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Discovery of β-benzamido hydroxamic acids as potent, selective, and orally bioavailable TACE inhibitors

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Abstract—β-Benzamido hydroxamic acids were discovered as potent TACE inhibitors. A computer model was constructed to help understanding the binding activities and guiding SAR study. SAR optimization led to the discovery of compound **30** which met all in vitro and in vivo criteria for the program and was selected for further evaluation.

TACE (TNF-α converting enzyme) is a zinc metalloprotease that is primarily responsible for the release of soluble TNF-α (tumor necrosis factor-α).[1] Because TNF-α is involved in many inflammatory and immunological pathways[2] and anti-TNF biologics are broadly used to treat diseases such as rheumatoid arthritis, Crohn's disease, and psoriasis,[3] many organizations have attempted to develop small molecule TACE inhibitors to suppress TNF-α activity.[4]

We previously disclosed a potent and selective cyclic succinate inhibitor **1** (Fig. 1).[5] Unfortunately, compound **1** was not suitable for development because the 4-(2-methylquinolin-4-ylmethoxy)aniline moiety was positive in a bacterial reverse mutation (Ames) assay. Computer modeling suggested that the hydroxamic acid group of **1** binds in a manner similar to that observed for previous TACE inhibitors, that is, chelation to catalytic zinc and hydrogen bonding to Gly130 and the catalytic glutamic acid residue. The central amide carbonyl group appears to engage in hydrogen bonding with Leu129 and Gly130. The 4-(2-methylquinolin-4-ylmethoxy)phenyl group, which was found to impart selectivity and improve cellular activity,[6] is directed into the S1′ pocket as expected. To exploit this binding mode, we examined the possibility of reversing the central amide

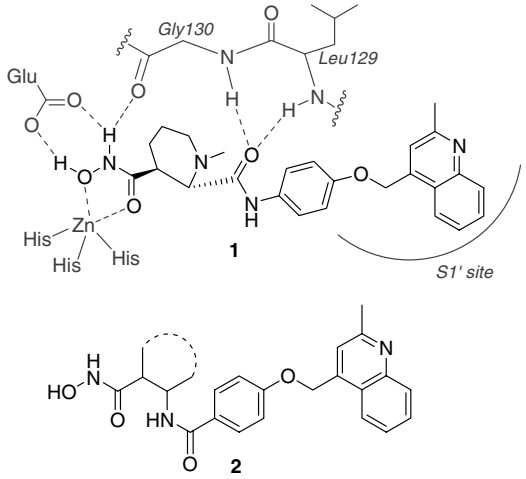

Figure 1. Cyclic succinate **1** and β-benzamido hydroxamic acid **2**.

moiety to give a series of β-benzamido hydroxamic acids **2**. By virtue of this amide reversal, we eliminated the aniline moiety and hence addressed the mutagenicity issue. Computer modeling suggested that **2** could be superimposed with **1** and maintains the aforementioned binding mode of **1**. Since the piperidine core in **1** is not involved in any critical interactions and is mostly solvent exposed in the model, we proceeded to test the β-benzamido hydroxamic acid concept with the readily accessible carbocyclic templates.

