Available online at www.sciencedirect.com
SCIENCE DIRECT
Bioorganic & Medicinal Chemistry Letters 16 (2006) 1028–1031
Bioorganic & Medicinal Chemistry Letters

Conversion of potent MMP inhibitors into selective TACE inhibitors

Robert J. Cherney,* Bryan W. King, John L. Gilmore, Rui-Qin Liu, Maryanne B. Covington, James J.-W. Duan and Carl P. Decicco

Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-4000, USA

Received 27 September 2005; revised 21 October 2005; accepted 24 October 2005
Available online 8 November 2005

Abstract—Novel sultam hydroxamates with potent MMP activity were transformed into potent TACE inhibitors, lacking MMP activity. To accomplish this we relied on structural differences between the MMP and TACE S1′ pockets and the known advantageous fit of a 2-methyl-4-quinolinylmethoxyphenyl group into this region. From this approach, compound **7d** was identified as a potent TACE inhibitor (IC_{50} = 3.7 nM) that lacked MMP-1, -2, -9, and -13 activity.

Several recently approved biologics have revolutionized the treatment of autoimmune/inflammatory conditions, including rheumatoid arthritis (RA) and Crohn's disease.[1] These agents work by sequestering tumor necrosis factor-α (TNF-α), which is an inflammatory cytokine overproduced in these diseases. There is a great deal of interest in finding a bioavailable small molecule that can mimic these marketed biologics.[2] We have pursued the inhibition of TNF-α converting enzyme (TACE or ADAM-17) as a means of TNF-α suppression.[3,4] TACE is the protease responsible for processing the membrane bound, pro-TNF-α (26 kDa) into the 17 kDa free form.[5] As a member of the ADAM (a disintegrin and metalloproteinase) family, TACE is contained within the metzincin superfamily, which also includes the matrix metalloproteinases (MMPs).[6] Initially, it was shown that MMP inhibitors could prevent the release of TNF-α from cells through their interaction with TACE.[5] Hence, many groups have used MMP inhibitors as a starting point in the design of TACE inhibitors.[3] Recently, we described a novel set of sultam hydroxamates (e.g., see compound **1**, Fig. 1) as MMP inhibitors that lacked TACE activity.[7] In this communication, we describe our efforts to convert these broad-spectrum MMP inhibitors into selective TACE inhibitors, which lack MMP activity (see Fig. 1).

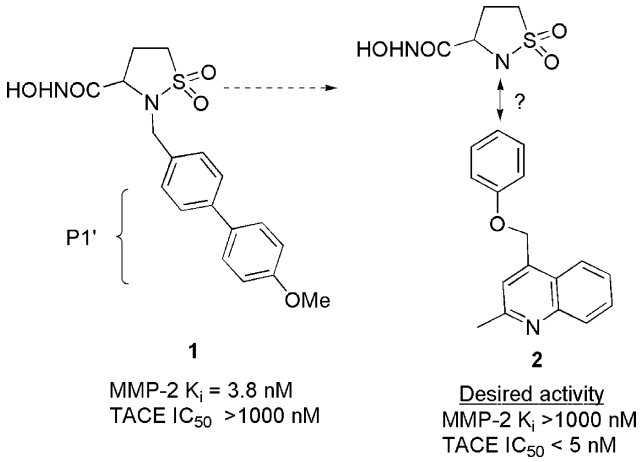


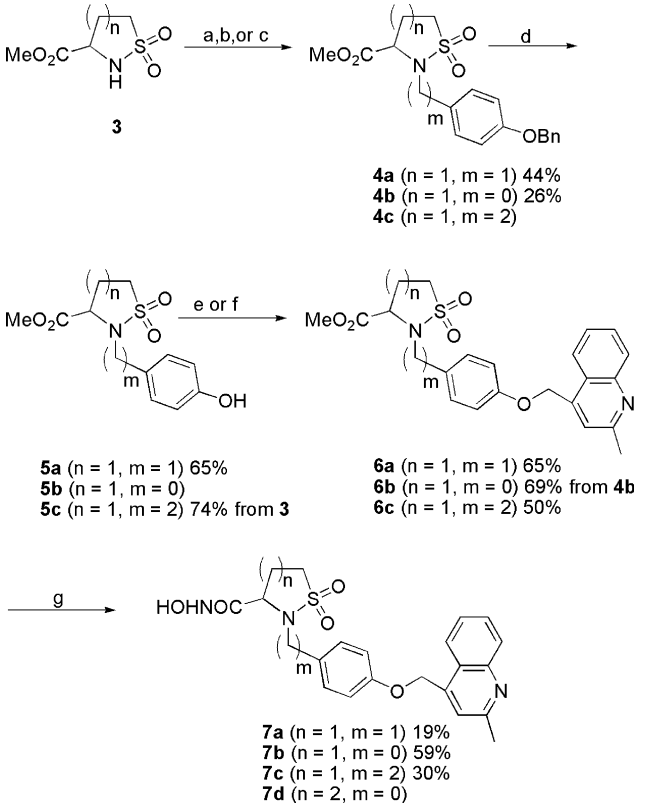
Figure 1. Design plan: from MMP inhibitor to TACE inhibitor.

