α converting enzyme) inhibitors might offer a higher therapeutic value. TNF-α (tumor necrosis factor) is a cytokine that is highly expressed in patients with RA.[3] TACE is responsible for the release of soluble TNF-α from its parent membrane-bound form. Recently, a number of small molecule TACE inhibitors have been reported to be highly potent and very selective over other matrix metalloproteases (MMPs).[4] Most TACE and MMP inhibitors contain a hydroxamic acid moiety as the zinc-binding group (ZBG).[4] Generally, hydroxamic acids exhibit poor oral absorption in vivo and significant metabolic liabilities (rapid hydrolysis and glucuronidation).[5] Therefore, we were interested in exploring non-hydroxamates as ZBGs for our investigation. Previous efforts utilizing a thiol as the ZBG group offered an advantage in imparting specificity in the inhibition of MMPs.[6] However, the use of a thiol as ZBG in TACE inhibitors has not been widely explored. In our previous paper,[7] we disclosed a series of thiol-containing sulfonamides that are very potent and selective TACE inhibitors. Compound **2** had shown excellent in vitro potency against the isolated TACE enzyme and good selectivity over MMP-2, -7, -9, and -13[7] (Fig. 1). The TACE potency of **2** is slightly lower than that of hydroxamic acid analog **1**, while its selectivity over other MMPs such as MMP-2, -8, and -13 is slightly higher.[7] Examination of the crystal structure of the thiol-based sulfonamide inhibitor in complex with TACE showed that the sulfonamide nitrogen is not required for any specific interaction and can be substituted with a methylene group. Modeling suggested that replacement of the sulfonamide group with a sulfone would not alter the bound conformation of the inhibitor and would main-



1 (K_i = 10 nM) **2** (K_i = 28 nM)

Figure 1. Hydroxamic acid and thiol-based TACE inhibitors.

Keywords: TACE inhibitors; MMP selectivity; Rheumatoid arthritis; Hydroxamates; Sulfones.
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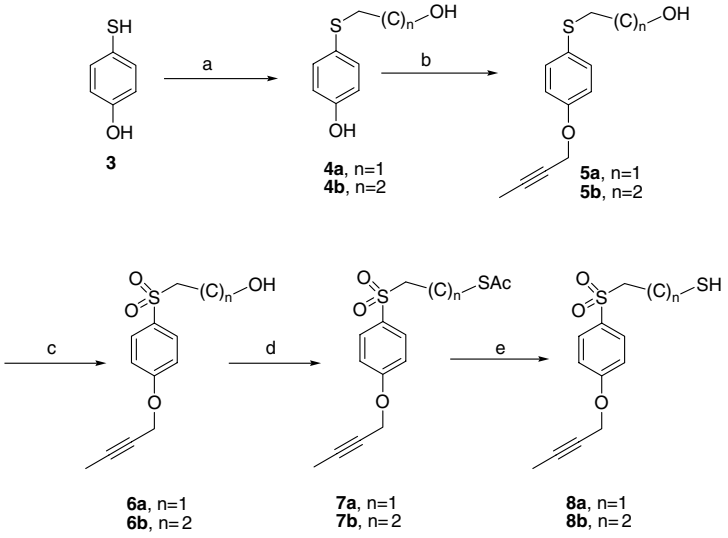
tain all the key interactions with the enzyme active site. In this study, we extended our investigation to design and synthesize thiol-containing sulfones as selective TACE inhibitors.

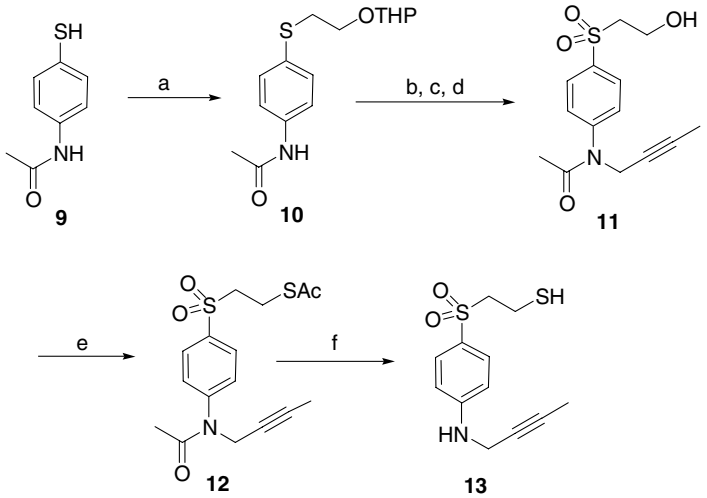
The general synthesis of sulfone thiols with butynyloxy tail is outlined in Scheme 1. Selective S-alkylation of the commercially available 4-hydroxythiophenol **3** with 2-chloroethanol or 3-chloropropanol and subsequent O-alkylation with butynyl bromide provided analogs **5** in workable yields. Subsequent oxidation of **5** with oxone gave sulfones **6**, which were then subjected to standard Mitsunobu conditions to provide thioacetates **7** in good yield. Hydrolysis of thioacetates **7** with aqueous sodium methoxide afforded the desired sulfone thiols **8**.

