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α,β-Cyclic-β-benzamido hydroxamic acids: Novel templates for the design, synthesis, and evaluation of selective inhibitors of TNF-α converting enzyme (TACE)

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Abstract—Selective inhibitors of TNF-α Converting Enzyme (TACE) based on (1*R*,2*S*)-cyclopentyl, (3*S*,4*S*)-pyrrolidinyl, and (3*R*,4*S*)-tetrahydrofuranyl β-benzamido hydroxamic acids have been synthesized and evaluated. This study has led to the discovery of novel inhibitors whose profiles include activity against TACE in an enzyme assay, potency in the suppression of LPS-stimulated TNF-α in human whole blood, selectivity against a panel of MMPs and oral bioavailability.

The dysregulation of members of the ADAM (A Disintigrin and Metalloprotease) and MMP (matrix metalloprotease) family, zinc-dependent proteolytic enzymes belonging to the metzincin superfamily, has been implicated in numerous pathological conditions including cancer, osteoarthritis, and rheumatoid arthritis.[1] Accordingly, small molecule inhibitors of MMPs and ADAMs have been extensively investigated as potential therapies.[2] In particular, ADAM-17, also known as TNF-α Converting Enzyme or TACE, has garnered considerable attention as the sheddase responsible for controlling the amount of circulating TNF-α.[3] The anti-TNF biologics entaneracept, inflixamab and adalimumab have validated the modulation of TNF-α clinically.[4] Thus, as an alternative mediator of TNF-α, small molecule inhibitors of TACE have been widely researched.[5] Furthermore, selective inhibitors are considered necessary since broad-based MMP inhibitors have led to negative clinical side effects.[6] Though distinct from the standpoint of the overall sequence homology, the MMPs and TACE have very similar active sites.[7] We[8] and others[9] have recognized the S1' pockets of these enzymes as unique elements and we have used these features to construct homology models for insights into designing selective inhibitors.[10]

Recent efforts from these laboratories directed toward the search for small molecule, non-peptidic inhibitors of TACE and MMPs have led to the discovery of several novel templates.[11] Efforts to further expand the structural diversity, selectivity profile and in vivo properties of these inhibitors have led to the discovery of constrained β-benzamido hydroxamic acid derivatives.[12a] Beyond pre-organization of the pharmacologically relevant moieties (i.e. hydroxamic acid, carbonyl and P1' groups), the constrained β-amino acid may impart distinct advantages noted for other β-peptides.[13] The purported molecular interactions of the *cis*-α,β-cyclic-β-amido hydroxamates are shown in Figure 1.[12a] The 4-((2-methylquinolin-4-yl)methoxy)phenyl P1' moiety was optimized for potency and selectivity on earlier scaffolds, was successfully migrated to the β-amino acid scaffold, and remains constant for this study of TACE inhibitors. Herein we report the synthesis and evaluation of novel TACE inhibitors based upon *cis*-α,β-cyclic-β-benzamido hydroxamic acids, with focus on five-membered ring motifs including substituted (1*R*,2*S*)-cyclo-

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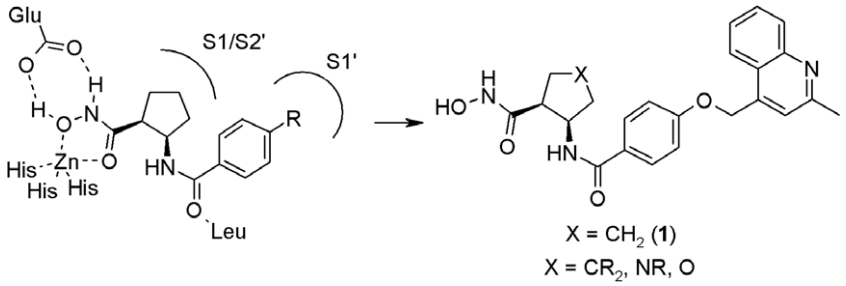


Figure 1. *cis*-α,β-cyclic-β-benzamido hydroxamic acid TACE inhibitors.

