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HETEROCYCLIC INHIBITORS OF TUMOR NECROSIS FACTOR-α CONVERTING ENZYME (TACE)

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Abstract – A variety of heterocyclic ring systems have been prepared as scaffolds for butynyloxyphenyl sulfonamide and sulfone hydroxamic acid inhibitors of TACE enzyme. All scaffolds provided highly active TACE inhibitors, but selectivity, and cellular activity was highly scaffold dependent.

INTRODUCTION

TNF-α converting enzyme, also known as TACE or ADAM-17, is a membrane bound zinc endopeptidase that cleaves membrane bound 26kDa TNF-α to provide the 17kDa soluble TNF-α, a pro-inflammatory cyctokine which exists as a homotrimer.[1,2] Orally bioavailable small molecule modulators of TNF have been highly sought after as potential therapeutics for inflammatory diseases, most notably rheumatoid arthritis (RA), since the TNF soluble receptor Enbrel® and TNF antibodies, including Remicade® and Humira®, all biologics administered by injection or infusion, have shown excellent efficacy in the treatment of RA.[3,4,5] The search for low molecular weight inhibitors of TACE began with the examination of inhibitors of a related family of more than 20 zinc dependent enzymes, the matrix metalloproteinases (MMPs). Although the homology between the active sites of the MMPs and TACE is low, the size and shape of the enzyme subsites surrounding the catalytic zinc of some of the MMPs share enough similarities so that a variety of MMP inhibitors were also found to be potent TACE inhibitors.[6,7] The majority of these early TACE inhibitors were potent in cell-free enzyme assays, but were not very selective for TACE over a variety of MMPs, nor were most of these compounds particularly active in assays measuring the inhibition of TNF production in cells or in human whole blood.[8,9] The development of homology models based on adamalysin[10,11] and atrolysin[12] provided insights allowing the design of more potent and more selective inhibitors of TACE. In 1998 the X-ray crystal structure of TACE with a peptidic hydroxamate small molecule inhibitor bound at the active site was published,[13] confirming the validity of the previous homology models and spurring the design of additional series of highly active TACE inhibitors with a wide spectrum of selectivity profiles over the MMPs.[5,14-24] At Wyeth Research the information revealed by this

X-ray structure on the size and shape of the TACE S1’ pocket resulted in the structure-based design of a class of TACE inhibitors characterized by a novel butynyloxy P1’ moiety, providing increased activity against TACE enzyme, enhanced activity in cells, and in some cases interesting selectivity profiles (Figure 1).

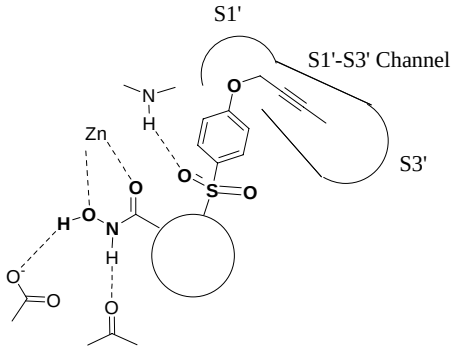
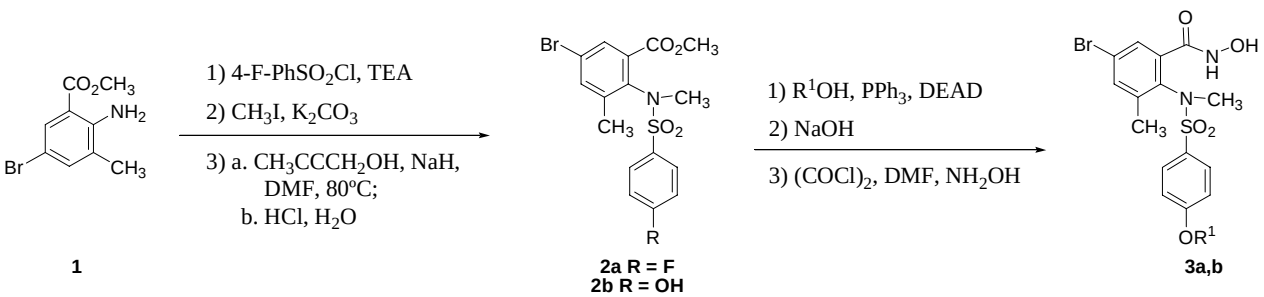


Figure 1

Thus, unlike any of the MMPs, it was found that the shallow S1’ pocket of TACE connects with the S3’ subsite via a narrow hydrophobic channel. The ether linkage of the butynyloxy P1’ group is able to make the required turn out of the S1’ pocket and approach the channel pointing toward the S3’ pocket at the correct angle, while the carbon-carbon triple bond sits snugly in the hydrophobic channel and the terminal methyl group projects slightly into the solvent exposed S3’ pocket. This review will cover the synthesis and structure activity relationships (SAR) of a selection of TACE inhibitors, from Wyeth and others, comprised of heterocyclic cores bearing this propargylic ether P1’ group.

AROMATIC AND HETEROAROMATIC CORES

The initial “proof of concept” SAR work on the butynyloxy P1’ inhibitor series was performed on a series of analogs derived from anthranilic acids, prepared as shown in Scheme 1.[11,25]



1 **2a R = F** **2b R = OH** **3a,b**

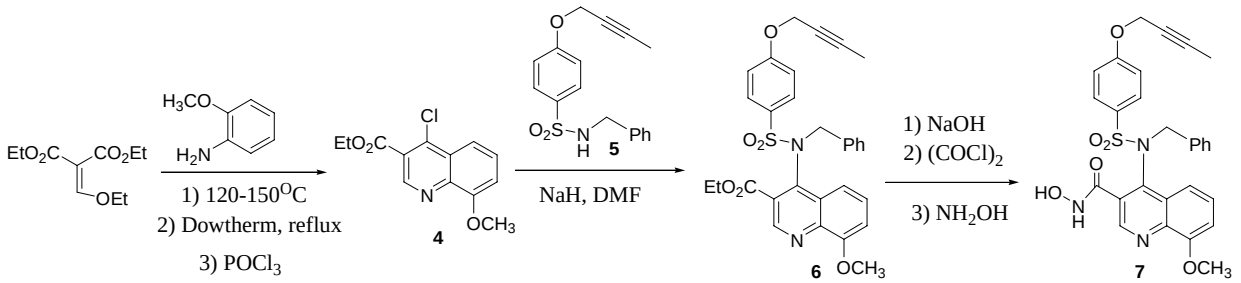
Comp	R^1	MMP-1[a]	MMP-9[a]	MMP-13[a]	TACE[a]
3a	CH_3	114	11	21	32
3b	CH_2CCCH_3	1616	304	154	16

[a]IC_{50} (nM).