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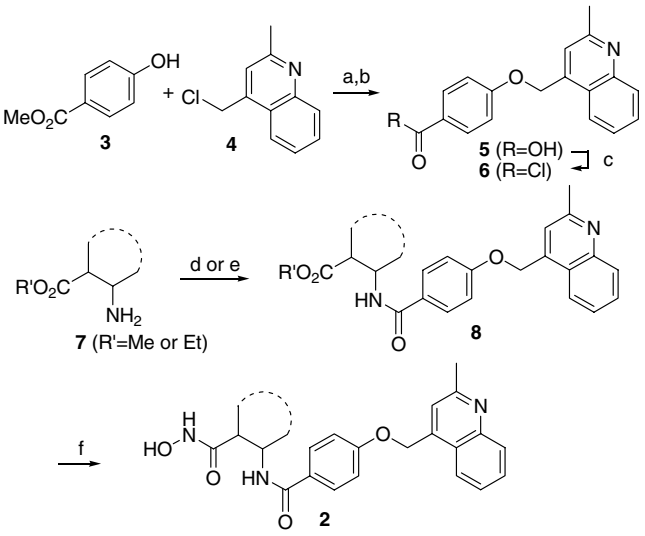
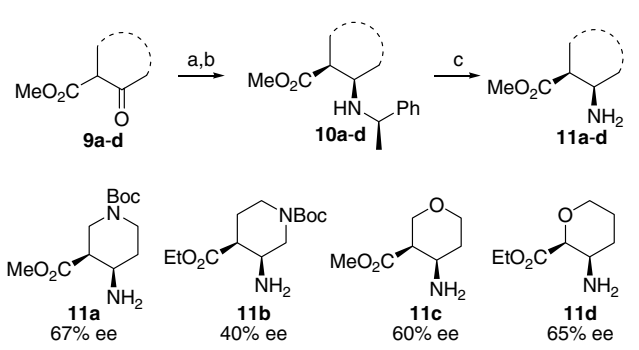
Scheme 1 outlines the general synthesis of the newly proposed β-benzamido hydroxamic acids. The common 4-(2-methylquinolin-4-ylmethoxy)phenyl P1′ group was introduced using benzoic acid **5** or benzoyl chloride **6**, which was prepared from methyl 4-hydroxybenzoate (**3**) and 4-chloromethyl-2-methylquinoline (**4**). Potassium carbonate-mediated coupling of **3** and **4** in the presence of Bu_4NI proceeded in near quantitative yield. Subsequent saponification gave acid **5**, which was converted to **6** using thionyl chloride. Coupling of **6** with β-aminoester **7** was effected using $NaHCO_3$ in biphasic H_2O–CH_2Cl_2 solvent mixture. Alternatively, compound **7** was coupled with acid **5** using BOP reagent. Finally ester **8** was reacted with excess hydroxylamine hydrochloride (10–20 equiv) using either NaOH or NaOMe to give hydroxamic acid **2**.

Carbocyclic analogues of **2** were synthesized from the corresponding commercially available β-amino acid or ester derivatives. Heterocyclic β-amino acids were not commercially available. Most of them were prepared following a sequence summarized in Scheme 2. Condensation of β-ketoester **9a–d**[7] with (*R*)-α-methylbenzylamine afforded an enamine intermediate. Ytterbium triflate was found to accelerate the reaction and prevent formation of an amide byproduct, derived from nucleophilic attack of (*R*)-α-methylbenzylamine to the ester group. Following a literature procedure,[8] the enamine was reduced with sodium triacetoxyborohydride in acetic acid and acetonitrile at 0 °C to give **10a–d**, which was debenzylated to provide two piperidine (**11a** and **11b**) and two tetrahydropyran analogues (**11c** and **11d**). The enantiomeric excess (ee) ranged from 40 to 67%. After conversion to intermediate **8** (Scheme 1), the enantiomeric excess was enriched to >95% either via recrystallization (**8a** and **8c**) or chiral HPLC separation (**8b** and **8d**). For the two piperidine isomers **8a** and **8b**, the Boc group was removed under acidic conditions (HCl or CF_3CO_2H) and the nitrogen further functionalized before conversion to hydroxamic acids.



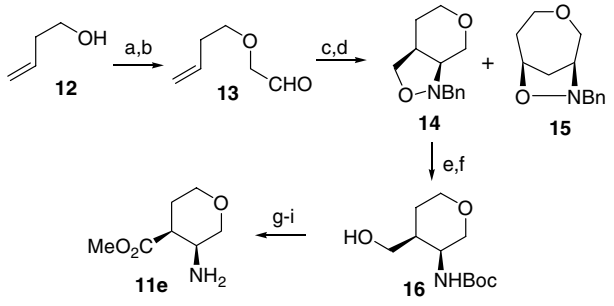
Scheme 1. Reagents and conditions: (a) K_2CO_3, Bu_4NI, CH_3CN, 80 °C (99%); (b) LiOH, H_2O, THF, MeOH (96%); (c) $SOCl_2$, CH_2Cl_2, at reflux (100%); (d) **5**, BOP, *i*-Pr_2NEt, DMF; (e) **6**, $NaHCO_3$, CH_2Cl_2, H_2O; (f) $NH_2OH{\cdot}HCl$, KOH or NaOMe, MeOH.