As shown in Scheme 1, the synthesis of the sultam hydroxamates follows that previously reported.[7] For example, the nitrogen of a five- or six-membered racemic sultam **3** (*n* = 1 or 2) was substituted via alkylation or copper-promoted arylation[8] to furnish **4**. Subsequent hydrogenolysis gave phenol **5**, which was substituted via an alkylation or Mitsunobu reaction to give **6**. Treatment of **6** with a basic hydroxylamine solution afforded the target hydroxamates **7a**–**d**.

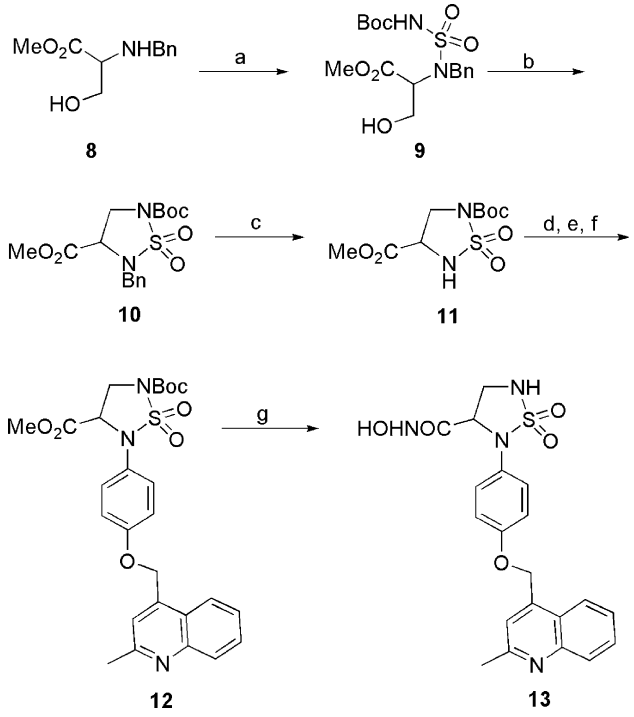
As shown in Scheme 2, the route was adapted to produce the cyclic sulfamide **13**. In this case, the nitro-

Keywords: TACE inhibitor; ADAM-17 inhibitor.
* Corresponding author. Tel.: +1 609 252 3066; fax: +1 609 252 6601; e-mail: robert.cherney@bms.com

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.10.078



Scheme 1. Reagents and conditions: (a) 4-(benzyloxy)benzyl chloride, K_2CO_3, Bu_4NI, DMF, 44%; (b) 4-(benzyloxy)benzene boronic acid, $Cu(OAc)_2$, Et_3N, 4 Å MS, CH_2Cl_2, 26%; (c) 1-(2-bromoethyl)-4-(phenylmethoxy)benzene, NaH, THF/DMF; (d) H_2, Pd/C, MeOH; (e) 4-(hydroxymethyl)-2-methylquinoline, DEAD, PPh_3, THF, 65% (**6a**); 69% (**6b**); (f) 4-(chloromethyl)-2-methylquinoline, K_2CO_3, MeCN, Δ, 50%; (g) 1.6 M H_2NOH, KOH, MeOH, 19–59%.

