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Discovery of low nanomolar non-hydroxamate inhibitors of tumor necrosis factor-α converting enzyme (TACE)

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Abstract—Using a pyrimidine-2,4,6-trione motif as a zinc-binding group, a series of selective inhibitors of tumor necrosis factor-α converting enzyme (TACE) was discovered. Optimization of initial lead **1** resulted in a potent inhibitor (**51**), with an IC_{50} of 2 nM in a porcine TACE assay. To the best of our knowledge, compound **51** and related analogues represent first examples of non-hydroxamate-based inhibitors of TACE with single digit nanomolar potency.
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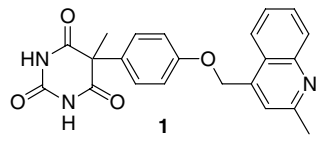
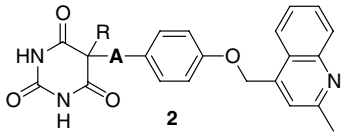
Tumor necrosis factor-α (TNFα) converting enzyme (TACE) and matrix metalloproteinases (MMPs) are both zinc endopeptidases. Most of the inhibitors of TACE and MMPs were derived using hydroxamic acid as zinc-binding group.[1] Because hydroxamic acids are often poorly absorbed and are prone to metabolic degradation and glucuronidation, there has been considerable interest in discovering alternative groups to the hydroxamic acid. While significant progress has been made toward non-hydroxamate MMP inhibitors,[2] the TACE inhibitor arena still relies mostly on the hydroxamic acid group.[1a]

As a part of the effort to discover new inhibitors of TNFα for the treatment of rheumatoid arthritis and other inflammatory diseases, we reported a series of TACE inhibitors using a pyrimidine-2,4,6-trione in place of the commonly used hydroxamic acid.[3] Even though pyrimidinetriones were reported by several groups as MMP inhibitors,[4] they had not been used in TACE inhibitors prior to our publication. We synthesized a 1 μM inhibitor of TACE (**1**) by combining the pyrimidinetrione with a 4-(2-methylquinolin-4-ylmethoxy)phenyl group, which was previously designed and optimized for TACE in our laboratories.[5] Preliminary SAR study led to inhibitors with potency around 100 nM and good selectivity against several MMPs. While encouraging for non-hydroxamate TACE inhibitors, the potency level was 1–2 orders of magnitude weaker than most of the optimized hydroxamate inhibitors. Furthermore, the series was inactive in cellular assays. Continuing the SAR study, we investigated the effect of different linkers between the pyrimidinetrione and 4-(2-methylquinolin-4-ylmethoxy)phenyl groups (linker –**A**– in compound **2**), including elongation with alkylene, alkenylene, ether, and amide. This letter discloses the results from this study as well as attempts to improve cell activity.

Scheme 1 depicts synthesis of analogues with 3-carbon linkers between the pyrimidinetrione and the phenyl side chain. Treatment of **3**[6] with dimethyl methylmalonate





Keywords: TACE inhibitor; ADAM-17 inhibitor; Pyrimidinetrione.
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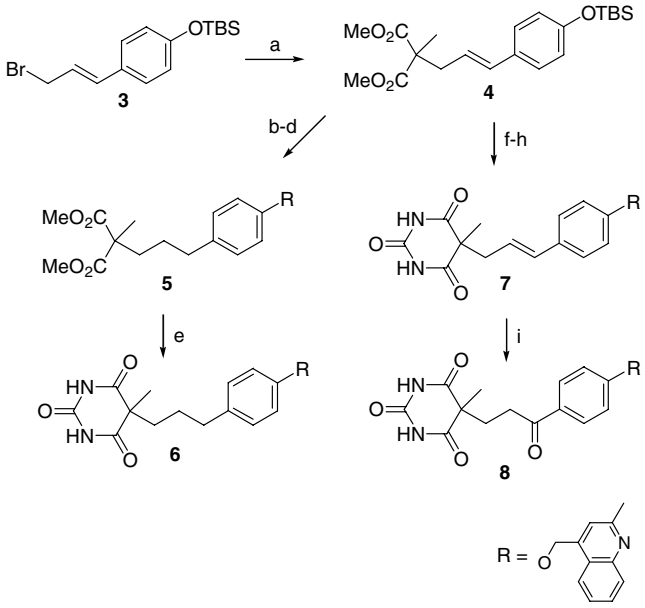
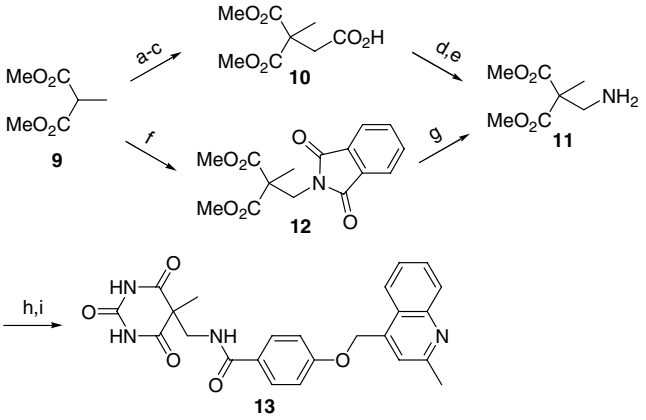


