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

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Abstract—A novel series of achiral TNF-α converting enzyme (TACE) inhibitors has been discovered. These compounds exhibited activities from 0.35 to 11 nM in a porcine TACE assay and inhibited TNF-α production in an LPS-stimulated whole blood assay with an IC_{50} value of 23 nM for the most potent one. They also have excellent selectivities over related metalloproteases including aggrecanases.

Tumor necrosis factor-α (TNF-α)[1] is a potent proinflammatory cytokine which is primarily produced by monocytes and macrophages and exists as a 26 kD membrane bound propeptide (pro-TNF-α). Pro-TNF-α is processed by sheddases to release the 17 kD soluble form (s-TNF-α). Disregulation of TNF-α is implicated in chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, and Crohn's disease.[2] Marketed biologics that work by sequestering pro-TNF-α and s-TNF-α, such as enbrel, remicade, and humira, have clinically validated anti-TNF therapy for the treatment of these chronic inflammatory diseases.[3] While these biologics are effective, they are expensive and must be administered parenterally.

An alternate approach is to inhibit the release of s-TNF-α via inhibitors of TNF-α converting enzyme (TACE). TACE is a member of the metzincin family and is the primary sheddase for releasing soluble TNF-α from cells.[4] It has been shown that inhibition of TACE blocks soluble TNF-α release; thus, a small molecule that can selectively inhibit TACE may represent a valid approach to anti-TNF-α therapy.[5] Selectivity over other MMPs is desirable since some broad spectrum and partially selective MMP inhibitors have been reported to cause musculoskeletal side effects.[6] This paper will disclose a novel series of selective, achiral TACE inhibitors.

Earlier efforts in our TACE program led to the discovery of an acyclic β-aminohydroxamic acid analog **1** (Fig. 1). This compound has an IC_{50} of 1 nM in a pTACE[7] assay and is selective against several matrix metalloproteinases (MMPs); however, it is not effective

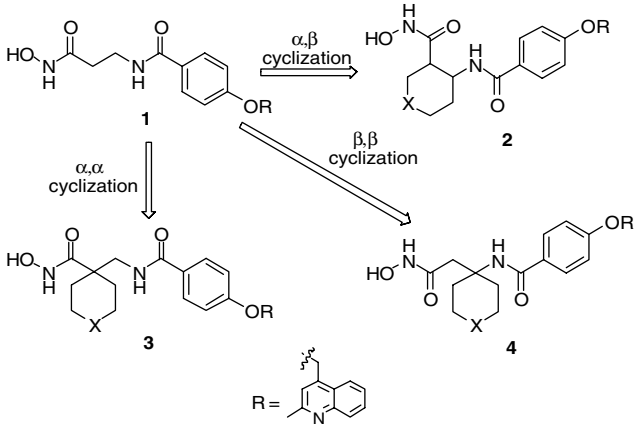

Figure 1. β-Aminohydroxamic acid series (**1**–**4**).

Keywords: TACE inhibitors; Metazincin; Metalloprotease; Sheddase; Tumor necrosis factor; Antiinflammatory; Hydroxamic acid.
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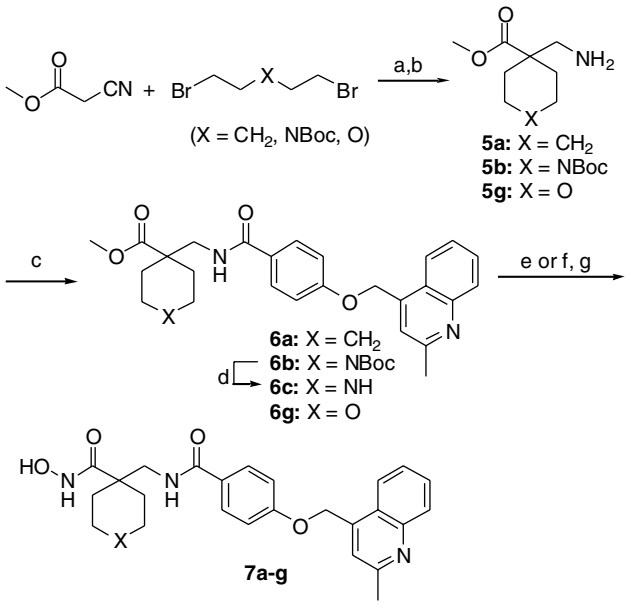
in inhibiting TNF-α production in human whole blood assay (WBA). In classic fashion, this compound is thought to work by forming a bidentate bond between the hydroxamic acid moiety and the catalytic Zn ion in the active site. Additionally, the carbonyl group of the central amide forms two important hydrogen bonds to Gly163 and Leu164 of the protein backbone.[8] The [(2-methyl-4-quinolinyl)methoxy]phenyl P1′ group is the critical determinant of selectivity for TACE relative to other MMPs.[9–11]

