Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 4678–4682

Synthesis and structure–activity relationship of a novel, non-hydroxamate series of TNF-α converting enzyme inhibitors

John L. Gilmore,* Bryan W. King, Naoyuki Asakawa, Kimberly Harrison, Andrew Tebben, James E. Sheppeck II, Rui-Qin Liu, Maryanne Covington and James J.-W. Duan

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

Received 6 March 2007; revised 21 May 2007; accepted 22 May 2007
Available online 7 June 2007

Abstract—A novel series of TNF-α converting enzyme (TACE) inhibitors which are non-hydroxamate have been discovered. These compounds use a triazolethione moiety as the zinc binding ligand and exhibit IC_{50} values from 1.5 to 100 nM in a porcine TACE assay. They also have excellent selectivities over other MMPs.

Tumor necrosis factor-α (TNF-α)[1] is a potent proinflammatory cytokine that is primarily produced by monocytes and macrophages, and is implicated in a variety of chronic inflammatory diseases such as rheumatoid arthritis (RA), inflammatory bowel disease, psoriasis, and Crohn's disease.[2] Marketed anti-TNF-α biologics, such as Enbrel, Remicade, and Humira, work by sequestering TNF-α thus blocking its action at the TNF-α receptor. Such biologics have clinically validated anti-TNF-α therapy for the treatment of chronic inflammatory diseases.[3] While these agents are a significant advance in the treatment of many inflammatory diseases, the high cost and need to be administered parenterally have led to an interest in developing orally active small molecules that suppress TNF-α activity.

An alternate approach is to inhibit the release of soluble TNF-α via inhibitors of TNF-α Converting Enzyme (TACE).[4] TACE is a member of the metzincin family and is the primary sheddase for releasing soluble TNF-α from cells. It has been shown that inhibition of TACE blocks soluble TNF-α release; thus a small molecule inhibitor of TACE may represent a valid approach to anti-TNF-α therapy.[5]

The majority of TACE inhibitors reported in the literature rely on hydroxamic acids and 'reverse' hydroxamic acids as the zinc binding ligands.[6] Because hydroxamic acids are often poorly absorbed and carry potential metabolic liabilities such as *O*-glucuronidation and hydrolysis in vivo to give the corresponding acid and toxic hydroxylamine,[7] there is considerable interest in the discovery of non-hydroxamate TACE inhibitors.[6b] Recently, we have reported using 5-phenylpyrimidine-2,4,6-trione (barbiturate) derivatives,[8] hydantoin derivatives[9,10] and triazolone derivatives[9,10] as selective, non-hydroxamate inhibitors of TACE.

From our previous work utilizing hydantoins and barbiturates as the zinc binding group (ZBG), we have elucidated a pharmacophore model for the criteria that can be used for the design of selective, non-hydroxamate TACE inhibitor (Fig. 1).[10] In the active site, the ZBG must form either a bidentate or monodentate interaction with the Zn. Additionally, a hydrogen bond donating group is required for an interaction with a conserved active site glutamate (E406), and an additional group is required for a hydrogen bond to a glycine (G349) amide carbonyl. A linker group which induces a U-turn between the ZBG and the P1′ group must be present and this linker must contain a hydrogen bond acceptor which is capable of interacting with the mainchain G349 and leucine (L348) as observed in many other MMP inhibitor-MMP crystal structures.[11,14] Finally, an appropriately functionalized P1′ group anchors the molecule and is largely responsible for conferring the desired selectivity over MMPs.

Keywords: TACE; Inflammation; Rheumatoid arthritus.
* Corresponding author. Tel.: +1 609 252 3153; e-mail: john.gilmore@bms.com