Scheme 2. Reagents and conditions: (a) (*R*)-α-methylbenzylamine, $Yb(OTf)_3$, benzene, at reflux; (b) $NaBH(OAc)_3$, AcOH, CH_3CN, 0 °C; (c) H_2, $Pd(OH)_2/C$, HCl, EtOH.

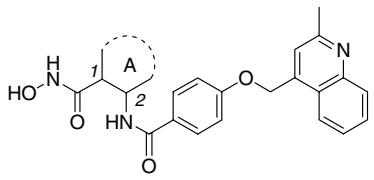
An alternative route was developed to prepare tetrahydropyran analogue **11e** (Scheme 3). 3-Buten-1-ol (**12**) was treated with NaH and sodium iodoacetate followed by iodomethane to give a methyl ester, which was reduced with DIBAL to give aldehyde **13**. Condensation with *N*-benzylhydroxylamine yielded a nitrone, which, when heated in toluene at 60 °C, underwent intramolecular [3+2]-dipolar cycloaddition with the terminal olefin, to provide the desired *cis*-fused-bicyclo[4.3.0]-intermediate **14** in 50–60% yield along with a bridged-bicyclo[4.2.1]-byproduct **15** (10%). Treatment of **14** with H_2 and $Pd(OH)_2/C$ effected cleavage of the N–O bond and removal of the benzyl group. The amino group was protected with $(Boc)_2O$ to give **16**. The primary alcohol was oxidized and esterified to give **11e** after removal of the Boc group. The two enantiomers were resolved by chiral HPLC after conversion to intermediate **8**.

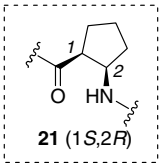
Replacing the piperidine moiety in **1** (Fig. 1) with a cyclohexane and reversal of the central amide resulted in a β-benzamido hydroxamic acid **17** (Table 1). We were delighted to find that **17**, as a racemic mixture, was slightly more potent than **1**, with an IC_{50} of 2 nM in a porcine TACE (pTACE) assay.[9,10] The cyclopen-



Scheme 3. Reagents and conditions: (a) NaH, ICH_2CO_2Na, DMF, then MeI (84%); (b) DIBAL, CH_2Cl_2, −78 °C (73%); (c) BnNHOH, $MgSO_4$, Et_2O; (d) toluene, 60 °C (50–60% yield of **14**); (e) H_2, $Pd(OH)_2/C$, HCl, MeOH; (f) $(Boc)_2O$, Et_3N, MeOH, CH_2Cl_2 (52% for 2 steps); (g) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O (100%); (h) $TMSCHN_2$, MeOH, benzene (95%); (i) CF_3CO_2H, CH_2Cl_2 (95%).

Table 1. In vitro potency in pTACE and WB LPS/TNF-α[a]





21 (1*S*,2*R*)

	A	pTACE IC_{50}[b] (nM)	WB LPS/TNF-α IC_{50}[c] (nM)
1	—	6	20
17	*trans*-Cyclohexane	2	>3000
18	*trans*-Cyclopentane	30	>3000
19	*cis*-Cyclohexane	2	890
20	*cis*-Cyclopentane	2	662
21	(1*S*,2*R*)-Cyclopentane	1	475
22	(1*R*,2*S*)-Cyclopentane	200	—
23	$–CH_2CH_2–$	1	2860

[a] All compounds were selective over MMP-1 (>4900 nM), -2 (>3300 nM), and -9 (>2100 nM).
[b] pTACE IC_{50} values were from a single determination.
[c] Inhibition of TNF-α release from WB was determined with three donors.