In an effort to discover compounds which have both pTACE as well as WBA activities, several series of cyclic-β-aminohydroxamic acids were designed and synthesized (**2**–**4**). The first series was formed by cyclizing α,β to the hydroxamic acid (Fig. 1, **2**). The synthesis and evaluation of these compounds will be disclosed in another paper.[12] Alternatively, we envisioned generation of two new series formed by cyclizing α,α and β,β to the hydroxamic acid (Fig. 1, **3** and **4**).

The α,α cyclization series was studied first. The α,α substitution was designed to help in vivo stability of the hydroxamic moiety through steric hindrance since this is known to be a problem in other series. The synthesis of the α,α-cyclic-β-aminohydroxamic acids (**7a**–**g**) is outlined in Scheme 1. Methyl cyanoacetate was alkylated with various dibromides followed by reduction of the nitrile using platinum oxide to afford the cyclic primary amines **5a**,**b**, and **g**. These amines were coupled to the P1′ side chain 4-[(2-methyl-4-quinolinyl)methoxy]benzoic acid using BOP reagent to afford compounds **6a**,**b**, and **g**. Compound **6b** was deprotected using TFA to give **6c**; which was further functionalized at the piperidine



Scheme 1. Reagents and conditions: (a) NaH or K_2CO_3, THF; (b) PtO_2, H_2, MeOH, concd HCl; (c) 4-[(2-methyl-4-quinolinyl)methoxy]benzoic acid, BOP reagent, *N*-methylmorpholine, DMF; (d) TFA, CH_2Cl_2; (e) various acids, BOP reagent, *N*-methylmorpholine, DMF; (f) propionaldehyde $NaH(OAc)_3$, 1,2-dichloroethane; (g) NH_2OH, KOH, MeOH.

nitrogen. The final step was conversion of the methyl ester to the hydroxamic acid using a hydroxylamine/KOH/MeOH solution to give compounds **7a**,**b**, and **d**–**g**. The Boc-protected compound **7b** was deprotected with TFA to give **7c**.

These compounds were tested and found to have activities ranging from 2 to 12 nM in the pTACE assay and were selective against other MMPs (data not shown); however, they showed no WBA activity (Table 1).

The scaffold was then modified by migrating the ring attachment from the α-carbon to the β-carbon (Fig. 1, **4**). Although there is no substitution α to the hydroxamic acid to help prevent possible metabolism, this skeleton is 'neopentyl like' with regard to the hydroxamic acid and it was hoped that this would provide enough steric hindrance to prevent metabolism of the hydroxamic acid.