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.05.100

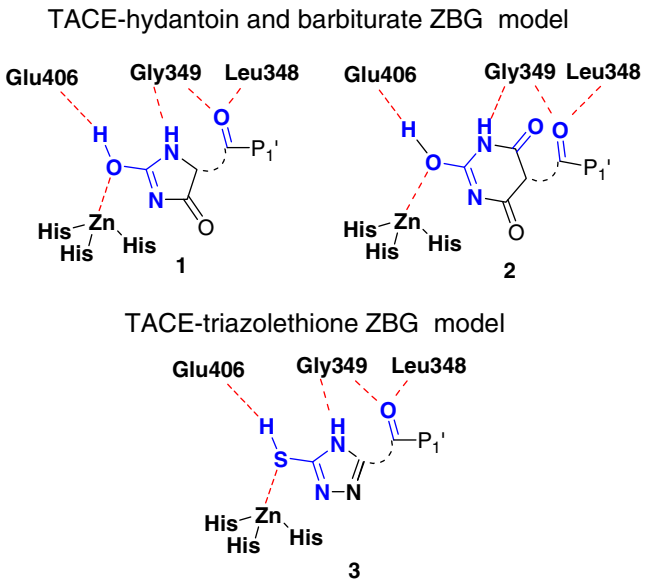
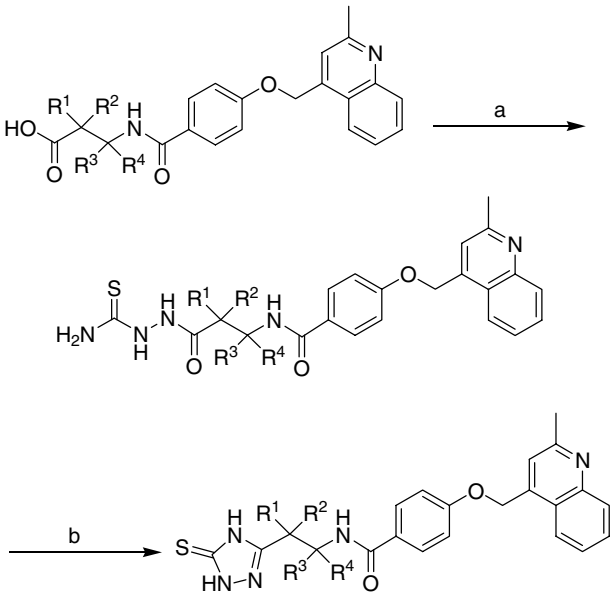


Figure 1. Pharmacophore model for non-hydroxamate TACE inhibitors (shown as enol tautomers).



Scheme 1. Reagents and condition: (a) thiosemicarbazide, HATU, *N*-methylmorpholine or diisopropylethylamine, DMF; (b) 2 N NaOH, △. Yields 18–70%.

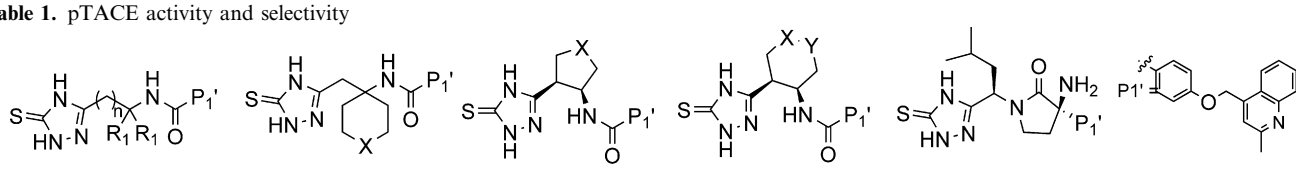
This paper discloses a new series of non-hydroxamate inhibitors which uses a 1,3,4-triazole-2-thione scaffold as the zinc binding ligand (Fig. 1, compound **3**). The triazolethione moiety contains the necessary elements to make all of the active site interactions discussed above. The thiocarbonyl can interact with the zinc in the active site. One of the NH groups of the thiourea moiety has a pK_a of 7 which can tautomerize to thiol **3** thus creating a strong hydrogen bond to the active site E406 (or deprotonation by E406 to form the thiolate). Finally, the other NH of the thiourea can form a hydrogen bond to the mainchain G349 carbonyl. With our proposed ZBG identified, we needed to find the optimal linker groups that would give the desired conformation to take advantage of our TACE-selective P1′ group.[12] We began by utilizing previously synthesized scaffolds from our laboratories which worked well with a hydroxamic acid as the zinc binding ligand.[13] While the size of the hydroxamate and triazolethiones are clearly different, the ease of synthesis from established scaffolds justified their preparation. The hydroxamic acids were replaced with a triazolethione scaffold and tested for their porcine TACE (pTACE) activity. Porcine TACE was used because of its availability and high homology to human TACE, and MMP-2,-3,-7,-12, and -13 were used as a representative selectivity panel that possesses both shallow and deep S1′ pockets. To achieve the desired selectivity, we used our previously disclosed TACE- selective 4-[methyl(quinolinylmethoxy)phenyl] P1′ side chain.[12]

The triazolethione compounds were synthesized according to Scheme 1. The corresponding acids were coupled with thiosemicarbazide using HATU, and the resulting compounds were cyclized by treatment with 2 N NaOH at 100 °C to afford the desired triazolethiones in low to moderate yields.