tane counterpart **18** (racemic) was also active for pTACE, albeit approximately 15-fold less potent than **17**. The two *cis* analogues (**19** and **20**) were unexpectedly potent, both were 2 nM inhibitors. The two enantiomers of **20** were synthesized individually from the homochiral amino acids and the (1*S*,2*R*)-enantiomer **21** was found to be 200-fold more potent than the antipode **22**. Interestingly, the cyclic template is not required. A simple β-alanine analogue **23** was equally potent, with an IC_{50} of 1 nM. Also noteworthy here is that compounds **17**–**23** maintained similar selectivity profile to compound **1** against three related matrix metalloproteinases (MMP-1 >4900 nM, MMP-2 >3300 nM, and MMP-9 >2100 nM), suggesting that these benzamido derivatives adopt a similar binding mode to succinate **1**.

A computer model of **23** in the active site of TACE was constructed to help understanding the aforementioned activities (Fig. 2). In this model, the β-alanine backbone adopts a U-shaped conformation to engage the hydroxamic acid group in chelation with the catalytic zinc and to project the 4-(2-methylquinolin-4-ylmethoxy)phenyl group into the S1′ pocket. The central amide carbonyl appears to be within hydrogen bonding distance with Leu129 and Gly130 residues of the β-strand above the catalytic site. The pro-*R* hydrogen on the α-carbon of the alanine seems to be in tight contact with the protein, whereas the pro-*S* hydrogen and the two hydrogens on the β-carbon are oriented toward the solvent exposed area of the active site. This model explains why both *cis* and *trans* isomers are active and predicts that the (1*S*,2*R*) enantiomer of the *cis*-pair (confirmed with **21**) and the (1*S*,2*S*) enantiomer of the *trans*-pair are responsible for activity.

Despite its binding affinity, compound **23** was a weak inhibitor of TNF-α production in LPS-stimulated whole blood assay (WB IC_{50} 2860 nM, Table 1). The exact

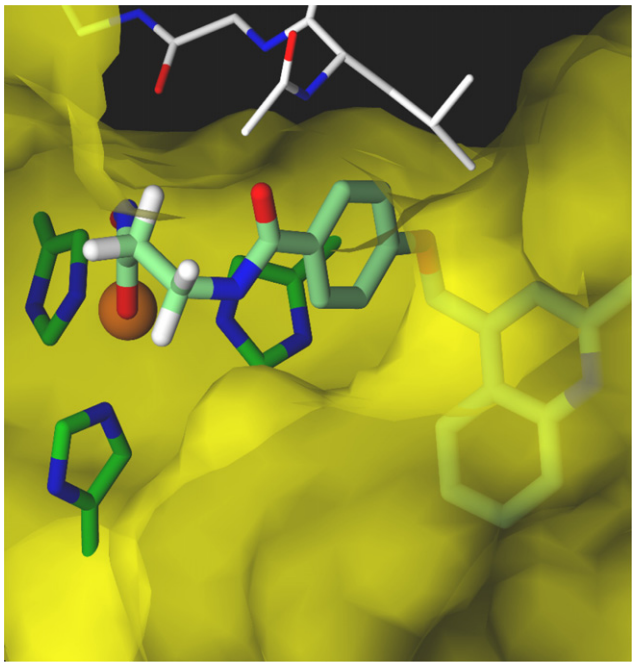
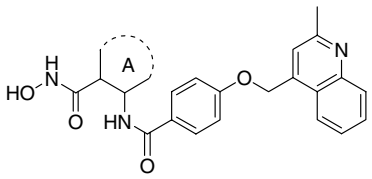


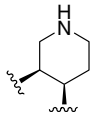
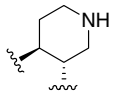
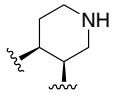
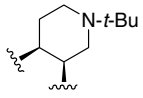
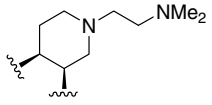
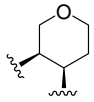
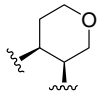
Figure 2. Computer model of hydroxamic acid **23** in TACE. Compound **23** is shown in light green except for oxygens (red) and nitrogens (blue). Hydrogens on the inhibitor are not shown for clarity except for the four hydrogens on the β-alanine backbone (white). The surface representation of TACE (yellow) is truncated to expose backbone atoms of Leu129 and Gly130, catalytic zinc (orange), and three imidazole side chains of histidines ligating to the zinc. The Leu129 and Gly130 are shown in white and the imidazoles in green except for nitrogens (blue) and oxygens (red).