Scheme 1

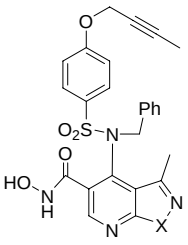
The key step is the novel displacement of 4-fluorophenyl sulfonamide (**2a**) with 3-butyn-1-ol and sodium hydride in DMF and subsequent *in situ* deprotection to provide phenol (**2b**) that can be derivatized via Mitsunobu alkylation with desired alcohols.[26] Comparison of the TACE enzyme activity of methyl ether (**3a**) with the designed butynyl ether (**3b**) demonstrates a 2-fold increase in activity for the butynyl ether. In addition, the butynyl ether is 100-fold selective over MMP-1, and approximately 20- and 10-fold selective over MMP-9 and MMP-13, respectively, while the methyl ether is less than 4-fold selective against MMP-1 and more potent against MMP-9 and MMP-13 than against TACE.

Analogs of anthranilate sulfonamide (**3b**) with bicyclic heteroaromatic cores, including quinolines, pyrazolopyridines, isoxazolopyridines, and isothiazolopyridines, were prepared according to Scheme 2, as depicted for a member of the quinoline series.[27] In this synthetic approach the displacement of the chloride of intermediate (**4**) with *N*-alkylsulfonamide (**5**) affords the *N*-heteroaryl sulfonamide (**6**), which can then be converted into the corresponding desired hydroxamic acid, **7**. As with the anthranilate series, the bicyclic heteroaromatic scaffold provides potent inhibitors of TACE enzyme, irrespective of the type of ring fused to the pyridine ring. The most potent and selective analog is the isoxazolopyridine (**8a**), a 6 nM TACE inhibitor with greater than 300-fold selectivity over MMP-1, and 40- and 20-fold selectivity over MMP-9 and MMP-13, respectively. The quinoline (**7**), and isothiazolopyridine (**8b**), and pyrazolopyridine (**8c**), are each slightly less potent against TACE and less selective over all three MMPs screened as compared to **8a**. Of these, the quinoline derivative (**7**) also proved to be active at a dose of 100 mg/kg ip bid in an *in vivo* mouse collagen induced arthritis model, an effect comparable to that of Enbrel® dosed at 150 μg/day in the same model, demonstrating the potential utility of TACE inhibition.



Comp	MMP-1[a]	MMP-9[a]	MMP-13[a]	TACE[a]
7	875	33	9	17
8a	1911	244	150	6
8b	2333	95	34	14
8c	~1000	~100	~100	30

[a]IC_{50} (nM).

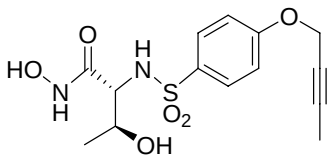


8a X = O
8b X = S
8c X = NCH$_3$

Scheme 2

7-MEMBERED RING CORES

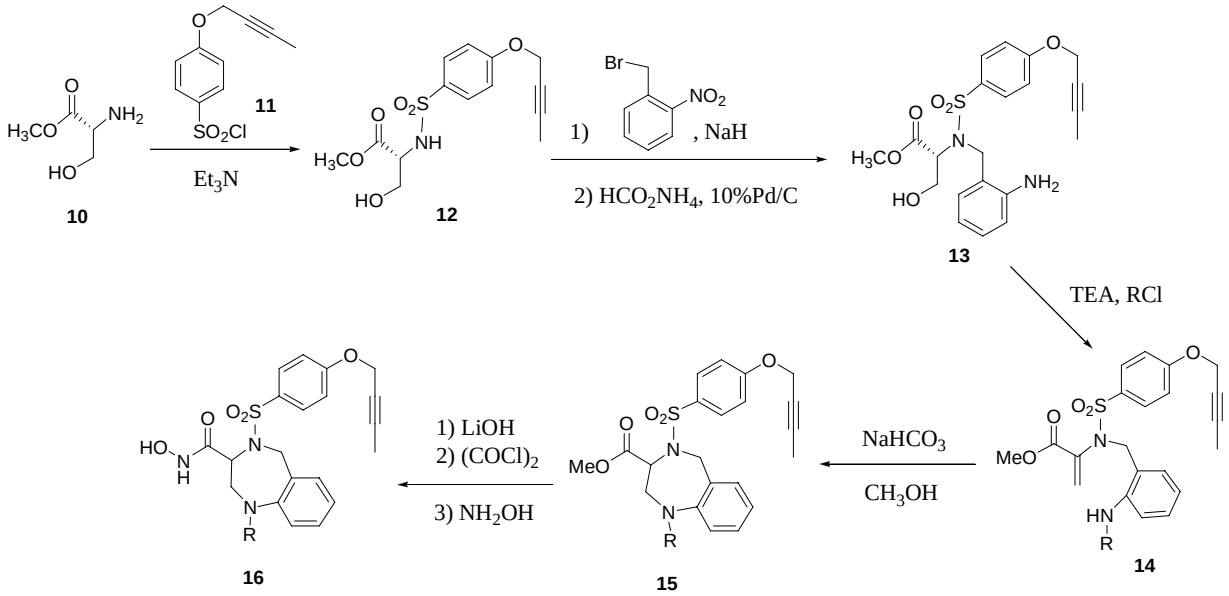
Non-aromatic scaffolds are also useful cores for sulfonamide hydroxamate inhibitors of TACE. After demonstrating that sulfonamide hydroxamate derivatives of acyclic α-amino acids, exemplified by threonine analog (**9**) (Figure 2),[28,29] provide potent and selective inhibition of cell-free TACE and are also excellent inhibitors in human whole blood and in *in vivo* efficacy models, the activity of sulfonamide hydroxamate derivatives of heterocyclic α-amino acids was explored.



9

Figure 2

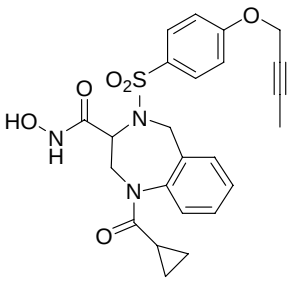
Thus, the benzodiazepine scaffold (**16**) was constructed according to the route shown in Scheme 3, starting from serine.[30] The benzodiazepine ring, **15**, arose from dehydration of serine sulfonamide (**13**) to give the unsaturated ester analog (**14**), which then cyclized in the presence of methanolic sodium bicarbonate. Conversion of ester (**15**) into the corresponding hydroxamic acid then gave the desired targets (**16**).