Scheme 1. Reagents and conditions: (a) NaH, dimethyl methylmalonate, THF (52%); (b) H_2, Pd/C, EtOAc, MeOH (88%); (c) TBAF, THF (94%); (d) 4-chloromethyl-2-methylquinoline, Cs_2CO_3, DMF (61%); (e) urea, Mg, MeOH, at reflux (4%); (f) TBAF, THF (99%); (g) 4-chloromethyl-2-methylquinoline, Cs_2CO_3, DMF (87%); (h) urea, Mg, MeOH, at reflux (19%); (i) $Pd(OAc)_2$, $HClO_4$, benzoquinone, CH_3CN, H_2O (71%).

and NaH gave di-substituted malonate **4** in 52% yield. After reduction of the olefin moiety and removal of the silyl-protecting group, the resultant phenol was reacted with 4-chloromethyl-2-methylquinoline and Cs_2CO_3 in DMF to yield the desired 2-methylquinolin-4-ylmethyl ether **5**. Treatment with urea and $Mg(OMe)_2$, generated in situ, in MeOH at reflux provided pyrimidinetrione **6**. Truncated analogues **28** and **29** were prepared in a similar fashion. Intermediate **4** was also used to synthesize analogues **7** and **8**. Toward this end, the silyl ether in **4** was replaced with a 2-methylquinolin-4-ylmethyl ether via desilylation and alkylation. Subsequent reaction with urea and $Mg(OMe)_2$ in MeOH provided pyrimidinetrione **7**. Conversion of **7** to **8** was accomplished regio-specifically in 71% yield using a modified Wacker oxidation,[7] namely palladium(II) acetate, perchloric acid, and benzoquinone in CH_3CN and water.

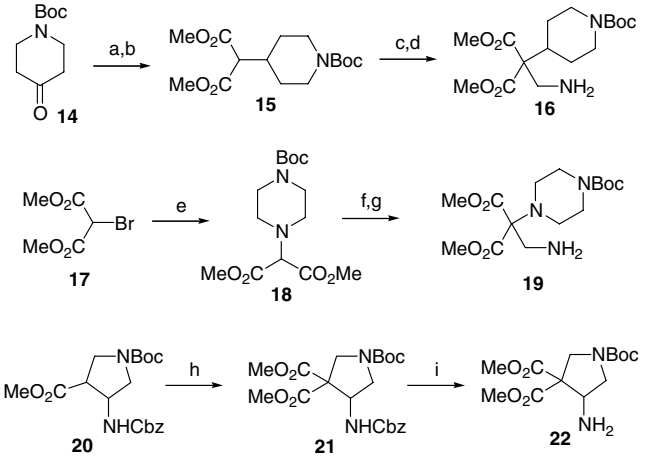
The synthesis of a functionalized 5-(aminomethyl)pyrimidine-2,4,6-trione analogue **13** is outlined in Scheme 2. Dimethyl methylmalonate (**9**) was deprotonated with NaH and reacted with allyl bromide. The allylated product was degraded via ozonolysis and oxidized to acid **10** using sodium chlorite. Curtius rearrangement using diphenylphosphoryl azide (DPPA) and benzyl alcohol provided amine **11** after removal of the Cbz group. Alternatively, diester **9** was treated with NaH and *N*-(bromomethyl)phthalimide in DMF to give **12** in 90% yield. Removal of the phthaloyl-protecting group with hydrazine in MeOH at reflux provided amine **11**. Coupling with 4-(2-methylquinolin-4-ylmethoxy)benzoyl chloride[8] and subsequent reaction with urea and