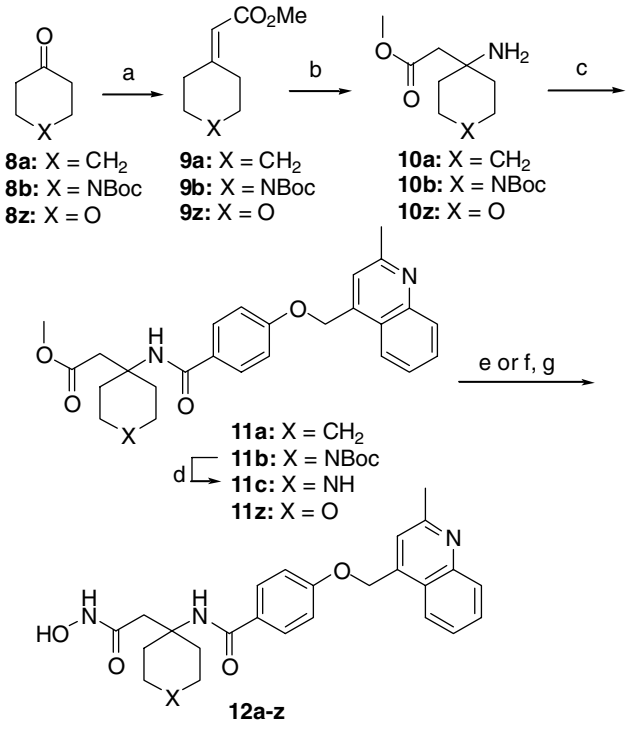
These compounds were synthesized according to Scheme 2. Ketone **8** was subjected to a Wittig olefination to provide esters **9a**,**b**, and **z**. Addition of ammonia in a Michael fashion proceeded in good yield at 80 °C in a sealed tube to provide amines **10a**,**b**, and **z**. These amines were coupled to the P1′ side chain using BOP reagent to give esters **11a**,**b**, and **z**. The Boc-protected piperidine compound **11b** was deprotected with TFA to give **11c** and then functionalized with a variety of R groups to afford compounds **11d**–**y**. Finally, the methyl ester was converted to a hydroxamic acid by treatment of a hydroxylamine/KOH/MeOH solution to afford compounds **12a**–**z**.

These β,β-cyclic β-aminohydroxamic acid analogs were tested for their activities (Table 2). All the compounds in this series were active in the pTACE assay with IC_{50}s ranging from 1 to 8 nM. The excellent selectivities for these compounds against MMP-1, -2, -9, and -13 can be attributed to the [(2-methyl-4-quinolinyl)methoxy]-phenyl P1′ group.[8] The cyclohexyl derivative, **12a**, exhibited some WBA activity at 737 nM. Replacing the cyclohexyl with a piperidine scaffold gave more exciting results. The first compound prepared in this series was the Boc-protected piperidine **12b**. This compound was twice as potent in the WBA as **12a** at 370 nM. Removal of the Boc group to give **12c** resulted in a compound which was remarkably potent in the

Table 1. In vitro potency of **7a**–**g** in pTACE and WBA

Compound	X	pTACE Inhibition IC_{50}[a] (nM)	WBA IC_{50}[b] (μM)
7a	CH_2	8.6	>3.0
7b	NBoc	2.4	>3.0
7c	NH	4.9	>3.0
7d	*N*-Propyl	11	>3.0
7e	N(CO)′Bu	2.3	>3.0
7f	*N*-SO_2Me	1.9	>3.0
7g	O	2.3	>3.0

[a] pTACE IC_{50} and MMP K_i values are from a single determination.
[b] Inhibition of TNF-α release in WBA was determined with three donors.



Scheme 2. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Me$, PhMe, Δ; (b) NH_3, MeOH, 80 °C, sealed tube; (c) 4-[(2-methyl-4-quinolinyl)methoxy]benzoic acid, BOP reagent, *N*-methylmorpholine, DMF; (d) TFA, CH_2Cl_2; (e) various acids, BOP reagent, *N*-methylmorpholine, DMF; (f) various aldehydes $NaBH(OAc)_3$, 1,2-dichloroethane; (g) NH_2OH, KOH, MeOH.

WBA assay with an IC_{50} of 36 nM; however, **12c** was found to have very low Caco-2 permeability. An effort was made to try to increase the Caco-2 permeability by substituting the piperidine nitrogen.