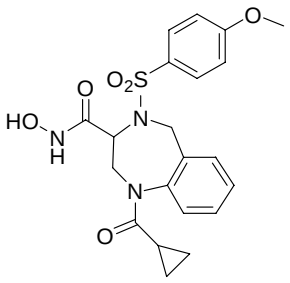
Scheme 3

Benzodiazepine cyclopropylamide (**16a**) is the most potent member of this series, a 10 nM inhibitor of TACE enzyme with greater than 80-fold selectivity over MMP-1 (Table 1). However, it is less than

50-fold selective over both MMP-9 and MMP-13. In this case the butynyloxy P1' moiety provides a significant improvement in activity against TACE and in selectivity over MMP-1, relative to the methoxy P1' analog (**17**). Unfortunately, **16a** produced only 59% inhibition of LPS-induced TNF production at 3 μM in THP-1 cells, a line of human monocytes. The incorporation of polar functionality on the phenyl ring of the benzodiazepine provided analog (**18**) with substantially improved cellular activity, 81% inhibition of TNF production at 3 μM in THP-1 cells, but slightly reduced selectivity over MMP-1.[31] Despite this significant activity in cells the pendant basic amine in derivative (**18**) does not endow this analog with activity *in vivo*, perhaps due to poor pharmacokinetics.



16a



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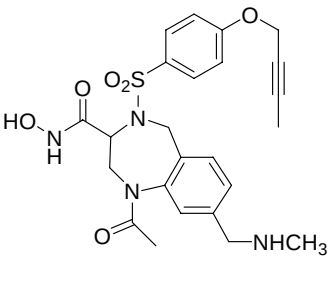


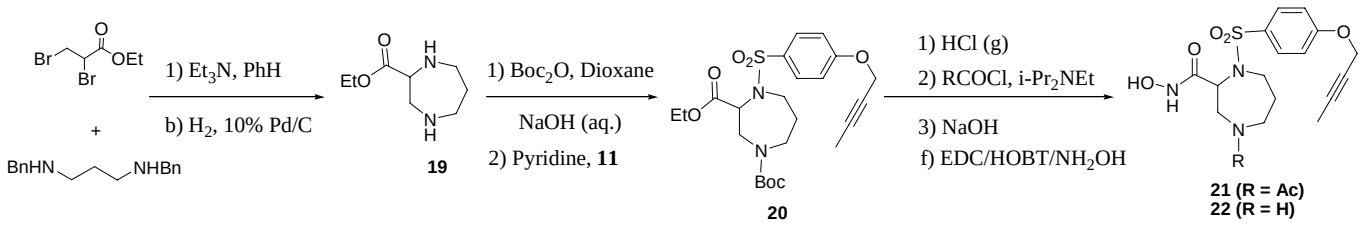
18

Comp	MMP-1[a]	MMP-9[a]	MMP-13[a]	TACE[a]
16a	841	33	29	10
17	171	4	3	69
18	456	--	32	14

[a]IC_{50} (nM).

Table 1

Diazepines and thiazepines, with no fused aromatic ring, are also effective scaffolds for TACE inhibition.[32] The racemic 1,4-diazepine-2-carboxylic acid core was prepared as shown in Scheme 4. The reaction of *N, N'*-dibenzyl-1,3-propanediamine with ethyl 2,3-dibromopropionate gives the desired 7-membered ring system (**19**). Selective protection of the less hindered amine followed by sulfonylation affords **20**, which can be deprotected and functionalized on the diazepine nitrogen prior to hydroxamate formation. Diazepine acetamide (**21**) is a 4 nM inhibitor of TACE and greater than 500-fold selective over MMP-1, considerably more selective than the analogous benzodiazepine. This compound also shows moderate activity in THP cells, providing 74% inhibition at 3 μM. The NH diazepine analog (**22**) formed from **20** by ester hydrolysis and hydroxamate formation, followed by removal of the Boc protecting group, is an 11 nM TACE inhibitor with only 50-fold selectivity over MMP-1 and greatly reduced activity in THP cells, demonstrating the ability of substituents at this position to modulate *in vitro* activity.

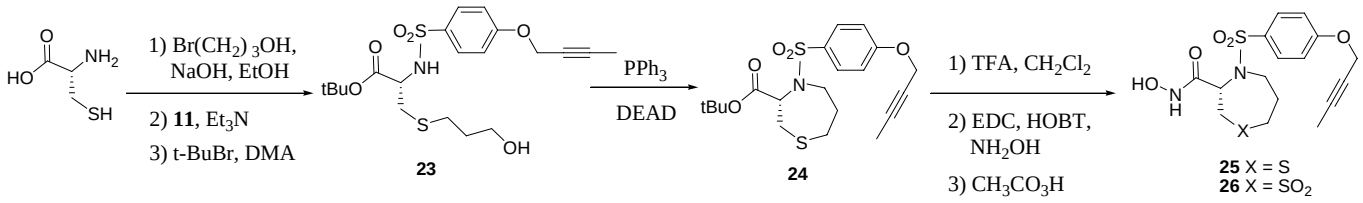


Comp	MMP-1[a]	MMP-13[a]	TACE[a]
21	2117	305	4
22	576	225	11

[a]IC_{50} (nM).