reasons for the loss of cellular activity are unclear. One possible factor is its high molecular flexibility, which can adversely affect cell membrane permeation rate[11] and hence its ability to inhibit intracellular TACE activity.[12] Although not a direct measurement, compound **23** was found to have low permeation rate in Caco-2 cells (P_{app} of 0.4×10^{-6} cm/s). Cyclic analogues **19** and **20**, with reduced number of rotatable bonds and hence reduced molecular flexibility, were found to have higher Caco-2 permeation rates (3.4×10^{-6} and 9.0×10^{-6} cm/s, respectively). Both compounds exhibited improved activity in the WB assay (890 and 662 nM). For reasons not understood, the two *trans* analogues **17** and **18** were inactive in the WB assay.

The effect of heterocyclic constraint to the β-alanine backbone was evaluated next. Of the three piperidine isomers studied, the unsubstituted analogues **24**–**26**[13] showed promising WB potency (Table 2). The WB potency for each isomer can be improved by derivatization of the piperidine nitrogen. For example, introducing *t*-butyl and 2-(*N*,*N*-dimethylamino)ethyl groups to **26** improved WB potency to 44 and 55 nM, respectively (**27** and **28**). Unfortunately, functional groups beneficial to WBA potency often resulted in reduced permeability and erosion of oral bioavailability. After extensive SAR efforts, we were unable to identify a piperidine lead that had potent WB activity (<200 nM) and adequate oral exposure in rodent.

Table 2. In vitro potency in pTACE, WB LPS/TNF-α, and permeation rate in Caco-2 cells



	A	pTACE IC_{50}[a] (nM)	WB LPS/ TNF-α IC_{50}[b] (nM)	Caco-2[c]
24		24	620	0.2
25		<1	393	—
26		1	187	0.2
27		2	44	0.6
28		2	55	0.1
29		3	4114	0.06
30		<1 (K_i = 0.15)	130	2.3
31		<1	290	0.4

[a] pTACE IC_{50} values were from a single determination.
[b] Inhibition of TNF-α release from WB was determined with three donors.
[c] Caco-2 permeation rates were determined as n of 3 and are reported as P_{app} value in $\times 10^{-6}$ cm/s.

Tetrahydropyran rings were also well tolerated as evidenced by the potent pTACE activity (**29**–**31**, Table 2). In the WB assay, **30** was most potent with an IC_{50} of 130 nM. In contrast, **29**, which differs from **30** only by transposition of the ether oxygen, was 30-fold less potent. The location of the ether oxygen also impacted Caco-2 permeability. The 2-acid **29** was not permeable in Caco-2 assay, whereas the 3-acid **30** was most permeable with a P_{app} value of 2.3×10^{-6} cm/s.

Further testing revealed that **30** was a highly potent inhibitor of pTACE with a K_i of 0.15 nM (Table 2). It was also selective for pTACE relative to 16 other metalloproteases (Table 3). The selectivity was extraordinarily high (>2000-fold) against MMP-1, -2, -8, -9, -13, -14, -15, and -16 ADAMTS-4 and -5,[14] and ADAM-9 and -10. Although K_i values for the four remaining MMPs (MMP-3, -7, -10, and -12) were under 100 nM, compound **30** still maintained respectable selectivity for pTACE.