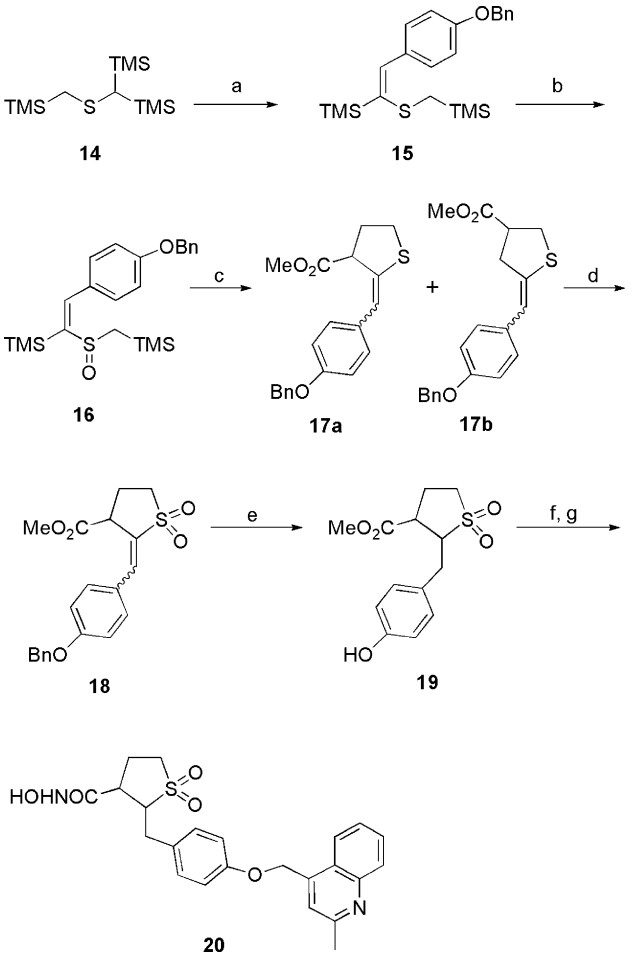


Scheme 2. Reagents and conditions: (a) (i) chlorosulfonyl isocyanate, *t*-BuOH, CH_2Cl_2; (ii) **8**, Et_3N, CH_2Cl_2, 53%; (b) DIAD, PPh_3, CH_2Cl_2, 67%, (c) H_2, $Pd(OH)_2$, MeOH, 26%; (d) 4-(benzyloxy)benzene boronic acid, $Cu(OAc)_2$, Et_3N, 4 Å MS, CH_2Cl_2, 20%; (e) H_2, $Pd(OH)_2$, MeOH; (f) 4-(chloromethyl)-2-methylquinoline, K_2CO_3 CH_3CN, 33%; (g) $H_2NOH{\cdot}HCl$, NaOMe, MeOH, 22%.

gen of *N*-benzyl serine **8** was substituted to afford compound **9** through the action of *N*-*tert*-butoxycarbonylsulfamoyl chloride. Compound **9** was then cyclized via an intramolecular Mitsunobu reaction to give **10**. Hydrogenolysis gave **11**, which was then arylated, hydrogenated, and alkylated as before to afford **12**. Final conversion to the target hydroxamate **13** was accomplished with a basic hydroxylamine solution.

As illustrated in Scheme 3, a 1,3-dipolar cycloaddition was utilized to synthesize the cyclic sulfone **20**. Using the sequence of Achiwa et al.,[9] silane **14** was condensed with 4-benzyloxybenzaldehyde to give **15**, which was oxidized to **16**. The cycloaddition was performed with methyl acrylate to afford the regioisomers **17a** and **17b**. Oxone oxidation of the mixture (**17a** and **17b**) followed by chromatographic separation gave the desired sulfone **18**. Subsequent hydrogenation of **18** provided compound **19**. The phenol was substituted via a Mitsunobu reaction and was then converted to the target hydroxamate **20** as a racemic mixture of diastereomers.