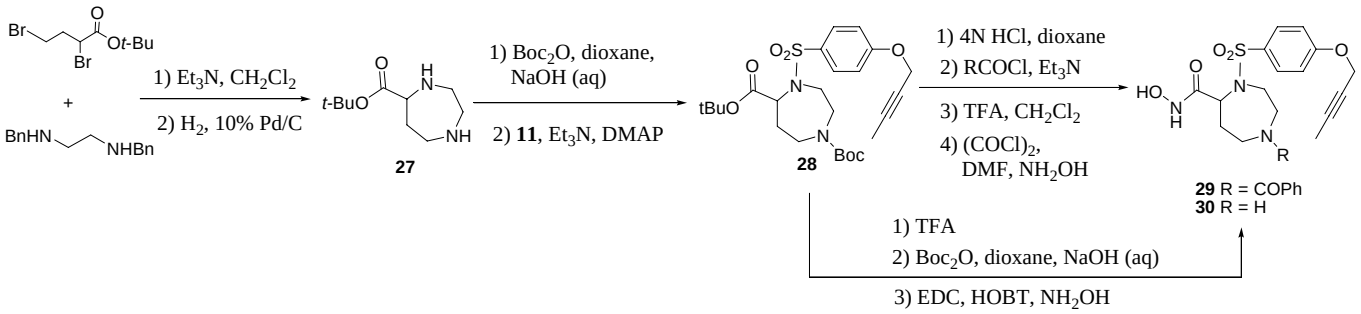
Scheme 4

Thiazepine (**25**), analogous to the 1,4-diazepine-2-hydroxamate (**22**), prepared starting from D-penicillamine via intra-molecular Mitsunobu alkylation of sulfonamide alcohol (**23**), as shown in Scheme 5, is somewhat less potent against TACE (IC_{50} = 20 nM) and only 20-fold selective over MMP-1 (IC_{50} = 408 nM). Oxidation of this analog with peracetic acid to the corresponding sulfone (**26**) affords a 28 nM TACE inhibitor with *in vivo* activity in the mouse LPS model. Thus, a 50 mg/kg oral dose of **26** gives 77% inhibition of TNF production one hour after administration of LPS.



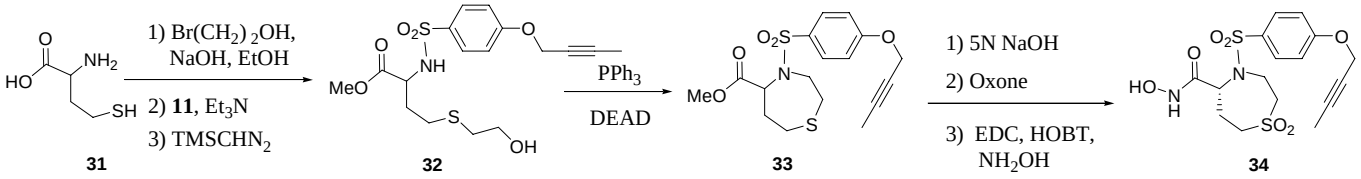
Scheme 5

Transposition of a nitrogen in the diazepine ring of **21** yields the related 1,4-diazepine-5-carboxylate skeleton, which was prepared according to the route shown in Scheme 6, starting with the alkylation of *N,N'*-dibenzyl-1,2-ethanediamine with 2,4-dibromobutyric acid *tert*-butyl ester. The resulting diazepine sulfonamide hydroxamates are similar in potency against TACE enzyme to the 1,4-diazepine-2-hydroxamates, and less selective over MMP-1 and MMP-13, but their ability to inhibit TNF production in cells is greatly improved. For example benzamide derivative (**29**) is a 10 nM inhibitor of TACE with only 10-fold selectivity over MMP-1, but it gives 93% inhibition of TNF production at 3 μM. The NH 1,4-diazepine-5-hydroxamate (**30**) is less active against TACE (IC_{50} = 24 nM) and also only 10-fold selective over MMP-1, but it performs well in THP cells (83% inhibition at 3 μM), is highly active *in vivo*, with a 50 mg/kg oral dose providing 97% inhibition of LPS-stimulated TNF production one hour after dosing in the mouse, and is efficacious in a collagen-induced arthritis model of RA at 20 mg/kg po bid.



Scheme 6

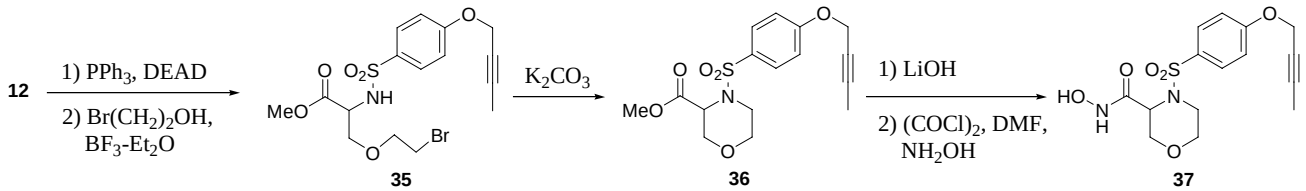
Sulfone (**34**), an analog of 1,4-diazepine-5-hydroxamate (**30**), prepared as shown in Scheme 7 starting from homocysteine, with the thiazepine ring formed by intra-molecular Mitsunobu reaction, is virtually equivalent in activity to the NH diazepine (**30**) *in vitro* and *in vivo* in the mouse LPS model.



Scheme 7

6-MEMBERED RING SCAFFOLDS

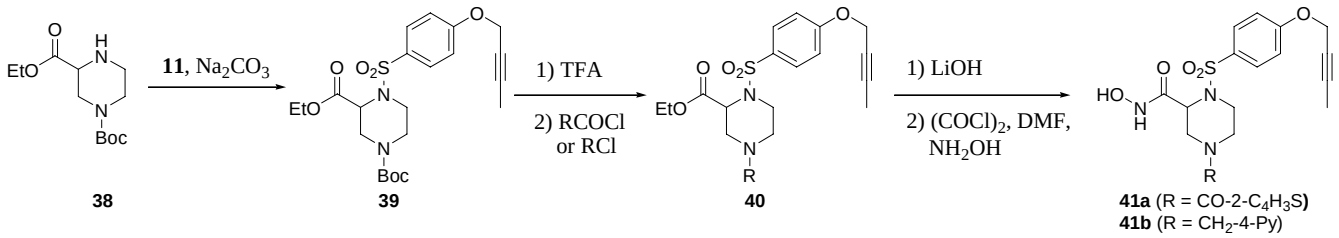
Six-membered ring heterocycles, including piperazines, morpholines, and thiomorpholines were also employed as cores in the sulfonamide hydroxamate series.[33,34] The morpholine core was synthesized as shown in Scheme 8 starting from serine methyl ester, via an intra-molecular alkylation of bromo-sulfonamide (**35**). The morpholine derivative (**37**) was quite potent against TACE enzyme (IC_{50} = 5 nM) and MMP-13 (IC_{50} = 26 nM), with modest selectivity of approximately 30-fold selectivity relative to MMP-1 and MMP-9. Cellular activity for **37** was good with 80% inhibition in THP cells at 3 μM.



