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2-(2-Aminothiazol-4-yl)pyrrolidine-based tartrate diamides as potent, selective and orally bioavailable TACE inhibitors

Chaoyang Dai [a,*], Dansu Li [a], Janeta Popovici-Muller [a], Lianyun Zhao [a], Vinay M. Girijavallabhan [b], Kristin E. Rosner [a], Brian J. Lavey [b], Razia Rizvi [b], Bandarpalle B. Shankar [b], Michael K. C. Wong [b], Zhuyan Guo [b], Peter Orth [b], Corey O. Strickland [b], Jing Sun [c], Xiaoda Niu [c], Shiying Chen [d], Joseph A. Kozlowski [b], Daniel J. Lundell [c], John J. Piwinski [a], Neng-Yang Shih [a], M. Arshad Siddiqui [a]

[a] Department of Chemistry, Merck Research Laboratories, 320 Bent Street, Cambridge, MA 02141, USA
[b] Department of Chemistry, Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033-0539, USA
[c] Department of Inflammation, Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033-0539, USA
[d] Department of Exploratory Drug Metabolism and Pharmacokinetics, Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, NJ 07033-0539, USA

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ABSTRACT

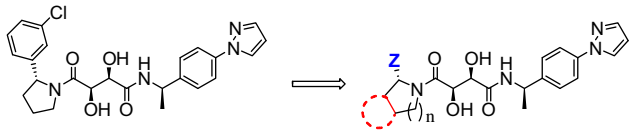
TNF-α converting enzyme (TACE) inhibitors are promising agents to treat inflammatory disorders and cancer. We have investigated novel tartrate diamide TACE inhibitors where the tartrate core binds to zinc in a unique tridentate fashion. Incorporating (*R*)-2-(2-*N*-alkylaminothiazol-4-yl)pyrrolidines into the left hand side amide of the tartrate scaffold led to the discovery of potent and selective TACE inhibitors, some of which exhibited good rat oral bioavailability.

Tumor necrosis factor-α (TNF-α) is a major mediator of inflammatory responses in various autoimmune disorders such as rheumatoid arthritis (RA), Crohn's disease, and psoriasis.[1] The success of anti-TNF-α biologics such as Enbrel®, Remicade®, and Humira® has demonstrated that inhibition of TNF-α could result in effective control of these inflammatory responses and autoimmune diseases. The search for small molecule, orally administered inhibitors of TNF-α production has been an area of intensive research.[2]

TNF-α is released into the bloodstream via the TNF-α converting enzyme (TACE) mediated cleavage of its membrane bound 26 kDa precursor form, pro-TNF-α to the 17 kDa soluble component.[3] Inhibition of TACE would decrease the level of TNF-α released into circulation and could hold promise for treating related inflammatory diseases.[4] Recently, studies have also shown that TACE inhibitors may be useful for inhibition of pathogenic EGFR signaling in cancer.[5]

The majority of known TACE inhibitors rely on hydroxamic acids as the zinc binding groups (ZBG).[6] However, hydroxamic acids are often poorly absorbed because of high renal clearance. They also carry potential metabolic liabilities such as O-glucuronidation and hydrolysis in vivo to give the corresponding carboxylic acids and hydroxylamine, which is toxic. Therefore, there is a considerable interest in identifying non-hydroxamate TACE inhibitors. Hydantoins,[7] barbiturates,[8] and thiols[9] have been reported as zinc binding groups.

Recently, we have discovered a novel series of tartrate diamide TACE inhibitors, which display a unique tridendate zinc binding mode with the tartrate scaffold.[10,11] The combination of a tertiary amide at the left hand side (LHS) and a secondary amide at the right hand side (RHS) of the tartrate core appears to be essential for their TACE activities. Through extensive structure–activity



1
TACE Ki = 0.8 nM
Cell IC_{50} = 886 nM
AUC = 2,949 nM.h
C_{6h} = 96 nM

n = 1–3;
Z = aryl, heteroaryl

Figure 1. Replacements of the 3-chlorophenyl group and pyrrolidine ring modifications on inhibitor **1**.

* Corresponding author.
E-mail addresses: chaoyang.dai@merck.com, chaoyangdai@hotmail.com (C. Dai).