The unbound fractions of **30** in rat, dog, and human serum were 3.8, 17.0, and 7.5%, respectively, with albumin the major component responsible for the serum binding.[15] CYP 3A4 was the major isozyme responsible for oxidative metabolism of **30** in vitro, but was not inhibited by **30** to a significant extent at concentrations of 20 μM. In rats and dogs, the major metabolites of **30** were the glucuronide of the parent compound on the hydroxamic acid moiety and carboxylic acid derivative of the hydroxamic acid. **30** was also screened at 1 μM and 10 μM concentrations in an extensive array of assays including receptor binding, ion channel effects, regulatory sites, and enzymes (Nova Screen), and showed no significant activity in any assay at either of the concentrations tested. Finally, **30** was not mutagenic in a bacterial reverse mutation (Ames) assay.

Compound **30** was tested in a mouse model of endotoxemia.[10] When dosed orally as a 0.5% citric acid and 0.2% Tween 80 water solution at doses of 0.3, 1.0, 3.0, 10, and 30 mg/kg, compound **30** inhibited LPS-induced TNF-α production in a dose dependent manner with an ED_{50} of 2.2 mg/kg. Compound **30** was also tested in a similar model in rat, and was found to suppress TNF-α production with an oral ED_{50} of 3.0 mg/kg.

To assess its pharmacokinetic profile, **30** was administered intravenously and orally to Sprague–Dawley rats and Beagle dogs, and the plasma samples were analyzed by LC-MS-MS.[10,16] In rats, **30** had a modest clearance rate of 0.7 L/h/kg and a short half-life (1.4 h, Table 4). The volume of distribution at steady state was 0.4 L/kg, suggesting limited distribution and tissue binding. It was rapidly absorbed after oral administration. The oral bioavailability in rats was 58%. More significantly, high blood exposure (AUC) was achieved after oral administration (65 μM·h at 40 mg/kg dose). Following iv administration in dogs, **30** had a larger volume of dis-

Table 3. pTACE selectivity of **30** against related metalloproteases

Enzyme	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-10	MMP-12
Selectivity (fold)	>30,000	>30,000	427	200	5500	>14,000	320	93
Enzyme	MMP-13	MMP-14	MMP-15	MMP-16	ADAMTS-4	ADAMTS-5	ADAM-9	ADAM-10
Selectivity (fold)	>30,000	>30,000	>40,000	>30,000	20,000	2267	>30,000	>50,000

Table 4. Pharmacokinetic profile of **30**

	Dose (mg/kg)	$t_{1/2}$ (h)	Cl (L/h/kg)	V_{ss} (L/kg)	AUC (μM·h)	*F*%	T_{max} (h)
Rat[a,b]	2 (iv)	1.4	0.7	0.4	5.7	—	—
	40 (po)	—	—	—	65	58	0.4
Dog[c,d]	2 (iv)	1.6	1.7	1.6	2.7	—	—
	8 (po)	—	—	—	11	96	0.2

[a] Determination of 3 for each dosing group.
[b] Dosed as a mono-trifluoroacetate salt in 50 mM citrate buffer.
[c] Determination of 2 for each dosing group.
[d] Dosed as a mono-trifluoroacetate salt in a saline solution.

tribution at steady state (V_{ss}, 1.6 L/kg), more than twice the total body water of 0.6 L/kg, indicating that **30** has extensive tissue distribution and binding in dogs. The difference of V_{ss} between the rat and dog may be attributed in part to the approximate 4-fold difference of the unbound fraction in serum between the two species. Following oral administration, **30** was rapidly and completely absorbed in dogs with peak concentration achieved within 1 h and oral bioavailability of 96%. A high oral AUC number was also achieved in dogs (11 μM·h after 8 mg/kg dose).

In summary, a series of β-benzamido hydroxamic acid TACE inhibitors was discovered. The TACE selectivity was addressed from onset by exploiting interactions of 4-(2-methylquinolin-4-ylmethoxy)phenyl group with the TACE S1′ specificity pocket. SAR work to address the cellular activity and oral bioavailability issues was guided by a computer-generated binding model and centered on constrained β-alanine analogues. Compound **30** emerged as an advanced lead with potent enzyme and cellular activity, good to excellent selectivity, potent oral efficacy in LPS-challenged mice and rats, and high oral bioavailability in rat and dog. The overall profile of **30** makes it a highly valuable molecule to evaluate in preclinical models and to assess the benefits associated with chronic inhibition of TACE as well as potential side effects.[17]