Scheme 8

The piperazine series of general structure (**41**) gave analogs with slightly less activity against TACE than morpholine (**37**), with enzyme and cell potency dependent on the functionality attached to the piperazine nitrogen. The synthesis of these analogs from the known the known *N*-Boc piperazine carboxylate

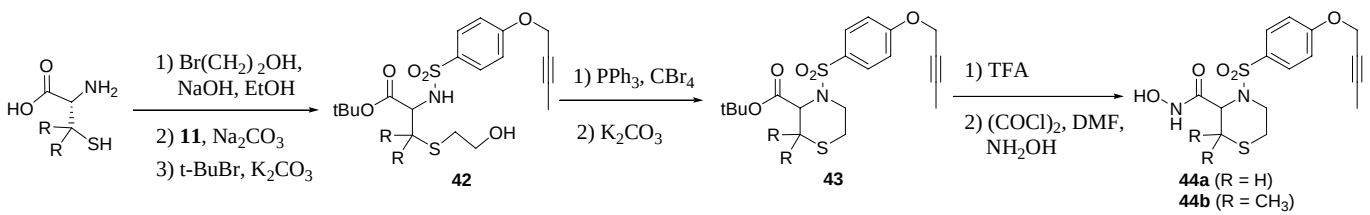
derivative (**38**), is shown in Scheme 9. The most potent derivative in this series is thiophene amide (**41a**), a 12 nM inhibitor of TACE with an MMP selectivity profile virtually identical to that of **37**. Cellular activity for **41a**, 86% inhibition of TNF in THP cells at 3 μM, was slightly better than for morpholine (**37**).



Scheme 9

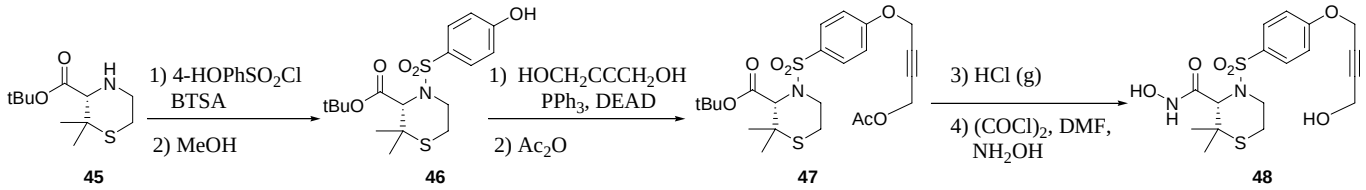
In contrast, the *N*-picolyl analog (**41b**) is slightly less potent against TACE enzyme (IC_{50} = 28 nM), and more potent against MMP-13 (IC_{50} = 49 nM), but offers far greater selectivity over MMP-1 (IC_{50} = 3197 nM). Perhaps due the fact that **41b** bears two basic amines, it is significantly less active in THP cells (25% inhibition at 3 μM) than **41a**.

The thiomorpholine (**44a**), available from cysteine via intra-molecular alkylation of the bromide derived from sulfonamide- alcohol (**42**), as shown in Scheme 10, is pharmacologically comparable in all respects to morpholine (**37**). It is a potent inhibitor of cell-free TACE (IC_{50} = 3 nM) and MMP-13 (IC_{50} = 12 nM), with modest 50-fold selectivity over MMP-1 and good activity in THP cells (84% inhibition at 3 μM). Interestingly, the addition of geminal dimethyl substituents on thiomorpholine (**44a**) to give **44b** completely abolishes any selectivity for TACE, making this analog essentially equipotent against TACE, MMP-1, MMP-9 and MMP-13, and dramatically boosts activity ion cell assays. Thiomorpholine (**44b**), derived from D-penicillamine, inhibits 94% of LPS-stimulated TNF production in THP cells at 3 μM, with a cell IC_{50} of 0.2 μM. Even in human whole blood compound (**44b**) remains a potent inhibitor of TNF production with an IC_{50} of 0.3 μM. This analog is also quite potent *in vivo* with an ED_{50} of 5 mg/kg po in the mouse LPS model and 10 mg/kg po bid in a prophylactic collagen-induced arthritis model with LPS boost.[35]



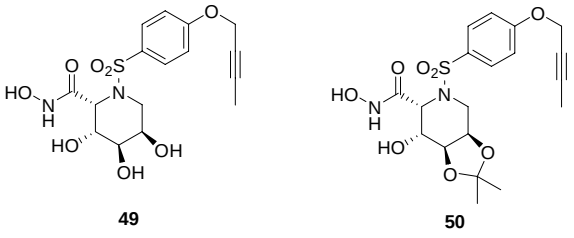
Scheme 10

Optimization of the physical properties of the penicillamine derived thiomorpholine series by functionalization of the terminus of the butynyloxy P1' moiety next led to the synthesis of propargylic alcohol (**48**).[36] This compound, is prepared from thiomorpholine *t*-butyl ester (**45**)[37] as shown in Scheme 11. Thus, **45** was sulfonylated with *in situ* silylated 4-hydroxybenzene sulfonyl chloride followed by removal of the TMS-group with methanol to give **46**.[38] Mitsunobu alkylation of **46** with 2-butyn-1,4-diol and subsequent acetylation then gives **47**. Cleavage of the t-butyl ester followed by hydroxamate formation and concomitant cleavage of the acetyl group affords the desired propargylic alcohol (**48**). Compound (**48**) was pharmacologically equivalent *in vitro* and *in vivo* to the butynyl P1' analog (**44b**), but had enhanced aqueous solubility, microsomal stability, and oral bioavailability. Lengthening of the tether between the carbon-carbon triple bond and the terminal hydroxyl group negatively impacted both enzyme and cellular activity, and the corresponding amine analogs were also less active. Due to its excellent pharmacological profile and good physical properties propargylic alcohol (**48**) advanced to clinical trials for the treatment of rheumatoid arthritis.[39]



Scheme 11

Azasugars have also been used as cores for butynyloxyphenyl sulfonamide hydroxamate inhibitors of TACE (Figure 3).[40] Trihydroxy analog (**49**) and acetonide (**50**) are both very potent inhibitors of TACE enzyme. While **49** is greater than 100-fold selective for TACE over MMP-1, acetonide (**50**) is more than 1000-fold selective over MMP-1, and in addition is greater than 50-fold selective for TACE over both MMP-3 and MMP-9. Compound (**49**) has been shown to potently inhibit (IC_{50} = 28 nM) the shedding heparin-binding EGF-like growth factor (HB-EGF).[41]



Comp	MMP-1[a]	MMP-3[a]	MMP-9[a]	TACE[a]
49	128	3.3	14	0.5
50	>850	30	78	0.6

[a]K_i (nM)

Figure 3

5-MEMBERED RING SCAFFOLDS

A 5-membered ring sulfonamide utilizing a thiol group as the zinc chelating functionality, rather than the ubiquitous hydroxamate, was prepared by Vertex and found to be a potent inhibitor of TACE. Thus, butynyloxyphenylsulfonamide (**51**) (Figure 4) has a K_i of 29 nM against TACE.[42] The cellular activity of this analog was not reported.