These triazolethione analogs were tested for their pTACE activities and their IC_{50} values are shown in Table 1. Compounds **4**–**6** were designed to probe the optimal length for the spacing group between the triazolethione and the P1′ group. The compound with a single methylene spacer (**4**) was found to be inactive, while the two methylene spacer (**5**) and the three-methylene spacers (**6**) were found to be active at 210 and 294 nM, respectively. By adding dimethyl substitution on the methylene group adjacent to the P1′ amide (**7**), a beneficial change in the hydroxamate series, the pTACE activity was also greatly improved in the triazolethione series giving an activity of 55 nM. Furthermore, transposing the β,β-dimethyl substitution to a spiroheterocyclic group also improved activity. The tetrahydropyran (**8**) and the N-Boc-piperidine (**9**) compounds gave activities of 24 and 36 nM, respectively. In an effort to further preorganize the P1′ side chain, the linker was annulated α, β relative to the triazolethione (**10**–**25**). These compounds were synthesized with a cis configuration since this was known to be the more active isomer in the hydroxamate series.[13b] Both the five- and six-membered ring systems were prepared. The cyclopentyl compound (**10**) was active at 41 nM and the cyclopentyl containing a spirotetrahydrofuranyl ring (**11**) was very active at 5.6 nM. Additionally, a number of pyrrolidine compounds were prepared (**12**–**15**), all of which had good pTACE activities, especially when substituted on the pyrrolidine nitrogen. The most active compound was **14** which has an acetyl substitution at the pyrrolidine nitrogen and an IC_{50} of 1.5 nM. In the six-membered α,β-cyclic series, two regioisomeric series of piperidines (**17**–**25**) as well as a tetrahydropyran (**16**) were prepared and tested for their pTACE activities. The most active compounds in this series were the tetrahydropyran analog (**16**) and the *N*-acetylated piperidine analog (**20**) which had IC_{50} values of 8.1 and 2.5 nM, respectively.

We also tried replacing the hydroxamic acid with the triazolethione in our previously disclosed lactam series

Table 1. pTACE activity and selectivity



Compound	R^1	*n*	X	Y	pTACE inhibition IC_{50},[a] nM	MMP-2 K_i, nM	MMP-3 K_i, nM	MMP-7 K_i, nM	MMP-12 K_i, nM	MMP-13 K_i, nM
4	H	0	—	—	>1000	>3333	>4501	>6368	>6023	>5025
5	H	1	—	—	210	>3333	>4501	>6368	>6023	>5025
6	H	2	—	—	294	>3333	>4501	>6368	>6023	>5025
7	CH_3	1	—	—	55	>3333	>4501	>6368	>6023	>5025
8	—	—	O	—	24	1598	2105	635	223	753
9			NBoc	—	36	>3333	>4501	>6368	>6023	>5025
10	—	—	CH_2	—	41	>3333	>4501	>6368	>6023	>5025
11	—	—	Spirotetrahydrofuryl	—	5.6	>3333	>4501	>6368	>6023	>5025
12	—	—	NBoc	—	14	>3333	>4501	>6368	3560	>5025
13	—	—	NH	—	92	>3333	>4501	>6368	>6023	>5025
14	—	—	$NC(O)CH_3$	—	1.5	>3333	>4501	>6368	>6023	>5025
15	—	—	N $CH_2CH_2CH_3$	—	9.9	>3333	>4501	>6368	>6023	2462
16	—	—	O	CH_2	8.1	>3333	>4501	>6368	>6023	>5025
17	—	—	NH	CH_2	43	>3333	>4501	>6368	>6023	>5025
18	—	—	CH_2	NBoc	75	>3333	>4501	>6368	>6023	>5025
19	—	—	CH_2	NH	9.4	>3333	>4501	>6368	>6023	>5025
20	—	—	CH_2	$NC(O)CH_3$	2.5	>3333	>4501	>6368	>6023	3136
21	—	—	CH_2	N $CH_2CH_2CH_3$	15	>3333	>4501	>6368	>6023	>5025
22	—	—	CH_2	NSO_2CH_3	28	>3333	>4501	>6368	>6023	>5025
23	—	—	CH_2	NCH_3	16	>3333	>4501	5371	958	>5025
24	—	—	CH_2	$NCH(CH_3)_2$	31	>3333	>4501	>6368	>6023	>5025
25	—	—		*N*-Propargyl	73	>3333	>4501	>6368	>6023	>5025
26					>1000	>3333	>4501	>6368	>6023	>5025

All compounds are enantiomerically and diastereomerically pure with the stereochemistry shown.
[a] pTACE IC_{50} and MMP K_i values are from a single determination.