Scheme 2. Reagents and conditions: (a) NaH, allyl bromide, THF; (b) O_3, CH_2Cl_2, PPh_3 (75% for two steps); (c) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH, THF, H_2O; (d) DPPA, Et_3N, BnOH, benzene, at reflux (79% for two steps); (e) H_2, Pd/C, MeOH (100%); (f) NaH, *N*-(bromomethyl)phthalimide, DMF (90%); (g) NH_2NH_2, MeOH, at reflux (53%); (h) 4-(2-methylquinolin-4-ylmethoxy)benzoyl chloride, $NaHCO_3$, CH_2Cl_2, H_2O (94%); (i) urea, Mg, MeOH, at reflux (21%).

$Mg(OMe)_2$ completed the synthesis of **13**. Compounds **31**–**36** were synthesized in an analogous fashion.

Several additional dimethyl (aminomethyl)malonate derivatives were synthesized during the SAR investigation. In one example, piperidone **14** was condensed with dimethyl malonate under the conditions of $TiCl_4$/pyridine in THF and CCl_4 (Scheme 3).[9] The olefin product was subjected to hydrogenation to yield **15**. Conversion of **15** to **16** was accomplished using the NaH/*N*-(bromomethyl)phthalimide and the hydrazine sequence described in the synthesis of **11**. Both steps proceeded in good efficiency (93% and 90% yield, respectively). Using conditions outlined in Schemes 1 and 2, amine **16** was converted to compounds **37**–**43**.



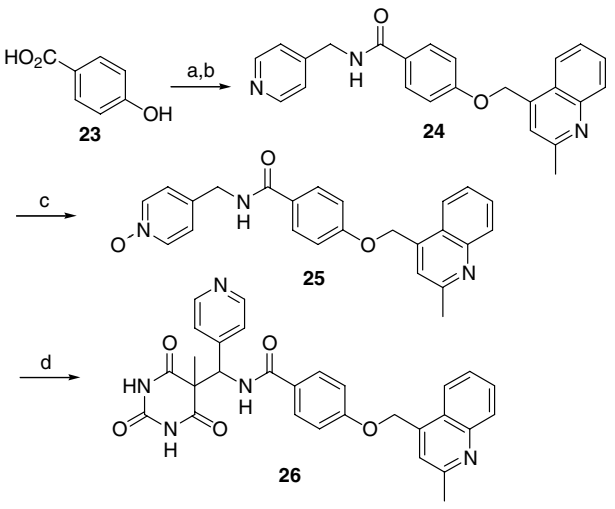
Scheme 3. Reagents and conditions: (a) dimethyl malonate, $TiCl_4$, pyridine, THF, CCl_4 (45%); (b) H_2, Pd/C, MeOH (98%); (c) NaH, *N*-(bromomethyl)phthalimide, DMF, 0 °C (93%); (d) NH_2NH_2, MeOH, at reflux (90%); (e) 1-Boc-piperazine, K_2CO_3, CH_3CN (85%); (f) Bn_2NH, $(HCHO)_n$, 90 °C (43%); (g) H_2, $Pd(OH)_2$/C, Et_3N, MeOH (91%); (h) LDA, $ClCO_2Me$, THF, −78 °C (82%); (i) H_2, $Pd(OH)_2$/C, HCl, MeOH (100%).

In another synthesis, bromomalonate **17** was converted to **18** by displacement with mono-Boc-protected piperazine (Scheme 3). Mannich reaction of **18** with excess paraformaldehyde and dibenzylamine at 90 °C proceeded in 43% yield. The benzyl-protecting groups were removed by hydrogenolysis to give amine **19**, which was used to prepare compounds **44**–**51**.

Furthermore, cyclic (aminomethyl)malonate **22** was synthesized from pyrrolidine **20** (Scheme 3).[10] Carbomethoxylation of **20** using LDA and $ClCO_2Me$ proceeded in 82% yield. The resulting diester **21** was converted to amine **22** upon removal of the Cbz protecting group. Compounds **55**–**59** were prepared from amine **22** using the chemistry outlined in Scheme 2. Similarly, compounds **52**–**54** were synthesized from the corresponding β-amino acid esters.