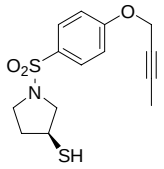


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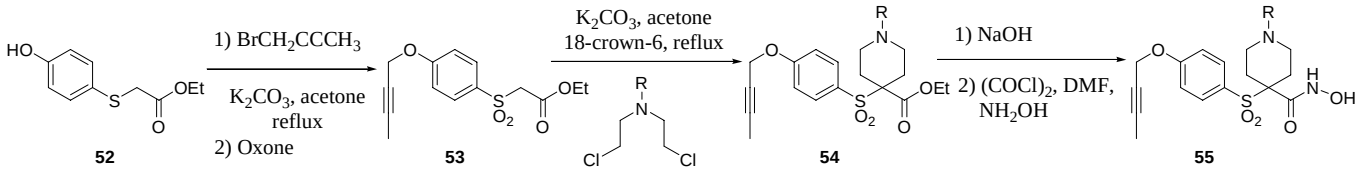
Figure 4

PIPERIDINE SULFONES

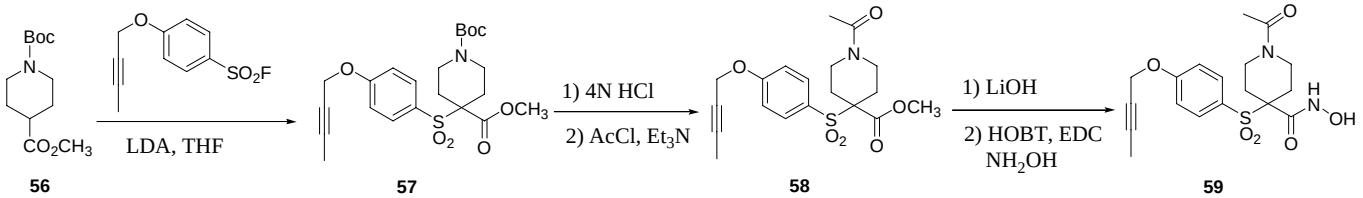
In addition to cores bearing the requisite butynyloxy P1' moiety appended to a phenyl sulfonamide, TACE inhibitors are also available from butynyloxy phenyl sulfones. Thus, 4,4-disubstituted piperidine α-sulfone hydroxamic acids of general structure (**55**) have been examined as scaffolds.[43] These compounds could be prepared by either initial synthesis of the sulfone ester (**53**) followed by formation of the piperidine ring via dialkylation, as shown in Scheme 12, or by sulfonylation of an isonipecotic acid ester with the appropriate sulfonyl fluoride, as shown for piperidine acetamide (**59**) in Scheme 13.



52 **53** **54** **55**

Scheme 12

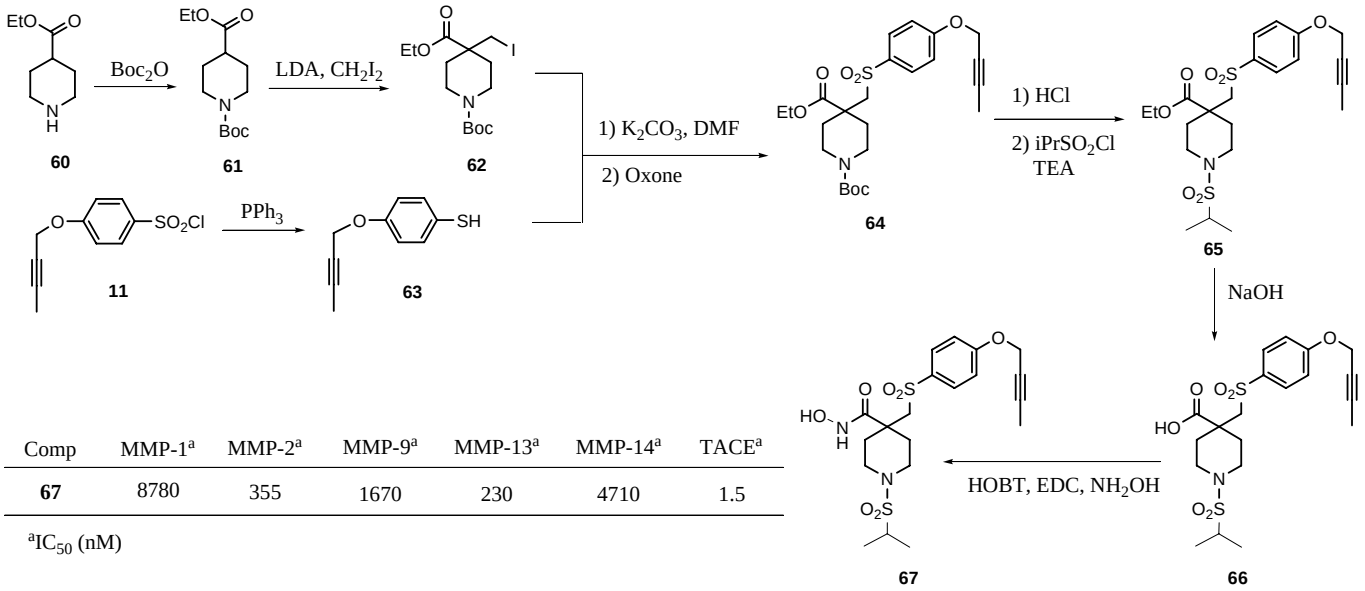
The sulfonyl fluoride was required since the use of the corresponding sulfonyl chloride as the electrophile provided significant amounts of the chlorinated isonipecotic acid ester.[44] However, the piperidine α-sulfone hydroxamates in general are only modestly potent inhibitors of TACE with enzyme IC_{50}s above 50 nM and weak activity in THP cells.