The synthesis of sulfone thiols-containing a butynylamino group is outlined in Schemes 2 and 3. Alkylation of commercially available **9** with THP-protected 2-bromoethanol gave **10** in high yield. Oxidation of **10** with m-CPBA followed by alkylation with butynyl bromide and removal of the THP group afforded **11**. Mitsunobu reaction of **11** gave thioacetate **12** in good yield. Hydrolysis of thioacetate **12** with 4 N HCl in dioxane gave desired thiol **13** in moderate yield. Michael reaction of **9** with acrolein gave aldehyde **14** which was reduced with $NaBH_4$ in methanol to afford **15**. Compound **15** was converted to desired thiol **16** in a manner similar to compound **13**.

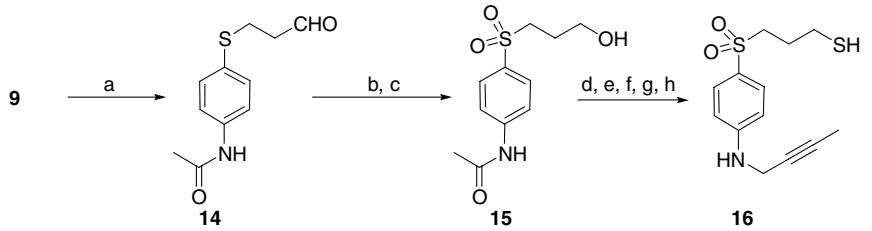
The synthesis of cyclic sulfone thiol **25** (Scheme 4) began with Michael addition of **9** to cyclohexenone to provide compound **17** in high yield. Reduction of ketone **17** with $NaBH_4$ followed by protection of the resulting alcohol with TBDMSCl gave compound **18** in moderate yield. Compound **18** was then alkylated with butynyl bromide to afford compound **19** in good yield. Oxone oxidation of **19** provided sulfone **20** and the subsequent



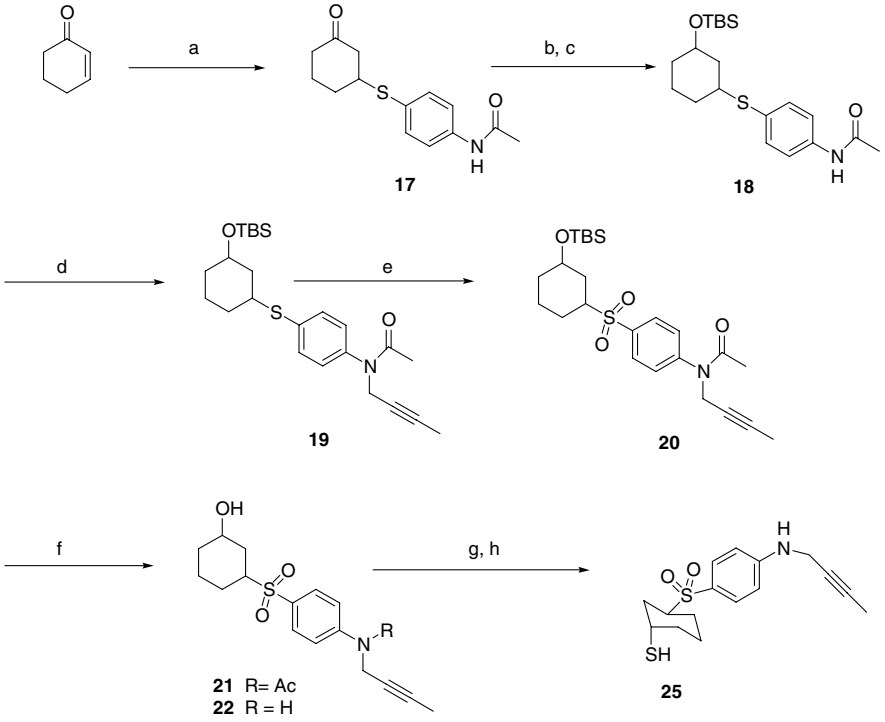
Scheme 1. Reagents and conditions: (a) $Cl(CH_2)_nOH$, K_2CO_3/DMF **4a** 49% **4b** 68%; (b) $CH_3CH{\equiv}CHCH_2Br$, K_2CO_3, DMF, **5a** 36% **5b** 41%; (c) oxone, MeOH/H_2O **6a** 82% **6b** 99%; (d) Ph_3P, DEAD, CH_3COSH, **7a** 07% **7b** 59%; (e) i—10% $NaOCH_3$, MeOH; ii—10% HCl, **8a** 70% **8b** 71%.