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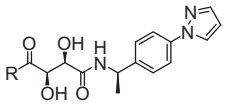
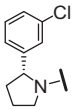
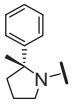
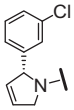
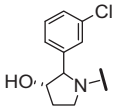
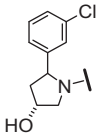
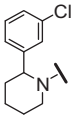
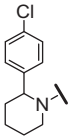
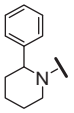
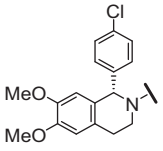
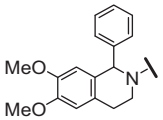
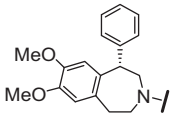
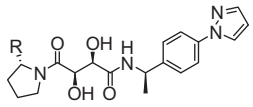
Table 1
TACE K_i and rapid rat PK of LHS 2-phenylpyrrolidine analogs



Compound	R	TACE K_i (nM)	AUC[a] (nM h)
1		0.8	2949
2		0.4	1465
3		0.5	461
(±)-**4**		6.7	4765
(±)-**5**		7.6	3908
(±)-**6**		87	nd
(±)-**7**		22	nd
(±)-**8**		14	nd
9		2.6	nd
(±)-**10**		0.9	1239
11		38	nd

[a] Sprague–Dawley rats were dosed orally with 10 mpk compounds in 0.4% MC; data were collected within 6 h after dosing and not determined.

Table 2
TACE K_i and rapid rat PK of LHS pyrrolidine-based tartrate diamides



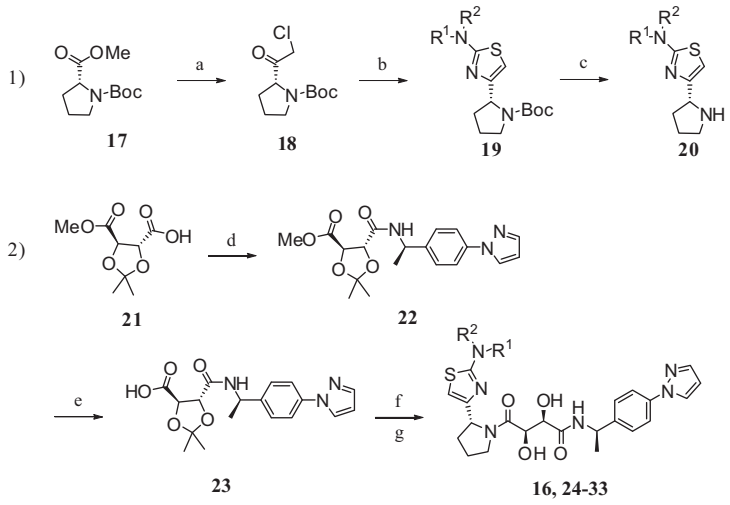
Compound	R	TACE K_i (nM)	AUC (nM h)	C_{6h}[a] (nM)
1		0.8	2949	96
12		5	578	0
13		4	2921	86
14		10	nd	nd
15		10	nd	nd
16		6	2276	247

[a] Compound concentration in plasma at the 6th hour after dosing.

relationship (SAR) investigations, we have identified several series of preferred RHS amine building blocks.[11] In particular, (*R*)-1-(4-(1*H*-pyrazol-1-yl)phenyl)ethanamine has emerged as an preferred RHS amine when combined with various 2-phenylpyrrolidine LHS pieces such as compound **1** which showed very good binding affinity and modest cellular activity and oral PK in the rat[12] (Fig. 1). We then turned our attention to optimizing the LHS amine building blocks in the hope of improving their oral PK profiles while maintaining or further improving its biochemical potencies. Our results are reported herein.

Initial efforts focused on the structural variation of the 2-(3-chlorophenyl)pyrrolidyl unit of **1** as a whole. Introduction of a quaternary methyl group at C-2 of the pyrrolidine ring (compound **2**, Table 1) improves potency slightly, but also leads to a reduced AUC relative to compound **1**. Likewise, the 3-pyrroline analog (**3**) shows similar activity, but the AUC is significantly eroded. Hydroxylation of the pyrrolidine ring at C-3 or C-4 (**4** and **5**, respectively) results in a slight improvement in AUC, but is accompanied by a 10-fold drop in activity. Ring expansion of the pyrrolidine to a piperidine ring while preserving the 3-chlorophenyl substituent (**6**) results in a 100-fold drop in TACE activity relative to **1.** The 4-chlorophenyl and unsubstituted phenyl analogs (**7** and **8**, respectively) do not suffer as great a reduction in activity, but are still less potent than **1**. The benzannulated analogs **9** and **10** both show a 10-fold improvement in activity over their monocyclic congeners **7** and **8**, respectively. The activity of **10** is comparable to that of compound **1** but disappointingly, the pharmacokinetic profile of **10** is not improved over that of compound **1**. Further ring expansion to yield the benzazepine **11** results in a significant loss of activity over **1** and **10**. The preparation of compounds **2**–**11** followed previously described procedures.[13]