56 **57** **58** **59**

Scheme 13

Much improved activity against TACE can be seen for the analogous 4,4-disubstituted piperidine β-sulfone hydroxamic acids.[45] This series of derivatives provides low nanomolar inhibitors of TACE whose selectivity over MMPs can be modulated by the choice of the P1 substituent on the piperidine nitrogen. The most potent and selective of these analogs is the isopropyl sulfonamide P1 analog (**67**), prepared as shown in Scheme 14. Protected ethyl isonipecotate (**61**) is alkylated with diiodomethane to give iodomethyl piperidine derivative (**62**), followed by displacement of the iodine with thiol (**63**). The resulting thioether is then oxidized to the sulfone with Oxone to give **64**. Removal of the Boc protecting group and functionalization of the piperidine nitrogen, followed by ester hydrolysis and hydroxamate formation then provides the desired piperidine β-sulfone analog (**67**). Isopropyl sulfonamide (**67**) is a 1.5 nM inhibitor of TACE enzyme with greater than 100-fold selectivity over MMP-1, -2, -9, -13, and -14. Less bulky substituents on the piperidine nitrogen produced less profound selectivity for TACE over the MMPs. This compound is also a moderately potent inhibitor of LPS-stimulated TNF production in human whole blood, with an IC_{50} of 1.5 μM, and is active *in* vivo in the mouse LPS model at a dose of 25 mg/kg po, giving 72% inhibition of TNF production one hour after LPS administration.



Comp	MMP-1[a]	MMP-2[a]	MMP-9[a]	MMP-13[a]	MMP-14[a]	TACE[a]
67	8780	355	1670	230	4710	1.5

[a]IC_{50} (nM)

Scheme 14

In summary, a variety of heterocyclic scaffolds have been used as cores to appropriately position a hydroxamic acid group, a sulfonamide or sulfone, and a butynyloxy phenyl substituent within the active site of the metalloenzyme TACE to produce extremely potent inhibitors of this important zinc endopeptidase. Both monocyclic and bicyclic cores have been used to equal effect, as well as 6- and 7-membered rings. Although activity against cell-free TACE enzyme was almost uniformly excellent for these inhibitors, selectivity profiles for MMP inhibition varied greatly, and wide disparities were seen in

their ability to inhibit TNF production in cells and human whole blood, with the diazepine and thiomorpholine scaffolds affording the most potent analogs in cellular assays. The scaffold-dependent differences seen in selectivity for TACE over MMP-1, for example, for analogs which all bear the same butynyloxy P1' group, might be explained in part by differences in the conformational mobility of these scaffolds, as has been seen for acyclic sulfonamide hydroxamate TACE inhibitors.[46] On the other hand, factors that determine the ability of inhibitors from each of these scaffolds to function in human whole blood, and *in vivo*, have proven to be more difficult to discern. The exploration of the SAR of these analogs has led to the selection of penicillamine derivative (**48**) as a clinical candidate for the treatment of rheumatoid arthritis.

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REFERENCES

1. R. A. Black, *Int. J. Biochem. Cell B.*, 2002, **34**,1.
2. L. Killar, J. White, R. Black, and J. Peschon, *Ann. N. Y. Acad. Sci.*, 1999, **878**, 442.
3. R. C. Newton and C. P. Decicco, *J. Med. Chem.* 1999, **42**, 2295.
4. M. A. Palladino, F. R. Bahjat, E. A. Theodorakis, and L. L. Moldawer, *Nat. Rev. Drug Discovery* 2003, **2**, 736.
5. J. S. Skotnicki and J. I. Levin, *Ann. Rep. Med. Chem*. 2003, **38**, 153.
6. V. Lukacova, Y. Zhang, D. M. Kroll, S. Raha, D. Comez, and S. Balaz, *J. Med. Chem*., 2005, **48**, 2361.
7. B. G. Rao, *Curr. Pharm. Design*, 2005, **11**, 295.
8. B. Watson, *IDrugs*, 2002, **5**, 1151.
9. F. C. Nelson and A. Zask, *Exp. Opin. Invest. Drugs*, 1999, **8**, 383.
10. F. X. Gomis-Reuth, E. F. Meyer, L. Kress, and V. Politi, *Protein Sci*., 1998, **7**, 283.
11. J. M. Chen, G. Jin, A. Sung, and J. I. Levin, *Bioorg. Med. Chem, Lett.*, 2002, **12**, 1195.
12. Z. R. Wasserman, J. J.-W. Duan, M. E. Voss, C.-B. Xue, R. J. Cherney, D. J. Nelson, K. D. Hardman, and C. P. Decicco, *Chem. Biol*., 2003, **10**, 215.
13. K. Maskos, C. Fernandez-Catalan, R. Huber, G. P. Bourenkov, H. Bartunik, G. A. Ellestad, P. Reddy, M. F. Wolfson, C. T. Rauch, B. J. Castner, R. Davis, H. R. G. Clarke, M. Petersen, J. N. Fitzner, D. P. Cerreti, C. J. March, R. J. Paxton, R. A. Black, and W. Bode, *Proc. Natl. Acad. Sci. U.S.A.*, 1998, **95**, 3408.
14. G. Wagner and S. Laufer, *Med. Res. Rev.*, 2006, **26**, 1.