Scheme 2. Reagents and conditions: (a) $THPO(CH_2)_2Br$, K_2CO_3, acetone, 82%; (b) m-CPBA, $CHCl_3$, 85%; (c) NaH, $CH_3CH{\equiv}CHCH_2Br$, DMF; (d) TsOH, MeOH/CH_2Cl_2, 36% over 2 steps; (e) Ph_3P, DEAD, CH_3COSH; (f) 4 M HCl in dioxane, 60 °C, 30 min, 28% over 2 steps.



Scheme 3. Reagents and conditions: (a) acrolein, $CHCl_3$; (b) $NaBH_4$, MeOH; (c) m-CPBA, $CHCl_3$, 96% over 3 steps; (d) *t*-$BuMe_2SiCl$, Et_3N; (e) NaH, $CH_3CH{\equiv}CHCH_2Br$, DMF, (f) HCl in dioxane, 0 °C, 30 min, 88% over 3 steps; (g) Ph_3P, DEAD, CH_3COSH; (h) 4 M HCl in dioxane, 60 °C, 30 min, 22% over 2 steps.



Scheme 4. Reagents and conditions: (a) i—**9**, Et_3N, MeOH, rt, 1 h; ii—recrystallization, 97%; (b) $NaBH_4$, MeOH, 78%; (c) TBSCl, imidazole, DMF, rt, 71%; (d) NaH, $CH_3CH{\equiv}CHCH_2Br$, DMF, 3 h, 56%; (e) oxone, MeOH, 78%; (f) TBAF, THF, rt, **21** 42%, **22** 21%; (g) Ph_3P, DEAD, CH_3COSH, 75%; (h) 4 M HCl in dioxane, 63%.

fluoride-mediated removal of the TBS group resulted in compounds **21** and **22** in a 2:1 ratio. Compound **22** was subjected to Mitsunobu conditions followed by hydrolysis of the resulting thioacetate, affording the desired thiol **25** in good yield. Compounds **23** and **24** (Fig. 2) were synthesized in a manner similar to **25** starting from cyclohexenone or cyclopentenone and 4-hydroxythiophenol. All final compounds were characterized by HPLC and ^1H NMR analysis. Purity of these compounds was >98%.

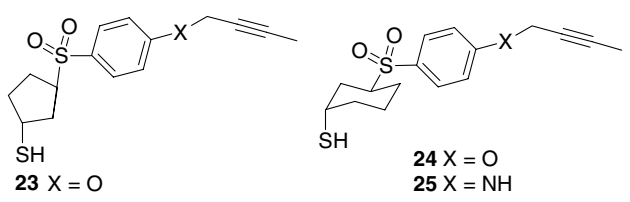


Figure 2.

In our previous publication on sulfonamides,[7] we found a three-atom spacer between the sulfonyl SO_2 and the thiol group to be optimal among the linear inhibitors. The same spacer length in the current sulfone series produced a slightly more potent compound, **8b**. We have obtained the X-ray crystal structure of this compound in complex with TACE,[8] which is shown in Figure 3. Compound **8b** binds to the enzyme active site in the same orientation as the sulfonamide inhibitor **2** described in our previous publication.[7] The thiol group makes a strong interaction with the active site Zn^{2+} ion forming a tetrahedral coordination around the metal ion along with the three histidine side-chains (His-405, His-409, and His-415). The hydrogen bond interaction between the sulfone oxygen and the backbone NH of Gly-349 remains strong. The phenyl ring of the inhibitor is in the hydrophobic environment of the S1′ pocket and is also involved in a stacking interaction with the His-405 side-chain. The butynyloxy tail occupies the narrow channel between the S1′ and S3′ pockets.