(**26**).[13c] Unfortunately, this compound has no pTACE activity indicating there are differences between the two ZBGs and not all scaffolds that work with hydroxamates will work with the triazolethiones. Models suggest that the lactams do not make a sharp enough U-turn to accommodate the triazolethione ZBG (data not shown). All of the compounds tested had excellent selectivity versus MMP-2,-3,-7,-12, and -13 except for compound **8** which had moderate selectivity over MMP-7,-12, and -13.

Figure 2 shows a model of triazolethione **14** in the active site of TACE (blue) overlayed with the crystallographic conformation[14a] of our previously disclosed hydroxamate, IK682 (shown in yellow).[12a] The model shows that the triazolethione ZBG makes three interactions in the active site of TACE. The triazolethione moiety interacts with the active site zinc via a monodentate interaction between the thiocarbonyl and the zinc, and this thiocarbonyl also forms a strong hydrogen bond to E406 in what resembles the thiol tautomer. This is reminiscent of the crystallographic conformation of thiadiazolethione scaffolds as the ZBG for the matrix metalloprotease stromelsin (MMP-3) in which they observe a monodentate interaction with zinc as well as a hydrogen bond to an active site glutamate.[15] The 4-position NH forms a hydrogen bond with the backbone carbonyl of G349. This model is consistent with the binding mode models

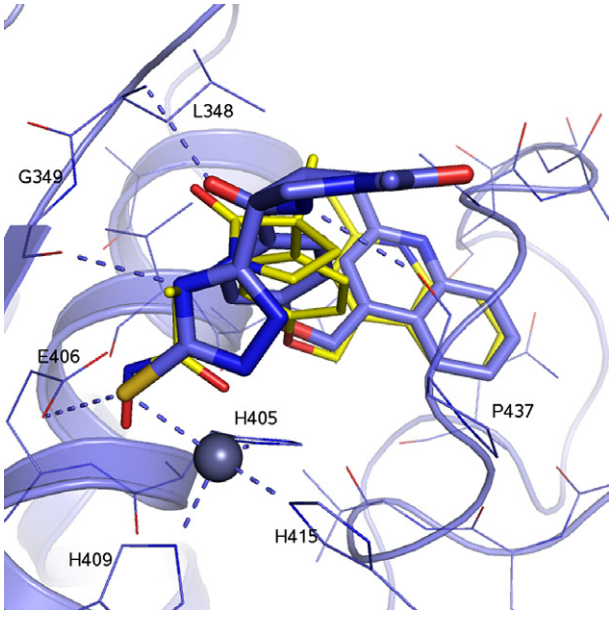


Figure 2. Triazolethione modeled in the active site of TACE (blue). The crystallographic conformation of the hydroxamate IK682[12a] is shown in yellow.[14a] The triazolethione moiety interacts with TACE via the thiourea, forming a monodentate interaction with the zinc and a hydrogen bond with the backbone carbonyl of G349. The thiocarbonyl also forms a hydrogen bond to E406. The central amide forms additional hydrogen bonds with the backbone NH of L348 and the backbone carbonyl of P437.

of the barbiturate, hydantoin, and triazolone ZBG groups.[10,11] By contrast, hydroxamate inhibitors form five interactions in the TACE binding site. Additionally, the central amide of the triazolethione inhibitors forms hydrogen bonds with the backbone NH of L348 and the backbone carbonyl of P437. The TACE selective quinolinylmethoxy P1′ side chain achieves a similar conformation between the crystallographic conformation of the hydroxamate and compound **14**.

Although the model suggests the triazolethiones have two less active site interactions than hydroxamates, they are very potent TACE inhibitors with excellent selectivity over MMP-2,-3,-7,-12, and -13. Furthermore, the triazolethiones appear to have intrinsically better potency than comparably substituted barbiturates, hydantoins, and triazolones, which are other ZBGs discovered in our laboratories. Our data suggest that this is in part due to their low pK_a of 7 which forms a tighter H-bond to general base E406 rather than any appreciable contribution from Zn–S d orbital stabilization. Modification of the spacer moiety between the triazolethione and the P1′ group led to the identification of several inhibitors with IC_{50}'s of less than 100 nM. The most active compound, **14**, has an activity of 1.5 nM in the pTACE assay which is comparable to hydroxamates.