The discovery of the simple alanine lead **24** and construction of binding model in TACE (Fig. 1) has not only led to the discovery of **30**, but also uncovered additional opportunities to constrain the β-alanine moiety to further improve in vitro and in vivo properties. Results from those approaches will be reported in the future.[18,19]

Acknowledgments

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References and notes

1. (a) Moss, M. L.; White, J. M.; Lambert, M. H.; Andrews, R. C. *Drug Discov. Today* **2001**, *6*, 417; (b) Black, R. A. *Int. J. Biochem. Cell Biol.* **2002**, *34*, 1.
2. (a) Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **1999**, *42*, 2295; (b) Feldmann, M.; Brennan, F. M.; Williams, R. O.; Cope, A. P.; Gibbons, D. L.; Katsikis, P. D.; Maini, R. N. *Prog. Growth Factor Res.* **1992**, *4*, 247; (c) Van Assche, G.; Rutgeerts, P. *Exp. Opin. Invest. Drugs* **2000**, *9*, 103; (d) Kristensen, M.; Chu, C. Q.; Eedy, D. J.; Feldmann, M.; Brennan, F. M.; Breathnach, S. M. *Clin. Exp. Immunol.* **1993**, *94*, 354.
3. (a) Moreland, L. W.; Baumgartner, S. W.; Schiff, M. H.; Tindall, E. A.; Fleischmann, R. M.; Weaver, A. L.; Ettlinger, R. E.; Cohen, S.; Koopman, W. J.; Mohler, K.; Widmer, M. B.; Blosch, C. M. *N. Eng. J. Med.* **1997**, *337*, 141; (b) Lipsky, P. E.; van der Heijde, D. M. F. M. E.; St. Clair, W.; Furst, D. E.; Breedveld, F. C.; Kalden, J. R.; Smolen, J. S.; Weisman, M.; Emery, P.; Feldmann, M.; Harriman, G. R.; Maini, R. N. *N. Eng. J. Med.* **2000**, *343*, 1594.
4. For a recent review of TACE inhibitors, see Le, G. T.; Abbenante, G. *Curr. Med. Chem.* **2005**, *12*, 2963.
5. (a) Xue, C.-B.; He, X.; Roderick, J. J.; Corbett, R. L.; Duan, J. J.-W.; Liu, R.-Q.; Covington, M. B.; Newton, R. C.; Magolda, R. L.; Wexler, R. R.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4293; (b) Xue, C.-B.; He, X.; Roderick, J. J.; Corbett, R. L.; Duan, J. J.-W.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Ribadeneira, M.; Vaddi, K.; Christ, D. D.; Newton, R. C.; Wexler, R. R.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4299.
6. (a) 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; (b) 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.
7. Compound **9a** was prepared from methyl 4-oxo-3-piperidinecarboxylate using Boc_2O, *i*-Pr_2NEt, and CH_2Cl_2. Compound **9b** was prepared from 1-benzyl-3-oxo-4-piperidinecarboxylate hydrochloride using H_2, $Pd(OH)_2/C$, Boc_2O, Et_3N, and EtOH. Compound **9c** was synthesized from 4-tetrahydropyranone using LiHMDS, $NCCO_2Me$, and HMPA in THF at −78 °C. Compound **9d** was prepared following a known procedure Moody, C. J.; Taylor, R. J. *J. Chem. Soc. Perkin Trans. I* **1989**, 721.
8. Cimarelli, C.; Palmieri, G. *J. Org. Chem.* **1996**, *61*, 5557.
9. The inhibitory activity was evaluated using porcine TACE as a result of its availability and homology to human TACE.