At this juncture, we decided to revise our optimization strategy by preserving the pyrrolidine ring of **1** and explore the effect of replacing the 3-chlorophenyl group of **1** with heteroaromatic groups. Among the heterocycles that were investigated, pyrazoles (**12** and **13**) and thiazoles (**14**–**16**) have emerged as promising aryl group replacements to maintain TACE potencies in the low nanomolar range (Table 2). Compound **16** is interesting in that its AUC (10 mpk, po) is only moderate, but the plasma concentration at the 6th hour still remains relatively high (C_{6h} = 247 nM) compared to the value for compound **1** (C_{6h} = 96 nM).[12] Moreover, the 2-aminothiazole moiety provides a good handle for further structural modifications to fine-tune the hydrophobicity and other properties of this series of compounds, hence to optimize their overall profiles.



Scheme 1. Reagents and conditions: (a) LDA, CH_2ICl, THF, −78 °C, 74%; (b) thioureas, DMF, rt; (c) HCl/dioxane, MeOH; (d) HATU, DIEA, DMF, 78%; (e) LiOH, THF, 93%; (f) **20**, HATU, DIEA, DMF, rt; (g) HCl/dioxane, water.

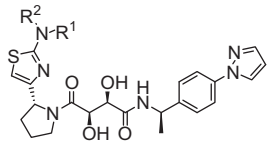
A series of N-substituted 2-aminothiazole-based tartrate inhibitors was readily synthesized (Scheme 1). Various 2-(2-*N*-alkylthiazol-4-yl)pyrrolidines (**20**) were obtained from D-Boc-proline methyl ester (**17**) through initial conversion to the corresponding α-chloroketone (**18**)[14] with chloroiodomethane and LDA. Subsequent condensation/cyclization with various thioureas in DMF afforded the corresponding 2-aminothiazoles, and a final acid-mediated deprotection gave the desired pyrrolidines (**20**). Separately, the acetonide-protected tartrate half acid (**21**) was firstly coupled with (*R*)-1-(4-(1*H*-pyrazol-1-yl)phenyl)ethanamine to form the mono-amide (**22**), which was subsequently saponified to acid (**23**). Amide coupling of **23** with the various LHS amines (**20**) afforded the corresponding tartrate diamide compounds (**16**, **24**–**33**) after acetonide deprotection.

As shown in Table 3, 2-(2-aminothiazol-4-yl)pyrroline amide **16** is a potent TACE inhibitor. The high binding affinities are largely maintained in compounds with mono-alkyl N-substitutions (**24**–**29**). Mono N-substitution with 2-fluorophenyl (**30**) or 3-pyridyl (**31**) groups also results in potent compounds. On the other hand, N,N-disubstitution is not well tolerated. For example, dimethyl compound **32** resulted in a loss of activity (K_i = 65 vs 6 nM in compound **16**), and the cyclic piperidine compound **33** is also less active.

The pharmacokinetic (PK) properties of these TACE inhibitors were studied through rapid rat PK analysis.[12] As shown in Table 3, mono N-alkylation on 2-aminothiazole dramatically improves its oral PK. For instance, simply adding an *N*-methyl group (**24** vs **16**) brings rapid rat AUC to 30,706 from 2278 nM h. Ethyl (**25**) and *n*-propyl (**26**) substitutions have similar effects. The isopropyl (**27**) and cyclopropyl (**28**) compounds show remarkably high AUCs and drug concentrations at the 6th hour remain high. On the other hand, N-aromatic substitution is not favored in terms of PK as seen in compounds **30** and **31**. Compared to the initial lead compound **1**, the thiazole analogs **24**–**29** have much improved oral exposure. However, they generally have weaker cellular activities (cell IC_{50} = 3016 nM for compound **28** vs IC_{50} = 886 nM for **1**).