Acknowledgment

We thank John Giannaris, Sherrill Nurnberg, and Paul Streminski for carrying out the enzyme and cell assays.

References and notes

1. Aggarwal, B. B.; Kohr, W. J.; Hass, P. E.; Moffat, B.; Spencer, S. A.; Henzel, W. J.; Bringman, T. S.; Nedwin, G. E.; Goeddel, D. V.; Harkins, R. N. *J. Biol. Chem.* **1985**, *260*, 2345.
2. (a) Aggarwal, B. B.; Natarajan, K. *Eur. Cytokine Netw.* **1996**, *7*, 93; (b) Eigler, A.; Sinha, B.; Hartmann, G.; Endres, S. *Immunol. Today* **1997**, *18*, 487; (c) Feldmann, M.; Brennan, F.; Elliott, M.; Katsikis, E.; Maini, R. *Circ. Shock* **1994**, *43*, 179.
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 Claire, 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; (c) Elliott, M.; Maini, R.; Feldmann, M.; Kalden, J.; Antoni, C.; Smolen, J.; Leeb, B.; Breedveld, F.; Macfarlane, J.; Bijl, H.; Woody, J. *Lancet* **1994**, *344*, 1105; (d) Elliott, M.; Maini, R.; Feldmann, M.; Long-Fox, A.; Charles, P.; Bijl, H.; Woody, J. *Lancet* **1994**, *344*, 1125; (e) Van Dullemen, H.; Van Deventer, S.; Hommes, D.; Bijl, H.; Jansen, J.; Tytgat, G.; Woody, J. *Gastroenterology* **1995**, *109*, 129; (f) Maini, R.; Feldmann, M. *Arthritus Res.* **2002**, *4*(Suppl 2), S22; (g) Scallon, B.; Cai, A.; Solowski, N.; Rosenberg, A.; Song, X.-Y.; Shealy, D.; Wagner, C. *J. Pharmacol. Exp. Ther.* **2002**, *301*, 418.
4. 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.; Bolani, N.; Schooley, K. A.; Gerhart, M.; Devis, R.; Fitzner, J. N.; Johnson, R. S.; Paxton, R. J.; March, C. J.; Cerretti, D. P. *Nature* **1997**, *385*, 729.
5. (a) Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **1999**, *42*, 2295; (b) Nelson, F.; Zask, A. *Expert Opin. Invest. Drugs* **1999**, *8*, 383.
6. For recent reviews of TACE inhibitors, see: (a) Skotnicki, J. S.; Levin, J. I. *Annu. Rep. Med. Chem.* **2003**, *38*, 153; (b) Le, G. T.; Abbenante, G. *Curr. Med. Chem.* **2005**, *12*, 2963; For a recent review of non-hydroxamate MMP inhibitors, see: (c) Breuer, E.; Frant, J.; Reich, R. *Exp Opin. Ther. Pat.* **2005**, *15*, 253; (d) Skiles, J. W.; Gonnella, N. C.; Jeng, A. Y. *Curr. Med. Chem.* **2001**, *8*, 425; (e) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735.
7. In vivo hydrolysis or proteolysis of hydroxamates is highly structure dependent and variable. However, it should be noted that hydroxylamine exposure in humans causes methemoglobinemia—an acute toxicity apparently not observed during safety studies of several hydroxamates that have passed phase II clinical trials.
8. (a) Duan, J. J.-W.; Lu, Z.; Wasserman, Z. R.; Liu, R.-Q.; Covington, M. B.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2970; (b) Duan, J. J.-W.; Chen, L.; Lu, Z.; Jiang, B.; Asakawa, N.; Sheppeck, J. W.; Liu, R.-Q.; Covington, M. B.; Pitts, W.; Kim, S.-H.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 266.
9. (a) Sheppeck, J. E., II; Gilmore, J. L.; Yang, A.; Chen, X.-T.; Covington, M. B.; Duan, J. J.-W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 297; (b) Sheppeck, James E.; Gilmore, John L.; Yang, Anle; Chen, Xiao-Tao; Xue, Chu-Biao; Roderick, John; Liu, Rui-Qin; Covington, Maryanne B.; Decicco, Carl P.; Duan, James J.-W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1413.
10. Sheppeck, J. E.; Gilmore, J. L.; Tebben, A.; Xue, C.-B.; Liu, R.-Q.; Decicco, C. P.; Duan, J. J.-W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2769.
11. Sheppeck, J. E.; Tebben, A.; Gilmore, J. L.; Yang, A.; Wasserman, Z. R.; Decicco, C. P.; Duan, J. J.-W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1408.
12. For selective TACE inhibitors reported from our group: (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) 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; (c) Xue, C.-B.; He, X.; Corbett, R. L.; Roderick, J.; Wasserman, Z. R.; Lu, Z.; Liu, R.-Q.; Jaffee, B. D.; Covington, M. B.; Qian, M.; Trzaskos, J. M.; Newton, R. C.; Magolda, R. L.; Wexler, R. R.; Decicco, C. P. *J. Med. Chem.* **2001**, *44*, 3351; (d) 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; (e) 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; (f) Xue, C.-B.; He, X.; Roderick, J.; Corbett, R. L.; Duan, J. J.-W.; Liu, R.-Q.; Covington, M.