15. K. Yokota and S.-I. Nishimura, *Expert Opin. Ther. Patents*, 2005, **15**, 421.
16. G. Li and G. Abbenante, *Curr. Med. Chem.*, 2005, **12**, 2963.
17. J. I. Levin, *Curr. Topics Med. Chem.*, 2004, **4**, 1289.
18. M. L. Moss, J. M. White, M. H. Lambert, and R. C. Andrews, *Drug Discov. Today*, 2001, **6**, 417.
19. J. J. Chen, N. Dewdney, X. Lin, R. L. Martin, K. A. M. Walker, J. Huang, F. Chu, E. Eugui, A. Mirkovic, Y. Kim, K. Sarma, H. Arenzo, and H. E. Van Wart, *Bioorg. Med. Chem . Lett.*, 2003, **13**, 3951.
20. M. A. Letavic, J. T. Barberia, T. J. Carty, J. R. Hardink, J. Liras, L. L. Lopresti-Morrow, P. G. Mitchell, M. C. Noe, L. M. Reeves, S. L. Snow, E. J. Stam, F. J. Sweeney, M. L. Vaughn, and C. H. Yu, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3243.
21. J. Holms, K. Mast, P. Marcotte, I. Elmore, J. Li, L. Pease, K. Glaser, D. Morgan, M. Michaelides, and S. Davidsen, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2907.
22. J. J.-W. Duan, L. Chen, Z. R. Wasserman, Z. Lu, R.-Q. Liu, M. B. Covington, M. Qian, K. D. Hardman, R. L. Magolda, R. C. Newton, D. D. Christ, R. R. Wexler, and C. P. Decicco, *J. Med. Chem.* 2002, **45**, 4954.
23. G. Kottirsch, G. Koch, R. Feifel, and U. Neumann, *J. Med. Chem.*, 2002, **45**, 2289.
24. M. A. Letavic, M. Z. Axt, J. T. Barberia, T. J. Carty, D. E. Danley, K. F. Geoghegan, N. S. Halim, L. R. Hoth, A. V. Kamath, E. R. Laird, L. L. Lopresti-Morrow, K. F. McClure, P. G. Mitchell, V. Natarajan, M. C. Noe, J. Pandit, L. Reeves, G. K. Schulte, S. L. Snow, F. J. Sweeney, D. H. Tan, and C. H. Yu, *Bioorg. Med. Chem. Lett.* 2002, **12**, 1387.
25. J. I. Levin, J. M. Chen, M. T. Du, F. C. Nelson, L. M. Killar, S. Skala, A. Sung, G. Jin, R. Cowling, D. Barone, C. J. March, K. M. Mohler, R. A. Black, and J. S. Skotnicki, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1199.
26. J. I. Levin and M. T. Du, *Synth. Commun*., 2002, **32**, 1401.
27. A. Zask, Y. Gu, J. D. Albright, X. Du, M. Hogan, J. I. Levin, J. M. Chen, L. M. Killar, A. Sung, J. F. DiJoseph, M. A. Sharr, C. E. Roth, S. Skala, G. Jin, R. Cowling, K. M. Mohler, D. Barone, R. Black, C. March, and J. S. Skotnicki, *Bioorg. Med. Chem. Lett*. 2003, **13**, 1487.
28. J. I. Levin, J. M. Chen, K. Cheung, D. Cole, C. Crago, E. Delos Santos, X. Du, G. Khafizova, G. MacEwan, C. Niu, E. J. Salaski, A. Zask, T. Cummons, T. Stratman, L. M. Killar, R. Mulvey, S. Skala, A. Sung, J. Xu, Y. Zhang, W. Xu, S. Ayral-Kaloustian, G. Jin, R. Cowling, D. Barone, K. M. Mohler, R. A. Black, and J. S. Skotnicki, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2799.
29. Y. Zhang, M. Hegen, J. Xu, J. C. Keith, Jr., G. Jin, T. Cummons, L. Sun, Y. Zhu, V. R. Rao, Q. Wang, W. Xu, R. Cowling, C. Nickerson-Nutter, J. Gibbons, L. Lin, J. Skotnicki, J. Clark, and J. Levin, *Int. Immunopharm*., 2004, **4**, 1845.

30. F. C. Nelson, E. Delos Santos, J. I. Levin, J. M. Chen, J. S. Skotnicki, J. F. DiJoseph, M. A. Sharr, A. Sung, L. M. Killar, R. Cowling, G. Jin, C. E. Roth, and J. D. Albright, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2867.
31. J. I. Levin, F. C. Nelson, E. Delos Santos, M. T. Du, G. MacEwan, J. M. Chen, S. Ayral-Kaloustian, J. Xu, G. Jin, T. Cummons, and D. Barone, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4147.
32. A. Zask, J. Kaplan, X. Du, G. MacEwan, V. Sandanayaka, N. Eudy, J. Levin, G. Jin, J. Xu, T. Cummons, D. Barone, S. Ayral-Kaloustian, and J. Skotnicki, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1641.
33. J. I. Levin, J. M. Chen, L. M. Laakso, M. Du, X. Du, A. M. Venkatesan, V. Sandanayaka, A. Zask, J. Xu, W. Xu, Y. Zhang, and J. S. Skotnicki, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4345.
34. L. S. Chupak, *U. S. Patent 6,387,901, 2002* (*Chem. Abstr.*, 2002, **136**, 369724).
35. Y. Zhang, J. Xu, J. Levin, M. Hegen, G. Li, H. Robertshaw, F. Brennan, T. Cummons, D. Clarke, N. Vansell, C. Nickerson-Nutter, D. Barone, K. Mohler, R. Black, J. Skotnicki, J. Gibbons, M. Feldman, P. Frost, G. Larsen, and L.-L. Lin, *J. Pharmacol. Exp. Ther*., 2004, **309**, 348.
36. J. I. Levin, J. M. Chen, L. M. Laakso, M. Du, J. Schmid, W. Xu, T. Cummons, J. Xu, G. Jin, D. Barone, and J. S. Skotnicki, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1605.
37. S. L. Bender and M. J. Melnick, *U. S. Patent 5,753,653*, 1998 (*Chem. Abstr.*, 1998, **129**, 16140).
38. J. I. Levin, M. T. Du, and K. Park, *Synth. Commun.*, 2004, **34**, 2772.
39. R. Fleischmann, A. J. Kivitz, C. Franklin, S. Pavlik-Gaylord, S. Sridharan, and T. M. Kirsch, *Ann. Rheum. Dis.*, 2005, **64** (Suppl. 3), 132.
40. T. Tsukida, H. Moriyama, Y. Inoue, H. Kondo, K. Yoshino, and S.-I. Nishimura, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1569.
41. H. Moriyama, T. Tsukida, Y. Inoue, K. Yokota, K. Yoshino, H. Kondo, N. Miura, and S.-I. Nishimura, *J. Med. Chem.*, 2004, **47**, 1930.
42. U. Bandarage, J. H. Come, E. Perola, G. Rao, Bhisetti, and J. O. Saunders, *PCT Int. Appl. WO04056766*, 2004 (*Chem. Abstr.*, 2004, **141**, 106363).
43. A. M. Venkatesan, J. M. Davis, G. T. Grosu, J. Baker, A. Zask, J. I. Levin, J. Ellingboe, J. S. Skotnicki, J. F. DiJoseph, A. Sung, G. Jin, W. Xu, D. Joseph McCarthy, and D. Barone, *J. Med. Chem*., 2004, **47**, 6255.
44. V. P. Sandanayaka, A. Zask, A. M. Venkatesan, and J. Baker, *Tetrahedron Lett.*, 2001, **42**, 4605.
45. K. Park, A. Aplasca, M. T. Du, L. Sung, Y. Zhu, Y. Zhang, and J. I. Levin, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3927.
46. F. J. Moy, P. K. Pranab, J. Chen, S. Cosmi, W. Edris, J. I. Levin, T. S. Rush, J. Wilhelm, and R. Powers, *J. Am. Chem. Soc.*, 2002, **124**, 12658.