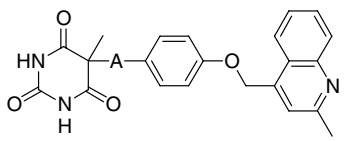
Scheme 4 depicts the synthesis of a pyridine-substituted analogue **26**. 4-Hydroxybenzoic acid (**23**) was coupled with 4-(aminomethyl)pyridine using BOP/Hunig's base conditions. The phenol group was reacted with 4-chloromethyl-2-methylquinoline and Cs_2CO_3 to yield **24**. Oxidation with Oxone® and $NaHCO_3$ in MeOH and H_2O resulted in a mixture of three products, the pyridine-*N*-oxide **25** (29%), the quinoline-*N*-oxide (12%), and the bis-*N*-oxide (18%). Using conditions reported by Brana et al.[11] **25** was condensed with 5-methylpyrimidine-2,4,6-trione in acetic anhydride at 80 °C to yield **26** in 32% yield.

The inhibitory activity was evaluated using porcine TACE (pTACE), as a result of its availability and homology to human TACE.[12] Compared to lead compound **1**, elongation with an oxygen between the pyrimidinetrione and the phenyl group did not significantly alter the activity in the pTACE assay (**27**, Table 1). The CH_2 analogue **28** had an IC_{50} of 2.2 μM, 2-fold less potent than compound **1**. Further elongation with ethyl-



Scheme 4. Reagents and conditions: (a) 4-(aminomethyl)pyridine, BOP, *i*-Pr_2NEt, DMF (54%); (b) 4-chloromethyl-2-methylquinoline, Cs_2CO_3, DMSO (88%); (c) Oxone, $NaHCO_3$, MeOH, H_2O, 50 °C (29%); (d) 5-methylpyrimidine-2,4,6-trione, Ac_2O, 80 °C (32%).

Table 1. In vitro potency in pTACE



Compound	–A–	pTACE IC_{50} (μM)
1	—	1.03
27	–O–	1.30
28	$–CH_2–$	2.20
29	$–CH_2CH_2–$	49.0
6	$–CH_2CH_2CH_2–$	>100
7	$–CH_2CH{=}CH–$[a]	11.0
8	$–CH_2CH_2C(O)–$	0.80
13	$–CH_2NHC(O)–$	0.026
30	–NHC(O)–	>100
31	$–CH_2NHC(O)CH_2–$	>100
32	$–CH_2C(O)NH–$	12.0
26[b]	–CH(4-pyridinyl)NHC(O)–	2.36

[a] Trans isomer.
[b] Tested as a racemic mixture.

ene (**29**) and propylene (**6**) resulted in more dramatic loss of activity (~50- and >100-fold, respectively). The activity was restored partially with a more rigid *trans*-$CH_2CH{=}CH$ group (**7**, 11 μM) and completely with a ketone linker (**8**, 0.8 μM). The potency increase from **6** (>100 μM) to **8** (0.8 μM) suggested that the carbonyl group in **8** could be involved in polar interactions with the active site of TACE. To probe this further, the ketone was replaced with an isosteric amide. This transformation was found to have a dramatic effect as the amide analogue **13** exhibited an IC_{50} of 26 nM for pTACE, a 30-fold increase compared to the ketone counterpart **8** and greater than 423-fold increase compared to the propenylene analogue **7**. The amide linker in **13** appears to be optimal. Shortening or lengthening the linker (**30** and **31**, respectively) proved detrimental to pTACE activity. Reversal of the amide moiety also attenuated the affinity for pTACE (**32**). Finally, a pyridine substitution at the methylene α- to the nitrogen resulted in a weaker inhibitor (**26**).

Previous work from our laboratories showed that the 4-(2-methylquinolin-4-ylmethoxy)phenyl P1′ group generally gave high selectivity for TACE relative to MMP-1, -2, and -9. Selectivity over MMP-3, -7 -12, -13, and related aggrecanase was dependent on the nature of the template. As summarized in Table 2, compound **13**

Table 2. In vitro potency of **13** in pTACE, MMPs and aggrecanase

Enzymes	μM
pTACE (IC_{50})	0.026
MMP-1 (K_i)	>4.95
MMP-2 (K_i)	>3.33
MMP-3 (K_i)	>4.50
MMP-7 (K_i)	>6.37
MMP-9 (K_i)	>2.13
MMP-12 (K_i)	>6.02
MMP-13 (K_i)	>5.02
Aggrecanase	0% at 1 μM

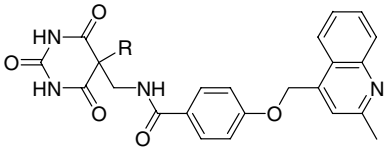
displayed excellent selectivity for pTACE, but did not show significant activity in all eight counter-screen assays.[12] In subsequent studies, MMP-3, -7 -12, -13, and aggrecanase were used as primary counter-screen assays.