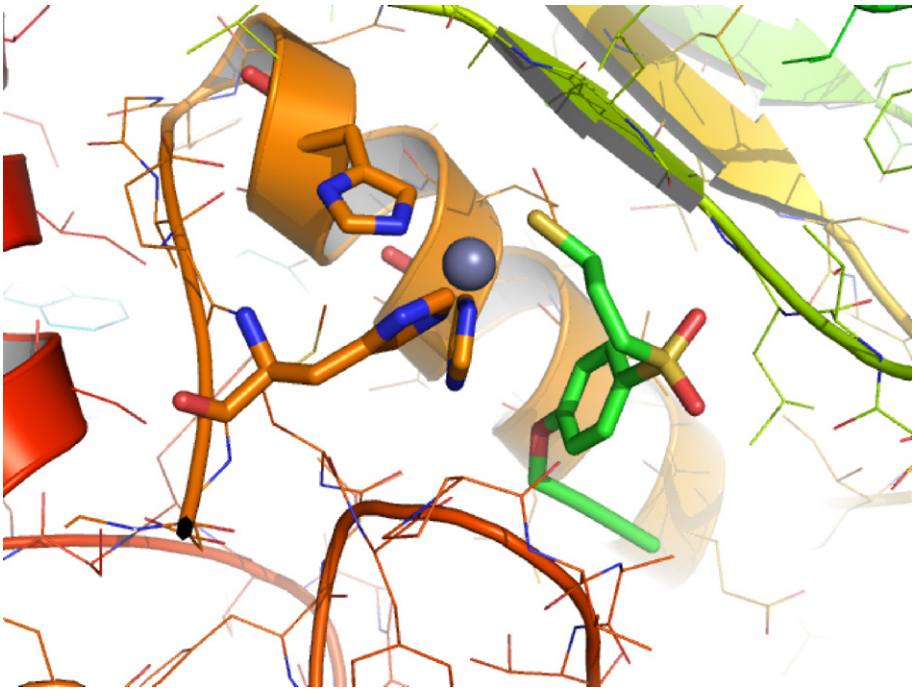
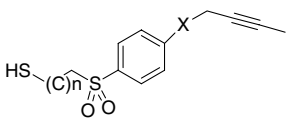


Figure 3. X-ray crystal structure of compound **8b** bound to TACE.

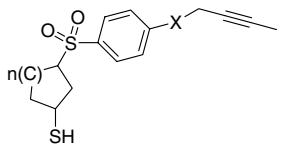
A closer examination of the X-ray crystal structure showed that the thiol moiety can be placed near the Zn^{2+} ion using a spacer that is one bond shorter. Therefore, compound **8a** with a shorter spacer was made and was found to be as potent as compound **8b**. The replacement of the butynyloxy tail of these two compounds with butynylamino tails (compounds **13** and **16**) resulted in very potent TACE inhibitors (Table 1, entries 3 and 4). These compounds are 2-fold more potent than their butynyloxy counterparts. However, cyclization of the linker into five-membered and six-membered rings produced compounds with reduced potencies. Cyclopentylsulfone thiol **23** is 5-fold less potent while cyclohexyl sulfone thiol **24** is 3- to 4-fold less potent than the corresponding acyclic inhibitors. Cyclohexyl sulfone thiol **24** appears to be slightly more potent than its cyclopentyl analog **23** (Table 2, entries 1 and 2). Replacement of the butynyloxy tail of compound **24** with butynylamino in compound **25** showed the usual 2-fold improvement in K_i (Table 2, entries 1 and 3). It should be noted that cyclization of the spacer did not affect binding in the case of sulfonamides,[7] whereas we observe a significant loss in binding in the current sulfone series. Cyclic sulfones (**23**, **24**, **25**) have one additional chiral center compared to the sulfonamide compounds and were produced as racemic mixtures of four compounds. Modeling analysis showed that some diastereomers of these compounds do not fit the active site as well as the linear compounds and are likely to have lower binding affinities for TACE. It is possible that the potency of a particular diastereomer is similar or better than those of the corresponding acyclic compounds (Table 3).

Table 1. In vitro potency of thiol-aryl sulfone series against TACE



Entry	Compound	*n*	X	TACE K_i (nM)
1	**8a**	1	O	8
2	**8b**	2	O	10
3	**13**	1	NH	2
4	**16**	2	NH	4.5

Table 2. In vitro potency of thiol-aryl sulfone series against TACE



Entry	Compound	*n*	X	TACE K_i (nM)
1	**23**	1	O	50
2	**24**	2	O	30
3	**25**	2	N	17

In summary, we have designed and synthesized a novel series of thiol-containing aryl sulfones as inhibitors of TACE. Most of these compounds show very potent inhibition in an enzyme assay using the isolated enzyme. One of the potent TACE compounds, **8b**, is far more selective against MMP-2, -7, -8, -9, -13 than previously reported analogs such as **1**. These results also demonstrate that in the scaffold explored here the sulfonamide moiety can be replaced with a sulfone without loss of TACE potency. The crystal structure of an inhibitor of this novel class bound to TACE enhances our understanding of the binding interactions with the TACE ac-

Table 3. Selectivity profile of selected compounds

Compound	TACE K_i (nM)	MMP-2 K_i (nM)	MMP-7 K_i (nM)	MMP-8 K_i (nM)	MMP-9 K_i (nM)	MMP-13 K_i (nM)
1	10	27	3400	43	800	17
2	28	5000	>6000	1900	200	1200
8b	10	1300	>2500	2700	6300	1700

tive site and facilitates the structure-based design of inhibitors with improved potency. Further exploration of this novel class of TACE inhibitors may provide new opportunities for the treatment of rheumatoid arthritis.

Acknowledgments

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