As described in the introduction, it was our desire to convert the non-selective MMP inhibitor **1** into a selective TACE inhibitor (see Fig. 1). From prior X-ray crystal structures, we knew the biaryl of sultam **1** was situated in a very linear section of the MMP S1′ pocket.[7] Counter to this was the TACE S1′ pocket, which has a pronounced curvature in about the same area. We were also aware of certain quinolines that when properly placed could fit into the curvature of the TACE pocket while clashing with the linear MMP pocket.[10] Hence, our strategy was to attach the quinoline moiety to the sultam template and probe the different levels of S1′ until we could obtain the proper fit. As shown in Table 1, the previously described **1** displayed good affinity for MMP-2, -9, and -13 while lacking affinity for TACE (IC_{50} > 1000 nM).[11] In compound **7a**, we introduced the quinolinylmethoxy into the P1′ region and this resulted in a 1000-fold loss of binding across the MMPs, while enhancing the affinity for TACE (TACE IC_{50} = 900 nM). From here we set about probing S1′ by deleting a methylene from **7a** to give compound **7b**. Compound **7b** appeared to have the proper fit of the quinoline as the TACE affinity increased 150-fold over compound **7a**, while maintaining selectivity over the MMPs. In order to secure this placement, compound **7c** was synthesized to extend the quinoline moiety further into S1′, however it lost substantial TACE activity as compared to **7b**. In an effort to optimize **7b**, the six-membered sultam **7d** was synthesized and it proved to be slightly more potent (TACE IC_{50} = 3.7 nM) than **7b**. Additionally, a nitrogen was inserted into the sultam ring to afford compound **13**, but this proved to be detrimental as **13** was less active (TACE IC_{50} = 8.3 nM) than **7b**. Removal of all the ring nitrogens gave cyclic sulfone



Scheme 3. Reagents and conditions: (a) *n*-BuLi, 4-benzloxybenzaldehyde, THF, 99%; (b) *m*-CPBA, CH_2Cl_2, −40 °C; (c) methyl acrylate, HMPA, 100 °C, 20% (from **15**); (d) oxone, MeOH, H_2O; (e) H_2, $Pd(OH)_2$, MeOH, 17%; (f) 4-(hydroxymethyl)-2-methylquinoline, DEAD, PPh_3, THF, 43%; (g) $H_2NOH{\cdot}HCl$, NaOMe, MeOH, 28%.

20 as a racemic mixture of diastereomers. Compound **20** did show promise as it displayed 6-fold more affinity for TACE when compared to the methylene linked compound **7a**.

In conclusion, we have successfully converted broad-spectrum, sultam-based MMP inhibitors into potent and selective TACE inhibitors. To accomplish this, we altered the length our inhibitor in P1′ by varying the distance between the known quinolinylmethoxyphenyl moiety and the sultam core. Proper placement of this moiety was achieved by direct attachment to the sultam core, which resulted in the desired activity and selectivity for TACE.

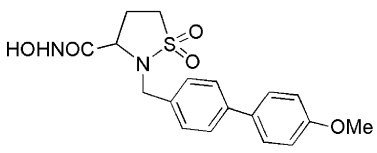
Acknowledgments

The authors thank Ruowei Mo and Dayton T. Meyer for substantial quantities of the sultam **3**. We acknowledge John V. Giannaras and Paul Strzemienski for K_i and IC_{50} determinations. We also thank Dr. Percy H. Carter for a critical review of the manuscript.

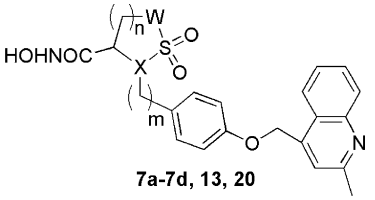
References and notes

1. (a) Haraoui, B. *J. Rheumatol. Suppl.* **2005**, *32*, 3; (b) Keating, G. M.; Perry, C. M. *BioDrugs* **2002**, *16*, 111; (c) Nanda, S.; Bathon, J. M. *Expert Opin. Pharmacother.* **2004**, *5*, 1175.
2. Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **1999**, *42*, 2295.
3. For a review on TACE inhibitors, see: Skotnicki, J. S.; Levin, J. I. *Annu. Rep. Med. Chem.* **2003**, *38*, 153.
4. For an ADAM review, see: Moss, M. L.; White, J. M.; Lambert, M. H.; Andrews, R. C. *Drug Discovery Today* **2001**, *6*, 417.

Table 1. In vitro evaluation



1



7a-7d, 13, 20

Compound	X	W	*n*	*m*	TACE[a] IC_{50} (nM)	K_i[a] (nM)			
						MMP-1	MMP-2	MMP-9	MMP-13
1	—	—	—	—	>1000	>4949	3.8	46.7	55
7a	N	CH_2	1	1	900	>4949	>3333	>2128	>5025
7b	N	CH_2	1	0	5.9	>4949	>3333	>2128	>5025
7c	N	CH_2	1	2	480	>4949	>3333	>2128	>5025
7d	N	CH_2	2	0	3.7	>4949	>3333	>2128	>5025
13	N	NH	1	0	8.3	>4949	>3333	>2128	>5025
20	CH	CH_2	1	1	150	>4949	>3333	>2128	>5025

[a] Values are an average from three determinations.