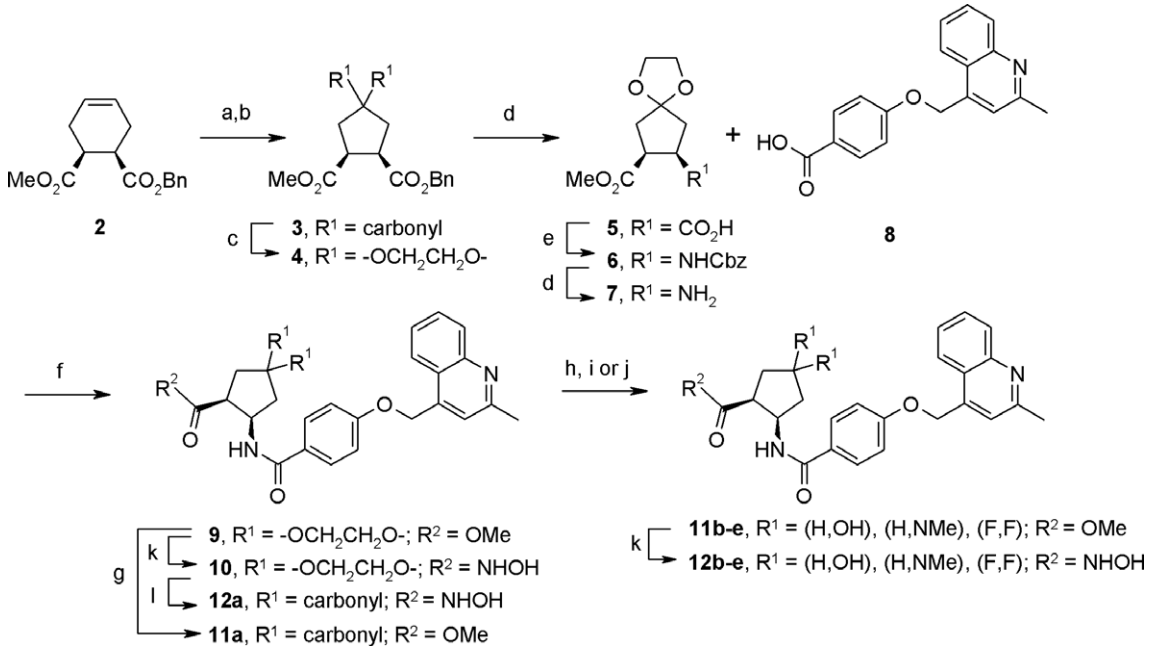
pentyl, (3*S*,4*S*)-pyrrolidinyl and (3*R*,4*S*)-tetrahydrofuranyl scaffolds.

The requisite relative and absolute stereochemistry of the (1*R*,2*S*)-cyclopentane β-benzamido acid core is derived from the commercially available (1*R*,2*S*)-2-methyl cyclohex-4-ene-1,2-dicarboxylate. The benzyl ester **2** (Scheme 1) undergoes an oxidative cleavage-decarboxylative cyclization procedure to afford **3**.[14,15] Ketone protection was followed by unmasking of the acid. Curtius rearrangement[16] of **5** installed the protected amine **6**. Removal of the Cbz-group followed by coupling to **8**[12a] afforded the amide **9**. Deketalization gave the common precursor **11a** suitable for analogue preparation. Reduction, reductive amination, and fluorination proceeded smoothly to give **11b–e**. Formation of the hydroxamic acid entailed treating the ester with a solution of hydroxylamine hydrochloride, methanol, and potassium hydroxide.