In spite of the high affinity for pTACE, compound **13** did not inhibit TNFα production in a LPS-stimulated human whole blood assay (WBA, $IC_{50} > 50$ μM). Because most TACE activity is intracellular,[13] activity in this assay relies on the ability of the inhibitor to penetrate into the cells. In addition, the whole blood assay is complicated by the effects of protein binding. In an attempt to gain additional binding potency for the pTACE and impart functional activity in WBA, a series of analogues was evaluated by replacing the methyl group at the 5-position of the pyrimidine-2,4,6-trione (R group, Table 3). Aliphatic groups, such as ethyl (**33**), benzyl (**34**), and isopropyl (**35**), all gave pTACE inhibitors of essentially the same potency as **13**. The Boc-protected amino analogue (**36**) was also comparable. In all cases, good selectivity over MMP-3, -7, and aggrecanase was maintained. Selectivity over MMP-12 and, to some extent, MMP-2, appeared to depend on the steric size of these substituents. Specifically, linear groups such as ethyl (**33**) and benzyl (**34**) gave sub-micromolar K_i's for MMP-12 and -2. The more bulky isopropyl and BocNH analogues (**35** and **36**) were less active for MMP-2 and inactive in the MMP-12 assay (>6.02 μM), hence were more selective for pTACE.

Previous studies indicated that piperidine and piperazine substituents at 5-position of the pyrimidinetrione could improve affinity for TACE.[3] Compounds **37**–**43** represented differently functionalized piperidin-4-yl analogues (Table 3). Potency in the pTACE assay was largely unaffected; most compounds displayed comparable potency to the methyl analogue **13**, with 1-Piv-piperidin-4-yl analogue **42** being most potent at 13 nM. These compounds also maintained good selectivity over the four MMPs and aggrecanase. For piperazine analogues (**44**–**51**), most compounds showed comparable or better potency for pTACE than **13**. Most notably, the IC_{50} values for the isopropyl, acetyl, and methanesulfonyl piperazine analogues (**47**, **48**, and **51**, respectively) were all less than 10 nM. The potency of **51** (2 nM) compared favorably to those of many hydroxamate-based inhibitors reported in the literature.[1b] Compound **51** was also greater than 500-fold selective in all five counter-screen assays. Unfortunately, the majority of the compounds in Table 3 suffered from poor activity in the WBA. The most active compounds (**42**, **43**, and **50**) showed IC_{50} values between 35 and 40 μM.

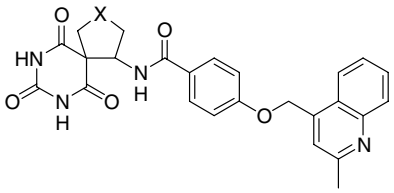
Finally, we attempted to chemically constrain the lead molecule **13** using spiro-pyrimidinetriones (Table 4). The cyclohexane-derived [6,6]-spiro compound **52** showed an IC_{50} of 0.138 μM in the pTACE assay, indicating that the spiro-template was tolerated, albeit the activity was 5-fold less than **13**. The cyclopentane-derived [5,6]-spiro analogue **53** displayed pTACE potency equivalent to **13**, further validating this approach. Unfortunately, **53** was inactive in the WBA (>50 μM). Hoping to improve the WBA activity, we decided to introduce a tetrahydrofuran and several pyrrolidines in place of the cyclopentane. The tetrahydrofuran-derived spiro analogue **54** was a 44 nM inhibitor of pTACE,