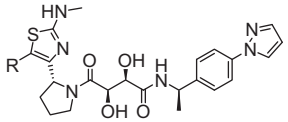
In order to improve the cellular activity of the thiazole series, it was decided to further explore the SAR around the 2-(2-aminothiazol-4-yl)pyrrolidine moiety. Therefore, the effect of a 5-substituent was investigated (Table 4). Starting from Boc-protected

Table 3
TACE inhibition potencies and rapid rat PK of 2-aminothiazole-based tartrate diamides

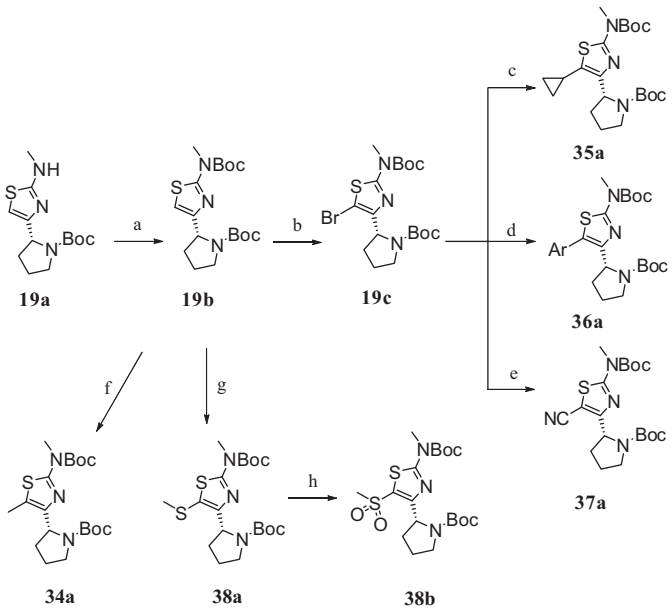


Compound	R^1	R^2	TACE K_i (nM)	Cell IC_{50} (nM)	AUC (nM h)	C_{6h} (nM)
16	H	H	6	4286	2276	247
24	H	Me	7	5799	30,706	2535
25	H	Et	7	5107	51,978	5967
26	H	*n*-Pr	4	4481	48,348	5403
27	H	*i*-Pr	17	6677	114,792	12,305
28	H	*c*-Pr	5	3016	134,267	17,646
29	H	*c*-Bu	4	2153	31,390	3542
30	H	2-Fluorophenyl	1	1143	130	0
31	H	3-Pyridyl	2	5552	0	0
32	Me	Me	65	nd	nd	nd
33			39	nd	1959	0

Table 4
TACE inhibition potencies and rat PK of 5-substituted-2-aminothiazole-based tartrate diamides



Compound	R	TACE K_i (nM)	Cell IC_{50} (nM)	AUC (nM h)
24	H	7	5799	30,706
34	Me	2	2217	5438
35	*c*-Pr	2	2574	11,423
36	4-Fluorophenyl	1	3245	nd
37	CN	2	3036	154
38	SO_2Me	0.4	720	0



Scheme 2. Reagents and conditions: (a) Boc_2O, DMAP, THF, rt, 95%; (b) NBS, $CHCl_3$, 50 °C, 95%; (c) cyclopropylboronic acid, $PdCl_2$(dppf), K_3PO_4, 80 °C, 85%; (d) 4-fluorophenylboronic acid $PdCl_2$(dppf), K_3PO_4, 80 °C, 88%; (e) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, 85 °C, 85%; (f) *n*-BuLi, MeI, −78 °C, 84%; (g) *n*-BuLi, MeSSMe, −78 °C, 64%; (h) *m*-CPBA, DCM, 95%.

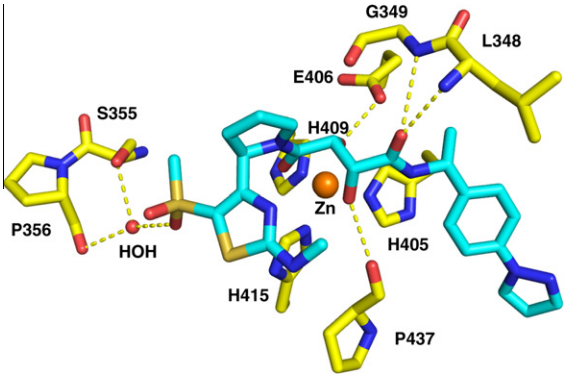
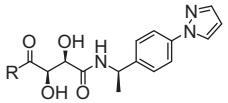
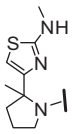
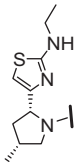
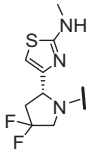
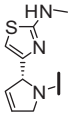
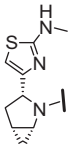
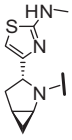
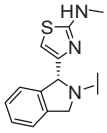
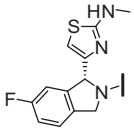
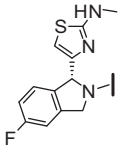
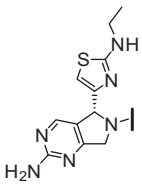


Figure 2. Crystal structure of **38** (cyan) bound to TACE (yellow). Only residues that involved in zinc binding and hydrogen bonding with the inhibitor (dashed yellow lines) are shown.