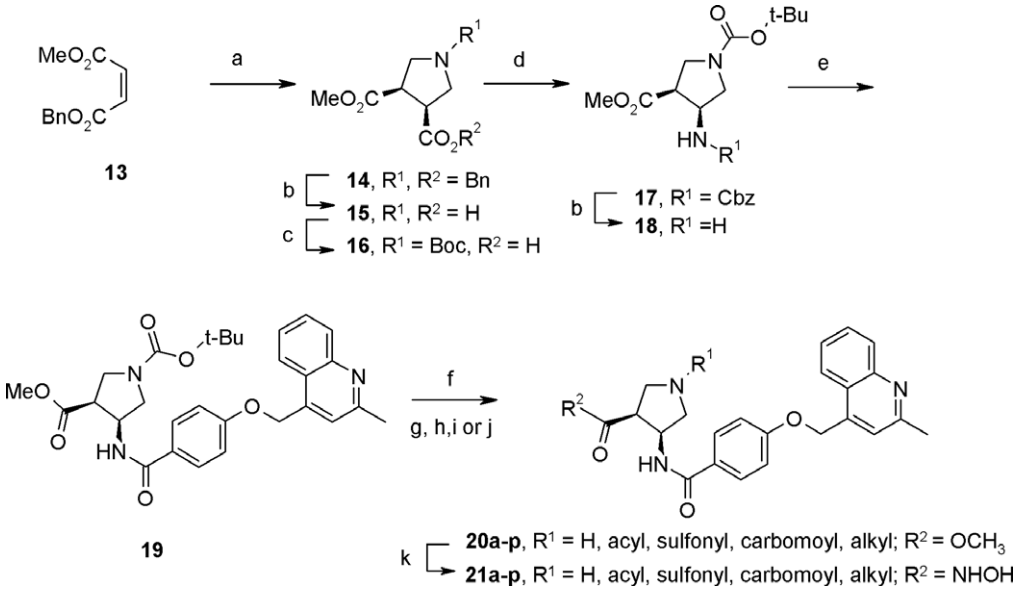
The racemic pyrrolidine dicarboxylate **14** arises from an azo-methine-ylid [3+2] cycloaddition of benzylglycine to benzyl methyl maleate **13** (Scheme 2).[17] Global debenzylation and reprotection of the amine gave **16**. Again, the protected β-amino ester **17** arises from a Curtius rearrangement. The free amine **18** was unmasked and coupled to give **19**. Preparative HPLC separation of the enantiomers at this stage gave the desired (3*S*,4*S*)-enantiomer. The derived secondary amine common precursor **20a** was converted to a variety of functionality including tertiary amine, sulfonamide, carbamate, and amide prior to hydroxamic acid formation.

The tetrahydrofuranyl scaffold resulted from a diastereoselective reduction of an appropriate enamine[18] (Scheme 3) derived from β-ketoester **22**.[19] The literature conditions, when applied to **23**, gave the reduction product **24** as an inseparable 3:1 mixture of diastereomers. Debenzylation gave the free amine **25**. Chiral HPLC analysis of **26** revealed an enantiomeric excess of 52%; the enantiomers were separated on preparative scale. The desired (3*R*,4*S*)-enantiomer was converted to **27**.

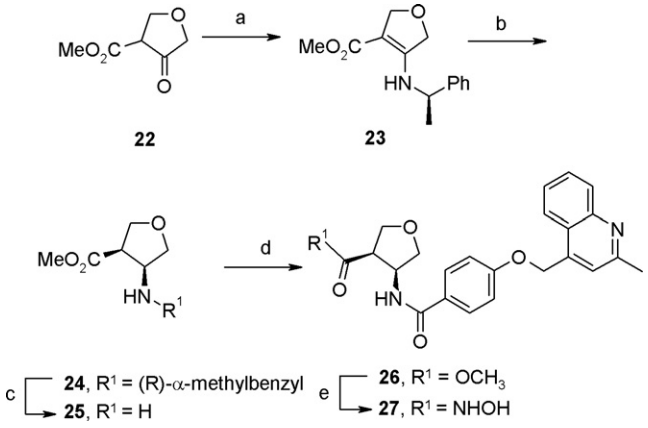
The (1*R*,2*S*)-cyclopentane β-amido hydroxamic analogue **1** provided the launching point for further optimization[20] since **1** displayed excellent in vivo properties,



Scheme 1. Reagents and conditions: (a) $KMnO_4$, H_2O (99%); (b) AcOH, NaOAc (62%); (c) ethylene glycol, *p*-TsOH, C_6H_6 (95%); (d) H_2, $Pd(OH)_2$/C, EtOAc (99%); (e) EtO_2CCl, TEA; NaN_3, H_2O; benzene, reflux; BnOH, *p*-TsOH, reflux (60%); (f) BOP reagent, DIPEA, DMF (99%); (g) 3 N HCl, THF; (h) $NaBH_4$, MeOH; (i) Me_2NH, $NaBH(OAc)_3$; (j) Et_2NSF_3, CH_2Cl_2; (k) NH_2OH, KOH, MeOH; (l) TFA, CH_2Cl_2 (99%).