10. For details of pTACE and WB LPS/TNF-α assays, MMPs, LPS-mouse TNFα, and dog pharmacokinetic studies, 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.
11. Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45*, 2615.
12. (a) Solomon, K. A.; Covington, M. B.; Decicco, C. P.; Newton, R. C. *J. Immunol.* **1997**, *159*, 4524; (b) Schlondorff, J.; Becherer, J. D.; Blobel, C. P. *Biochem. J.* **2000**, *347*, 131.
13. The *trans* analogue **25** was synthesized from the minor enantiomer of **8b** via epimerization with DBU in xylene at reflux, followed by removal of Boc under acidic conditions and hydroxamic acid formation.
14. Miller, J. A.; Liu, R.-Q.; Davis, G. L.; Pratta, M. A.; Trzaskos, J. M.; Copeland, R. A. *Anal. Biochem.* **2003**, *314*, 260.
15. For details of serum protein binding measurement, see Cherney, R. J.; Duan, J. J.-W.; Voss, M. E.; Chen, L.; Wang, 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.
16. Wu, J.-T.; Zeng, H.; Qian, M.; Brogdon, B. L.; Unger, S. E. *Anal. Chem.* **2000**, *72*, 61.
17. (a) Newton, R. C.; Solomon, K. A.; Covington, M. B.; Decicco, C. P.; Haley, P. J.; Friedman, S. M.; Vaddi, K. *Ann. Rheum. Dis.* **2001**, *60*, iii25; (b) Zhang, Y.; Hegen, M.; Xu, J.; Keith, J. C.; Jin, G.; Du, X.; Cummons, T.; Sheppard, B. J.; Sun, L.; Zhu, Y.; Rao, V. R.; Wang, Q.; Xu, W.; Cowling, R.; Nickerson-Nutter, C. L.; Gibbons, J.; Skotnicki, J.; Lin, L.-L.; Levin, J. *Int. Immunopharmacol.* **2004**, *4*, 1845.
18. For initial efforts to optimize β-benzamido hydroxamic acids, see (a) Gilmore, J. L.; King, B. W.; Harris, C.; Maduskuie, T.; Mercer, S.; Liu, R.-Q.; Covington, M.; Qian, M.; Ribadeneria, M. D.; Vaddi, K.; Trzaskos, J.; Newton, R. C.; Decicco, C. P.; Duan, J. J.-W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2699; (b) Chen, X.-T.; Ghavimi, B.; Corbett, R. L.; Xue, C.-B.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Vaddi, K. G.; Christ, D. D.; Hardman, K. D.; Ribadeneira, M. D.; Trzaskos, J. M.; Newton, R. C.; Decicco, C. P.; Duan, J. J.-W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1856.
19. (a) For preliminary accounts of optimization of β-benzamido hydroxamic acids, see: Duan, J. J.-W.; Ott, G. R.; King, B. W.; Maduskuie, T. P.; Xue, C.-B.; Chen, L.; Lu, Z.; Gilmore, J. L.; Asakawa, N.; Mercer, S. E.; Xu, M.; Harris, C. M.; Wasserman, Z. R.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Vaddi, K. G.; Christ, D. D.; Hardman, K. D.; Ribadeneira, M. D.; Newton, R. C.; Trzaskos, J. M.; Decicco, C. P. *Abstracts of papers*, 226th ACS National Meeting, New York, NY, 2003, MEDI-201; (b) Ott, G. R.; Lu, Z.; Asakawa, N.; Covington, M. B.; Qian, M.; Liu, R.-Q.; Newton, R. C.; Christ, D. D.; Decicco, C. P.; Duan, J. J.-W. *Abstracts of Papers*, 228th ACS National Meeting, Philadelphia, PA, USA, 2004, MEDI-324; (c) Lu, Z.; Anand, R.; Liu, R.-Q.; Covington, M.; Vaddi, K.; Qian, M.; Duan, J. J. -W.; Ott, G. R. *Abstracts of Papers*, 230th ACS National Meeting, Washington DC, 2005, MEDI 288; (d) Ott, G. R.; Asakawa, N.; Lu, Z.; Anand, R.; Liu, R.-Q.; Covington, M.; Vaddi, K.; Qian, M.; Duan, J. J.-W. *Abstracts of Papers*, 230th ACS National Meeting, Washington DC, 2005, MEDI 289.