The first series prepared were alkyl substituents on the piperidine nitrogen (**12d**–**m**). When increasingly lipophilic groups were introduced on the piperidine, there was an increase in Caco-2 permeability in compounds **12h**,**i**, and **l**; however, these compounds were less active in the WBA by 4- to 10-fold.

It was postulated that the high basicity of the piperidine nitrogen was preventing Caco-2 permeation. To try to improve the physical properties, additional piperidine derivatives **12n**–**q** were prepared which contained groups that would reduce the basicity of the piperidine nitrogen. Again these derivatives exhibited excellent pTACE activities. Compounds **12o**,**p**, and **q** exhibited marginal Caco-2 permeabilities and had WBA activities ranging from 45 to 119 nM.

Several compounds were selected to evaluate the relationship between the pK_a of the piperidine nitrogen, lipophilicity (HPLC Log *P*), and the Caco-2 permeation. As shown in Table 3, there seems to be an inverse correlation between the basicity of the piperidine nitrogen and Caco-2 permeation. The Caco-2 values were low until the pK_a of the piperidine was below 7. Of the compounds studied, only two were outlying compounds. Compound **12h** which had a pK_a of 7.75 and a Caco-2 P_{app} of 2.4×10^{-6} cm/s and compound **12p** which had a pK_a of 6.06 and a Caco-2 P_{app} of 0.55×10^{-6} cm/s. While there appears to be a good correlation of Log *P* with Caco-2, many compounds were found in this series with high Log *P* values (>3.5) and low Caco-2 permeability (data not shown).

The next series examined were non-basic derivatives (**12r**–**z**). These derivatives included amides, sulfonamides, and ureas of piperidines and a tetrahydropyran. Once again, these compounds had excellent pTACE activities ranging from 0.35 to 3 nM. The WBA activities were also good ranging from 23 to 212 nM. Compound **12r**, which has an acetyl group on the piperidine, was exceptionally good in the WBA at 23 nM. The Caco-2 permeability was not improved significantly in this series, and even extremely lipophilic compounds such as **12u** and **v** gave marginal Caco-2 permeability.

Many of these compounds were also evaluated in an LPS-mouse model and were found to have good anti-TNF-α activity. Compounds **12c**,**l**,**r**,**y** and **z** all had ED_{50}s of less than 8 mg/kg after oral administration (Table 2). Despite the low to marginal Caco-2 values, **12c** and **z** were examined in more depth. In an expanded panel of counterscreens, both compounds have excellent selectivity (>1000×) for pTACE relative to MMP-1, -2, -9, -13, -14, -15, and -16. Compound **12c** also showed over 50-fold selectivity for pTACE over MMP-3, MMP-8, ADAMTS-1, and ADAMTS-5, and 10-fold selectivity over MMP-7. Compound **12z** was found to be the more selective of the two with >1000-fold selectivity over MMP-8, ADAMTS-1, ADAMTS-4, and ADAMTS-5 as well as more than 80-fold selectivity over MMP-3 and MMP-7 (Table 4).

Studies using S9 liver cells were performed to assess the metabolic stability of **12c** and **z**. The stability of **12c** was excellent despite not having a substituent next to the hydroxamic acid. After incubation in S9 liver cells for 30 min at 37 °C, 100% of the parent compound was remaining in rat, dog, and chimp and 92% of the parent compound was remaining in human. Compound **12z** was less stable. After 30 min incubation in S9 liver cells, 83.8% remained in human and 36.7% in chimps.