Table 3. In vitro potency in pTACE, MMP-2, -3, -7, -12, aggrecanase, and WBA



Compound	R	pTACE IC_{50} (μM)	MMP-2 K_i (μM)	MMP-3 K_i (μM)	MMP-7 K_i (μM)	MMP-12 K_i (μM)	Aggrecanase (%) inh at 1 μM	WBA IC_{50} (μM)
33	Et	0.016	0.20	>4.50	>6.37	0.21	18	>50
34	Bn	0.018	0.37	3.69	>6.37	0.39	34	>50
35	*i*-Pr	0.019	0.93	>4.50	>6.37	>6.02	11	>50
36	BocNH	0.013	>3.33	>4.50	>6.37	>6.02	16	>50
37	piperidin-4-yl	0.055	>3.33	>4.50	>6.37	>6.02	1	48.7
38	1-Me-piperidin-4-yl	0.057	>3.33	>4.50	>6.37	>6.02	15	>50
39	1-*i*-Pr-piperidin-4-yl	0.052	>3.33	>4.50	>6.37	>6.02	21	>50
40	1-(tetrahydropyran-4-yl)-piperidin-4-yl	0.031	>3.33	>4.50	>6.37	>6.02	5	>50
41	1-Ms-piperidin-4-yl	0.029	>3.33	>4.50	>6.37	>6.02	36	>50
42	1-Piv-piperidin-4-yl	0.013	>3.33	>4.50	>6.37	>6.02	10	39
43	1-Boc-piperidin-4-yl	0.047	>3.33	>4.50	>6.37	>6.02	0	35
44	4-Me-piperazin-1-yl	0.058	>3.33	>4.50	>6.37	>6.02	21	>50
45	4-(propargyl)piperazin-1-yl	0.062	>3.33	>4.50	>6.37	>6.02	26	>50
46	4-Bn-piperazin-1-yl	0.014	2.7	>4.50	>6.37	4.1	22	>50
47	4-*i*-Pr-piperazin-1-yl	0.007	>3.33	>4.50	>6.37	>6.02	20	>50
48	4-Ac-piperazin-1-yl	0.005	>3.33	>4.50	>6.37	>6.02	21	>50
49	4-(nicotinoyl)piperazin-1-yl	0.010	>3.33	>4.50	>6.37	4.64	36	43
50	4-Piv-piperazin-1-yl	0.029	0.02	>4.50	>6.37	0.05	7	38
51	4-Ms-piperazin-1-yl	0.002	2.17	>4.50	>6.37	1.02	11	>50

Table 4. In vitro potency in pTACE, MMP-2, -3, -7, -12, aggrecanase, and WBA[a]



Compound	–X–	pTACE IC_{50} (μM)	MMP-2 K_i (μM)	MMP-3 K_i (μM)	MMP-7 K_i (μM)	MMP-12 K_i (μM)	MMP-13 K_i (μM)	Aggrecanase (%) inh at 1 μM	WBA IC_{50} (μM)
52	$–(CH_2)_2–$	0.138	0.11	—[b]	—[b]	—[b]	—[b]	29	—[b]
53	$–CH_2–$	0.024	>3.33	—[b]	—[b]	—[b]	—[b]	0	>50
54	–O–	0.044	>3.33	>4.50	>6.37	4.04	3.53	12	50
55	–N(Ac)–	0.055	>3.33	>4.50	>6.37	0.58	3.95	44	14
56	–N(Piv)–	0.111	>3.33	>4.50	>6.37	>6.02	—[b]	53	>50
57	–N(nicotinoyl)–	0.029	>3.33	>4.50	>6.37	0.13	1.31	17	18.4
58	–N(Ms)–	0.036	>3.33	>4.50	>6.37	1.29	3.72	26	12.6
59	–N(Boc)–	0.128	>3.33	>4.50	>6.37	1.03	>5.21	44	14

[a] All compounds were tested as racemic mixture.
[b] Not tested.

had good selectivity over all five MMPs and aggrecanase, but failed to improve potency in the WBA noticeably. In contrast, several of the pyrrolidine-derived spiro analogues exhibited promising activity in the WBA. Compounds **55**, **57**, **58**, and **59** all had IC_{50} values under 20 μM. These compounds also maintained good overall selectivity.

In summary, a new series of TACE inhibitors was discovered using a pyrimidine-2,4,6-trione as a hydroxamate replacement. Even though pyrimidinetrione is a significantly weaker ligand for zinc ion than hydroxamic acid, highly potent TACE inhibitors have been identified through optimization of the rest of the molecule. The most potent compound **51** had an IC_{50} of 2 nM in the pTACE-binding assay. To the best of our knowledge, **51** represents the first example of non-hydroxamate TACE inhibitors with single digit nanomolar potency. Some of the analogues also displayed moderate functional activity in a cellular assay. However, further improvement in functional activity is needed for these inhibitors to be useful in vivo.

Acknowledgments

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References and notes

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4-hydroxybenzoate, 4-chloromethyl-2-methylquinoline, K_2CO_3, Bu_4NI, CH_3CN (99%); (b) LiOH, H_2O, THF, MeOH (94%); (c) $SOCl_2$, CH_2Cl_2, at reflux (100%).
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