B.; Newton, R. C.; Trazaskos, J. M.; Magolda, R. L.; Wexler, R. R.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4293; (g) Xue, C.-B.; He, X.; Roderick, J.; Corbett, R. L.; Duan, J. J.-W.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Ribadeneira, M. D.; Vaddi, K.; Christ, D. D.; Newton, R. C.; Trazaskos, J. M.; Magolda, R. L.; Wexler, R. R.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4299.

13. For the synthesis of corresponding acids for compounds **7**–**8**: (a) Gilmore, J. L.; King, B. W.; Harris, C.; Maduskuie, T.; Mercer, S. E.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Ribadeneira, M. D.; Vaddi, K.; Trazaskos, J. M.; Newton, R. C.; Decicco, C. P.; Duan, J. J.-W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2699; (b) For the synthesis of corresponding acids for compounds **9**–**25**: Duan, J.; Ott, G.; Chen, L.; Lu, Z.; Maduskuie, T. P.; Voss, M. E.; Xue, C.-B. WO 2001/070673, 2001.; (c) For the synthesis of corresponding acid for compound **26**: Duan, J.; Decicco, C. P.; Wasserman, Z. R.; Maduskuie, T. P. US 2003/134827, 2003.
14. (a) Niu, X.; Umland, S.; Ingram, R.; Beyer, B. M.; Yan-Hui, L.; Sun, J.; Lundell, D.; Orth, P. *Arch. Biochem. Biophys.* **2006**, *451*, 43; (b) Maskos, K.; Fernandez-Catalan, C.; Huber, R.; Bourenkov, G. P.; Bartunik, H.; Ellestad, G. A.; Reddy, P.; Wolfson, M. F.; Rauch, C. T.; Castner, B. J.; Davis, R.; Clarke, H. R. G.; Petersen, M.; Fitzner, J. N.; Cerretti, D. P.; March, C. J.; Paxton, R. J.; Black, R. A.; Bode, W. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3408; (c) Levin, J. I.; Chen, J. M.; Laakso, L. M.; Du, M.; Schmid, J.; Xu, W.; Cummons, T.; Xu, J.; Jin, G.; Barone, D.; Skotnicki, J. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1605.
15. (a) Jacobsen, E. J.; Mitchell, M. A.; Hendges, S. K.; Belonga, K. L.; Skaletzky, L. L.; Stelzer, L. S.; Lindberg, T. J.; Fritzen, E. L.; Schostarez, H. J.; O'Sullivan, T. J.; Maggiora, L. L.; Stuchly, C. W.; Laborde, A. L.; Kubicek, M. F.; Poorman, R. A.; Beck, J. M.; Miller, H. R.; Petzold, G. L.; Scott, P. S.; Truesdell, S. E.; Wallace, T. L.; Wilks, J. W.; Fisher, C.; Goodman, L.; Powers, E. A.; Ledbetter, S. R.; Kaytes, P. S.; Vogeli, G.; Mott, J. E.; Trepold, C. M.; Staples, D. J.; Baldwin, E. T.; Finzel, B. C. *J. Med. Chem.* **1999**, *42*, 1525; (b) Stockman, B. J.; Waldon, D. J.; Gates, J. O.; Scahill, T. A.; Kloosterman, D. A.; Mizsak, S. A.; Jacobsen, E. J.; Belonga, K. L.; Mitchell, M. A.; Mao, B.; Petke, J. D.; Goodman, L.; Powers, E. A.; Ledbetter, S. R.; Kaytes, P. S.; Vogeli, G.; Marshall, V. P.; Petzold, G. L.; Poorman, R. A. *Protein Sci.* **1998**, *7*, 2281.