Table 5
TACE inhibition potencies and rapid rat PK of 2-aminothiazole-based tartrate diamides



Compound	R	TACE K_i (nM)	Cell IC_{50} (nM)	AUC (nM h)
(±)-**39**		9	13,811	2439
40		6	4040	5618
41		4	2769	1417
42		0.6	1338	1809
43		1	707	925
44		531	nd	nd
45		1	416	1133
46		16	384	237
47		2	288	nd
48		0.5	257	0

2-(2-*N*-methylaminothiazol-4-yl)pyrrolidine (**19a**), the protected amine building blocks **35a**–**37a** were obtained through Boc-protection, NBS bromination, and palladium catalyzed cross-couplings. Alternatively, deprotonation of **19b** with *n*-BuLi followed by MeI

Table 6
Selectivity profile of inhibitor **1**, **28**, and **45**

K_i (nM)	**1**	**28**	**45**
TACE	0.8	5	1
MMP1	>100 000	>40,000	>40,000
MMP2	43,660	20,500	>40,000
MMP3	—	>40,000	>40,000
MMP7	3769	18,100	13,500
MMP9	88,420	>40,000	10,100
MMP13	3300	>40,000	14,100
MMP14	1148	>40,000	16,400
ADAM10	166	1350	120

or MeSSMe quenching afforded compounds **34a** and **38a**, respectively. Further oxidation of **38a** with *m*-CPBA gave methyl sulfone **38b** (Scheme 2). These building blocks were then readily deprotected and coupled with tartrate half amide/acid **23** to provide 5-substituted-2-*N*-methylaminothiazole based tartrate diamides **34**–**38** (Table 4) by following the same procedure as in Scheme 1.

As shown in Table 4, introducing methyl (**34**), cyclopropyl (**35**), aryl (**36**), or cyano (**37**) groups at the 5-position of the thiazole ring slightly increases the potencies of the inhibitors versus **24**. The methylsulfonyl group at 5-position in compound **38** is the most effective one, showing approximately 10-fold improvement in both the biochemical and cellular activities (0.4 and 720 nM, respectively) versus compound **24** (7 and 5799 nM, respectively). X-ray crystallography[15] shows that the methylsulfonyl group makes hydrogen bonding interactions with a water molecule which in turn, makes hydrogen bonding interactions with Ser355 and Pro356 of the protein (Fig. 2). However, incorporation of the 5-methanesulfonyl group results in loss of oral exposure.

The effect of pyrrolidine ring modifications was also investigated. As shown in Table 5, simply adding a methyl group at 2- or 4-position (**39** and **40**) or 4,4-difluoro substitutions (**41**) on pyrrolidine does not have much effect on the TACE activities of the resulting tartrate diamide compound. However, when the pyrrolidine ring is flattened with a double bond (**42**), its potency is significantly improved (K_i = 0.6 nM). Therefore, cyclopropyl and phenyl fusions to the pyrrolidine ring were subsequently explored. It is interesting that the *cis* fusion compound (**43**) is highly potent (K_i = 1 nM) but the corresponding *trans* compound (**44**) loses activity (K_i = 531 nM). As anticipated, when the pyrrolidine ring is fused with phenyl (**45**), the corresponding compound gives rise to much improved enzymatic and cellular activities (K_i = 1 nM, cell IC_{50} = 416 nM) comparing to compound **24**. Fluoro substitutions on the phenyl ring are well tolerated (**46**, **47**). Finally, fusion with a 2-aminopyrimidine ring results in compound **48** with good cellular activity (cell IC_{50} = 257 nM). However, these compounds all exhibit low oral exposures in rat.

TACE inhibitors of this class are very selective against related MMPs, as exemplified by compound **28** and **45** (Table 6). Their selectivity profiles are similar to that of compound **1**.

In summary, we have further optimized the tartrate based TACE inhibitors by incorporating 2-heteroaryl substituted pyrrolidines as the left hand side amine groups and by pyrrolidine ring modifications. In particular, 2-(*N*-alkylamino)thiazole containing compounds afford potent and selective TACE inhibitors with improved oral bioavailability (i.e., compounds **24**–**29** show more than 10-fold AUC improvement). On the other hand, 5-methylsulfone substitution on thiazole (i.e., **38**) and flattening the pyrrolidine ring (i.e., **48**) give rise to compounds with significantly improved cellular activities.

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