Next, the pharmacokinetic profiles of these two compounds was evaluated (Table 5). The pharmacokinetics of **12c** was studied in Beagle dogs and Sprague–Dawley rats in a cassette dose fashion ($n = 3$) and the pharmacokinetics of **12z** was studied in the same two species in a discrete fashion. The compounds were administered intravenously and orally, and the plasma levels were analyzed by LC–MS–MS assay. Compound **12c** exhibited very low clearance in both species. This compound also showed low oral bioavailability as indicated by the *F*% values of 8 and 17. In dogs, compound **12z** had high systemic clearance with a terminal half-life of 4.2 h after iv administration. The volume of distribution at steady state was moderate at 2.5 L/kg. Oral bioavailability was excellent with an *F*% of 79. In rats, the clear-

Table 2. In vitro and in vivo profile of **12a–z**

Compound	X	pTACE Inhibition IC_{50}[a] (nM)	WBA IC_{50}[b] (nM)	MMP-1 K_i (nM)	MMP-2 K_i (nM)	MMP-9 K_i (nM)	MMP-13 K_i (nM)	Caco-2 P_{app} ($\times 10^{-6}$ cm/s)	LPS-mouse[c] at 10 mg/kg (po)
12a	CH_2	1.4	737	>4949	>3333	>2128	>5025	3.6	Not determined
12b	NBoc	7.7	370	>4949	>3333	>2128	>5025	8.2	Not determined
12c	NH	1.9	36	>4949	>3333	>2128	>5025	0.0	ED_{50} < 3.0 mg/kg
12d	*N*-Methyl	3.1	109	>4949	>3333	>2128	>5025	0.1	17%
12e	*N*-Ethyl	2.2	26	>4949	>3333	>2128	>5025	0.1	Not determined
12f	*N*-Propyl	2.0	96	>4949	>3333	>2128	>5025	0.1	Not determined
12g	*N*-^{t}Bu	3.7	56	>4949	>3333	>2128	>5025	0.1	29%
12h	*N*-$CH_2{}^t$Bu	2.6	143	>4949	>3333	>2128	>5025	2.4	38%
12i	*N*-Di-me-propargyl	2.3	490	>4949	>3333	>2128	>5025	3.2	Not determined
12j	*N*-Phenyl	1.9	52% at 3 μM	>4949	>3333	>2128	>5025	0.5	Not determined
12k	*N*-Benzyl	1.8	290	>4949	>3333	>2128	>5025	0.1	Not determined
12l	*N*-$(CH_3)_2COO^tBu$	1.9	272	>4949	>3333	>2128	2462	5.3	ED_{50} = 7.8 mg/kg
12m	*N*-$(CH_3)_2COOH$	3.2	50	>4949	>3333	>2128	>5025	0.1	24%
12n	*N*-2-(4,5-Dihydrothiazole)	1.2	30	>4949	>3333	>2128	>5025	0.1	100%[d]
12o	*N*-$CH_2CH_2SO_2Me$	1.2	45	>4949	>3333	>2128	>5025	0.81	Not determined
12p	*N*-$CH_2CH_2SO_2Et$	1.4	119	>4949	>3333	>2128	>5025	0.55	Not determined
12q	*N*-CH_2CH_2F	2.6	90	>4949	>3333	>2128	3136	0.55	Not determined
12r	*N*-C(O)Me	1.9	23	>4949	>3333	>2128	>5025	0.1	ED_{50} = 1.4 mg/kg
12s	*N*-C(O)Et	2.7	39	>4949	>3333	>2128	>5025	0.1	5%
12t	*N*-C(O)^{i}Pr	1.2	89	>4949	>3333	>2128	>5025	0.2	17%
12u	*N*-C(O)^{t}Bu	2.1	102	>4949	>3333	>2128	>5025	0.88	ED_{50} = 25.5 mg/kg
12v	*N*-$C(O)CH_2{}^t$Bu	1.9	212	>4949	>3333	>2128	>5025	0.79	Not determined
12w	*N*-C(O)^{i}Bu	2.2	105	>4949	>3333	>2128	>5025	0.56	48%
12x	*N*-SO_2Me	1.0	54	>4949	>3333	>2128	>5025	Not determined	Not determined
12y	*N*-$C(O)NMe_2$	2.8	152	>4949	>3333	>2128	>5025	Not determined	ED_5 < .3.0 mg/kg
12z	O	0.35[e]	150	>4949	>3333	>2128	>5025	0.8	ED_{50} = 4.7 mg/kg

[a] pTACE IC_{50} and MMP K_i values are from a single determination.
[b] Inhibition of TNF-α release in WBA was determined with three donors.
[c] See Ref. 11 for LPS-mouse model studies.
[d] LPS-mouse for **12n** is from ip administration.
[e] This is a K_i value.