Scheme 2. Reagents and conditions: (a) *N*-benzylglycine, $(HCHO)_n$, toluene, reflux (61%); (b) H_2, $Pd(OH)_2/C$, MeOH (79–99%) (c) BOC_2O, NaOH (96%); (d) DPPA, TEA, BnOH (73%); (e) **8**, BOP, DIPEA, DMF; HPLC separation of enantiomers (30%, >95% ee); (f) TFA, CH_2Cl_2 (100%); (g) aldehyde, DIPEA, CH_2Cl_2, $NaBH(OAc)_3$; (h) acyl chloride, DIPEA, CH_2Cl_2; (i) sulfonyl chloride, DIPEA, CH_2Cl_2; (j) alkyl halide, TEA, CH_2Cl_2; (k) NH_2OH, KOH, MeOH.



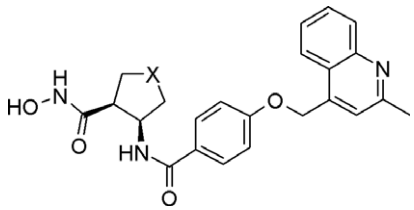
Scheme 3. Reagents and conditions: (a) (*R*)-α-methylbenzyl amine, $Yb(OTf)_3$, tol, reflux (48%); (b) $NaBH(OAc)_3$, AcOH, CH_3CN (36%, 3:1 mixture of diastereomers); (c) H_2, $Pd(OH)_2/C$, MeOH (100%); (d) **8**, BOP Reagent, DIPEA, DMF; HPLC separation of enantiomers; (e) NH_2OH, KOH, MeOH.

most notably oral bioavailability ($F = 68\%$ in dogs).[12a] Since TACE maturation and localization occurs intracellularly and that intracellular TACE is proteolytically active,[21] the initial objective centered on improving the moderate potency in the suppression of TNF-α in the human whole blood assay (WBA, $IC_{50} = 475$ nM). Prior experience suggested that increasing the polarity of the molecule would drive potency into the desired range ($IC_{50} < 200$ nM). Modeling predicted that the β-amino acid ring carbons were solvent exposed, thus, this region was attractive for manipulation.

We were gratified to find that the modifications to the 4-position of the scaffold led to retention of TACE activity (Table 1, **10**, **12a**–**e**) and importantly, added a significant boost in cellular potency (~20-fold for **10** vs. parent **1**). The ketone and hydroxyl substituted analogues (**12a**–**c**) were also potent in the WBA. The insertion of a difluoromethylene (**12e**) as an oxygen isostere[22] provided only a moderate improvement relative to **1**. Unfortunately, the addition of these substituents adversely impacted the Caco-2 permeability with the exception of the 1,3-dioxolane analogue **10** ($P_{app} = 1.8 \times 10^{-6}$ cm/s); the acid labile nature of the 1,3-dioxolane precluded further advancement.

Incorporation of polar functionality into the constrained β-amino acid ring system proved to be a successful tactic. A boost in cellular potency was realized with the pyrrolidine analogue **21a**. The addition of either a sulfonyl or acetyl substituent (**21b**, **21c**) did not alter cell potency. Permeability was low for both analogues and consistent with that result, **21b** showed poor oral bioavailabilty (3%). By altering the nitrogen substituent, we could modulate both cell potency (**21d**) and permeability (**21g**). Toward achieving an optimal balance between potency and permeability, a variety of tertiary alkyl amines were evaluated. Analogues with increased lipophilicity (**21i**) provided inroads with respect to permeability ($P_{app} = 1.3 \times 10^{-6}$ cm/s) while maintaining potency in the desired range ($IC_{50} = 196$ nM). As the size and lipophilicity of the alkyl substituent increased, a slight erosion in cellular potency was observed. Unsaturated groups proved advantageous; 2-methylallyl and propargyl derivatives **21l** and **21m** gave suitable potency as well as permeability. Importantly, **21m** displayed oral bioavailability in rat (Table 3, $F = 25\%$). Cycloalkyl attachments or aromatic substituents (**21n**–**p**) provided no benefit. Similar to the pyrrolidine motif, (3*R*,4*S*)-tetrahydrofuranyl analogue **27**, displayed excellent potency in the cellular assay (WBA $IC_{50} = 33$ nM), acceptable