5. (a) Gearing, A. J. H.; Beckett, P.; Christodoulou, M.; Churchill, M.; Clements, J.; Davidson, A. H.; Drummond, A. H.; Galloway, W. A.; Gilbert, R.; Gordon, J. L.; Leber, T. M.; Mangan, M.; Miller, K.; Nayee, P.; Owen, K.; Patel, S.; Thomas, W.; Wells, G.; Wood, L. M.; Woolley, K. *Nature* **1994**, *370*, 555; (b) Black, R. A.; Rauch, C. T.; Kozlosky, C. J.; Peschon, J. J.; Slack, J. L.; Wolfson, M. F.; Castner, B. J.; Stocking, K. L.; Reddy, P.; Srinivasan, S.; Nelson, N.; Boiani, N.; Schooley, K. A.; Gerhart, M.; Davis, R.; Fitzner, J. N.; Johnson, R. S.; Paxton, R. J.; March, C. J.; Cerretti, D. P. *Nature* **1997**, *385*, 729; (c) Moss, M. L.; Jin, S.-L. C.; Milla, M. E.; Burkhart, W.; Carter, H. L.; Chen, W.-J.; Clay, W. C.; Didsbury, J. R.; Hassler, D.; Hoffman, C. R.; Kost, T. A.; Lambert, M. H.; Leesnitzer, M. A.; McCauley, P.; McGeehan, G.; Mitchell, J.; Moyer, M.; Pahel, G.; Rocque, W.; Overton, L. K.; Schoenen, F.; Seaton, T.; Su, J.-L.; Warner, J.; Willard, D.; Becherer, J. D. *Nature* **1997**, *385*, 733.
6. (a) Stocker, W.; Grams, F.; Baumann, U.; Reinemer, P.; Gomis-Ruth, F.-X.; McKay, D. B.; Bode, W. *Protein Sci.* **1995**, *4*, 823; (b) Hooper, N. M. *FEBS Lett.* **1994**, *354*, 1.
7. Cherney, R. J.; Mo, R.; Meyer, D. T.; Hardman, K. D.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Wasserman, Z. R.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **2004**, *47*, 2981.
8. (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933; (b) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.
9. Aono, M.; Terao, Y.; Achiwa, K. *Heterocycles* **1995**, *40*, 249.
10. (a) Wasserman, Z. R.; Duan, J. J.-W.; Voss, M. E.; Xue, C.-B.; Cherney, R. J.; Nelson, D. J.; Hardman, K. D.; Decicco, C. P. *Chem. Biol.* **2003**, *10*, 215; (b) Duan, J. J.-W.; Chen, L.; Wasserman, Z. R.; Lu, Z.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Hardman, K. D.; Magolda, R. L.; Newton, R. C.; Christ, D. D.; Wexler, R. R.; Decicco, C. P. *J. Med. Chem.* **2002**, *45*, 4954; (c) Duan, J. J.-W.; Lu, Z.; Xue, C.-B.; He, X.; Seng, J. L.; Roderick, J. J.; Wasserman, Z. R.; Liu, R.-Q.; Covington, M. B.; Magolda, R. L.; Newton, R. C.; Trzaskos, J. M.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2035; (d) Cherney, R. J.; Duan, J. J.-W.; Voss, M. E.; Chen, L.; Meyer, D. T.; Wasserman, Z. R.; Hardman, K. D.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Mandlekar, S.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Magolda, R. L.; Wexler, R. R.; Decicco, C. P. *J. Med. Chem.* **2003**, *46*, 1811.
11. For assay conditions, see: Xue, C.-B.; Voss, M. E.; Nelson, D. J.; Duan, J. J.-W.; Cherney, R. J.; Jacobson, I. C.; He, X.; Roderick, J.; Chen, L.; Corbett, R. L.; Wang, L.; Meyer, D. T.; Kennedy, K.; DeGrado, W. F.; Hardman, K. D.; Teleha, C. A.; Jaffee, B. D.; Liu, R.-Q.; Copeland, R. A.; Covington, M. B.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Magolda, R. L.; Wexler, R. R.; Decicco, C. P. *J. Med. Chem.* **2001**, *44*, 2636.