Table 3. pK_a, Log *P*, and Caco-2 relationship

Compound	pK_a	HPLC Log *P*	Caco-2 P_{app} ($\times 10^{-6}$ cm/s)
12a	10.1	1.62	0
12g	~9	1.95	0.1
12c	8.4	2.13	0.1
12h	7.75	3.66	2.4
12q	7.2	2.70	0.2
12n	7.23	2.78	0.1
12i	6.58	3.43	3.2
12l	6.4	4.38	5.3
12p	6.06	2.48	0.55

Table 4. Selectivity profile of **12c** and **z**

Enzyme	**12c** K_i (nM)	**12z** K_i (nM)
pTACE	1.9[a]	0.35
MMP-1 (collagenase)	>4949	>4949
MMP-2 (gelatinase A)	>3333	>3333
MMP-3 (stremolysin-1)	91	82
MMP-7 (matrilysin)	18	25
MMP-8 (collagenase-2)	217	>3100
MMP-9 (gelatinase B)	>2128	>2128
MMP-13 (collagenase-3)	>5025	>5025
MMP-14 (membrane type-1 MMP)	>5290	>5290
MMP-15 (membrane type-2 MMP)	>7088	>7088
MMP-16 (membrane type-3 MMP)	>5554	>5554
ADAMTS-1	776	7800
ADAMTS-4 (aggrecanase-1)	1834	4600
ADAMTS-5 (aggrecanase-2)	97	1900

[a] This is an IC_{50} value.

ance (1.6 L/h/kg) was comparable to the dog study and the half-life (0.3 and 1.8 h) and volume of distribution at steady state (0.3 L/kg) were lower. Additionally, the oral bioavailability was not as good (15%).

In summary, we have discovered a novel, achiral series of TACE inhibitors. Our most promising compounds come from a series of β,β-cyclic β-aminohydroxamic acid analogs. As a class, these compounds have excellent pTACE activities, good WBA activities, and were very selective over other MMPs. Within this series, compound **12z**, which has a cyclic tetrahydropyran substitution at the β,β position, is our most promising lead. This compound exhibited a K_i of 0.35 nM in pTACE assays and an IC_{50} of 150 nM in WBA. Despite having low to moderate Caco-2 permeability, **12z** had good oral anti-TNF-α activity in the LPS model. Pharmacokinetic studies demonstrated that it

Table 5. Pharmacokinetic profiles of **12c** and **z** in dogs and rats

Compound	Dose (mg/kg)	Cl (L/h/kg)	$t_{1/2}$	V_{ss} (L/kg)	T_{max} (h)	C_{max} (nM)	AUC (nM h)	F (%)
12c (Dog: *N*-in-1)[a]	iv 0.5	0.3	1.5	0.3			2185	
	po 1.0		2.1		0.63	126	343	8
12c (Rat: *N*-in-1)[a]	iv 3.3	0.6	2.1	0.3			11359	
	po 6.7		2.2		0.3	2484	8358	17
12z (Dog: discrete)[b]	iv 2.0	2.3	4.2	2.5			1966	
	po 10.0		4.0		0.75	4488	7720	79
12z (Rat: discrete)[b]	iv 2.0	1.6	0.3	0.7			2208	
	po 30		1.8		0.4	3745	4860	15

[a] *N*-in-1 studies used an $n = 3$.
[b] Discrete dog and rat study is an average of three animals.

was orally bioavailable with an F value of 79% in dog and 15% in rat.

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