Table 1. In vitro data for **1**, **10**, **12a–e**, **21a–p**, **27**



Ex	X	pTACE[a] (IC_{50}, nM)	WBA[b] (IC_{50}, nM)	MMP-1 (K_i, nM)	MMP-2 (K_i, nM)	MMP-9 (K_i, nM)	P_{app}[c] ($\times 10^{-6}$ cm/s)
1	$-CH_2-$	1.0	475	>4948	>3333	>2128	6.0
10	C[-$O(CH_2)_2O$-]	1.0	24	>4948	2800	>2128	1.8
12a	–C(O)-	1.8	76	>4948	>3333	>2128	0.2
12b	–[α-OH]–	2.3	46	>4948	>3333	>2128	0.1
12c	–CH[β-OH]–	4.6	121	>4948	>3333	>2128	0.1
12d	–CH[α-NMe_2]–	<1.0	193	>4948	>3333	>2128	0.1
12e	$-CF_2-$	6.3	301	>4948	>3333	>2128	0.0
21a	N–H	6.3	75	>4948	>3333	>2128	–[d]
21b	N–Ms	1.6	79	>4948	>3333	>2128	0.3
21c	N–Ac	1.3	66	>4948	1700	>2128	0.2
21d	NC(O)–*i*-Pr	2.1	68	>4948	>3333	>2128	0.1
21e	N–Piv	2.7	196	>4948	>3333	>2128	0.3
21f	N–C(O)OCH3	1.0	223	>4948	2733	>2128	0.4
21g	N–C(O)O–*i*-Pr	1.5	403	>4948	1500	1851	1.7
21h	N–Me	1.6	50	>4948	>3333	>2128	0.2
21i	N–*i*-Pr	0.4	165	>4948	>3333	>2128	1.3
21j	N–*i*-butyl	1.1	254	>4948	>3333	>2128	0.3
21k	N–Allyl	0.94	97	>4948	>3333	>2128	0.1
21l	N–(2-Methylallyl)	1.5	210	>4948	>3333	>2128	9.8
21m	N–2-Propynyl	0.14	109	>4948	>3333	>2128	3.2
21n	N–*c*-Bu	1.0	191	>4948	>3333	>2128	0.1
21o	N–Bn	1.6	880	>4948	2633	>2128	—
21p	N–CH_2(2-furanyl)	2.0	320	>4948	>3333	>2128	1.1
27	O	1.0	33	>4948	>3333	>2128	1.0

[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.
[c] P_{app} (A → B) $\times 10^{-6}$ cm/s.
[d] —: Not determined.

Table 2. Selectivity profiles[a]

Enzyme	**21m** (K_i, nM)
pTACE (IC_{50})	0.14
MMP-1	>5000
MMP-2	1120
MMP-3	54
MMP-7	6
MMP-8	2000
MMP-9	1720
MMP-10	240
MMP-12	12
MMP-13	490
MMP-14	2800
MMP-15	>7100

[a] pTACE IC_{50} and MMP K_i values are from a single determination.

Table 3. Rat pharmacokinetic parameters[a]

	PK parameters	**21m**[b]	**27**[c]
IV	dose (mg/kg)	3.3	5.0
	$t_{1/2}$ (h)	2.9	2.1
	Cl (L/h/kg)	3.3	2.3
	V_{ss} (L/kg)	1.7	0.8
	AUC (nM × h)	2234	4061
PO	dose (mg/kg)	3.3	5.0
	$t_{1/2}$ (h)	3.1	2.9
	AUC (nM × h)	567	846
	F%	25%	21%

[a] Determination of 3 for each dosing group, average value.
[b] Determined from discrete dosing.
[c] Determined from n-in-1 cassette dosing.

permeability, and oral bioavailability in rats (Table 3, $F = 21\%$).

Indicative of inhibitors in this series, the selectivity profile of **21m** against a panel of MMPs is shown in Table 2. Inhibitor **21m** displays excellent selectivity (>1000-fold) for MMPs-1,-2,-8,-9,-10,-13,-14,-15. Activity was, however, evident for MMPs-3,-7,-12. The full pharmacokinetic parameters for lead heterocyclic inhibitors **21m** (pyrrolidinyl) and **27** (tetrahydrofuranyl) are listed in Table 3. Both display relatively low clearance and >20% oral bioavailability. Of note, oral half-lives are >2 h for each analog.

In summary, we have evaluated (1*R*,2*S*)-cyclopentanyl, (3*S*,4*S*)-pyrrolidinyl, and (3*R*,4*S*)-tetrahydrofuranyl β-

benzamido hydroxamic acids as privileged templates for the discovery of selective inhibitors of TACE. In particular, inhibitors **21m** and **27** proved to be potent for pTACE, selective over a panel of MMPs, potent in the suppression of LPS-induced TNF-α in human whole blood and orally bioavailable.

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