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A new 4-(2-methylquinolin-4-ylmethyl)phenyl P1′ group for the β-amino hydroxamic acid derived TACE inhibitors

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Abstract—A new P1′ group for TACE inhibitors was identified by eliminating the oxygen atom in the linker of the original 4-(2-methylquinolin-4-ylmethoxy)phenyl P1′ group. Incorporation of this 4-(2-methylquinolin-4-ylmethyl)phenyl group onto different β-aminohydroxamic acid cores provided compound **18**, which demonstrated potent porcine TACE (p-TACE) and human whole blood activity, excellent PK properties, and good selectivity against a variety of MMPs.

Tumor necrosis factor-α (TNF-α) is a pro-inflammatory cytokine, which plays a key role in initiating defensive immune responses upon exposure to diverse pathogens.[1] The pathological properties of over-expressed TNF-α have been well documented for diseases, such as rheumatoid arthritis,[2] Crohn's disease,[3] psoriasis,[4] and septic shock.[5] The clinical success of the anti-TNF-α biologics for the treatment of rheumatoid arthritis,[6] Crohn's disease,[7] and psoriasis[8] has provided validation for suppressing the circulating TNF-α as a therapeutic target. Thus, there has been broad interest in pursuing small molecules to intervene in the circulating TNF-α production. One such target is TNF-α converting enzyme (TACE),[9] which is responsible for the shedding of soluble TNF-α from membrane-bound pro-TNF-α.

The initial leads of TACE inhibitor disclosed in the literature were derived from broad spectrum MMP inhibitors, due to high sequence similarity in the active site regions of TACE and MMPs.[10] In fact, prior to the discovery of TACE in 1997, some synthetic hydroxamate-based inhibitors of MMPs were found to block TNF-α release in vivo upon endotoxin stimulation.[11] At the early stage of TACE discovery program, efforts were focused on the improvement of TACE potency through rational drug design based on MMP inhibitors.[12] Given the toxicity observed with most broad spectrum MMP inhibitors in the clinic,[13] recent efforts have been directed toward achieving TACE selectivity over MMPs. As a result, a number of potent and selective TACE inhibitors have been identified.[14]

More recently, we disclosed a number of constrained β-amino hydroxamic acids as potent and selective TACE inhibitors (**1**, **2**, and **3**) (Fig. 1),[15] that contain

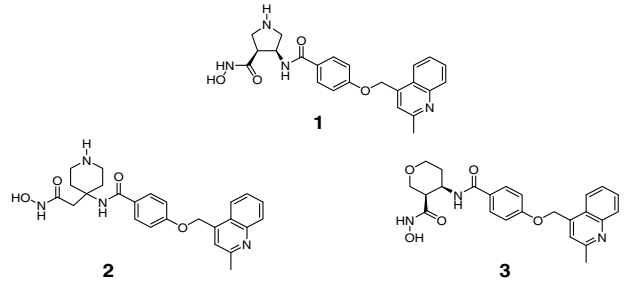

Figure 1. Previously disclosed β-amino hydroxamic acids as potent TACE inhibitors.

Keywords: Anti-inflammatory agent; TACE inhibitor; Matrix metalloproteinase inhibitor; β-Amino hydroxamic acid.
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the 4-(2-methylquinolin-4-ylmethoxy)phenyl P1′ group. A campaign to identify alternatives to this P1′ group was also carried out. Our goal was to identify either a different heterocycle replacement for the quinoline or an alternative linker between the phenyl and quinolinyl groups. Our efforts to identify different heterocycle replacements for the 2-methylquinoline group were recently disclosed.[16] Herein, we wish to describe our efforts on modification of the linker region, which eventually led to the identification of the 4-(2-methylquinolin-4-ylmethyl)phenyl as an effective P1′ group.

The initial structure–activity relationships (SAR) were carried out on the 4-aminopyrrolidine-3-carbohydroxamic acid series with a one-atom linker and the results are shown in Table 1. Using the TACE inhibitor **1** as a reference compound since it was potent in both porcine TACE assay (p-TACE)[9b,17] (IC_{50} = 6.3 nM) and human whole blood cell assay (WBA) (IC_{50} = 75 nM), shortening the tether length by removal of the methylene group gave compounds **4** and **5**, which retained activity against p-TACE (IC_{50} values of 1.3 and 3.5 nM for **4** and **5**, respectively). However, this alteration resulted in a 10-fold loss in WBA potency. In contrast, the methylene linker analogs (i.e., compounds **6** and **7**) had comparable biological activities in both p-TACE assay and WBA compared to the reference compound **1**. These results revealed that the two-atom linker in compound **1** can be shortened by eliminating the oxygen, but not the methylene group. Based on these results, further SAR studies were focused on the left-hand side of the molecule while keeping the new P1′ substituent with the methylene linker constant.

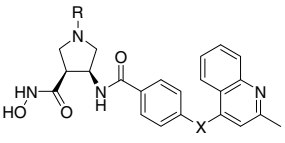
The SAR involving replacement of the hydrogen on the pyrrolidine nitrogen in compound **7** with different substituents is provided in Table 2. A variety of groups, such as methyl (**8**), branched alkyl (**9**–**10**), propargyl (**11**–**12**), pivaloyl (**13**), 1-butanesulfonyl (**14**), and alkoxycarbonyl (**6**, **15**), were well tolerated, affording IC_{50} values of 1.1–4.3 nM. However, the WBA potency and the cell permeability of these compounds were dependent on the nature of the substituents. The methyl compound **8** showed potent WBA activity but low Caco-2 permeability. Since low caco-2 permeability of a TACE inhibitor had consistently resulted in poor pharmacokinetic property as demonstrated at the early stage of this program, we tried to improve both Caco-2 permeability and WBA potency in parallel in our SAR investigation. Increasing the bulk of the substituent from methyl to isobutyl (**9**) and neopentyl (**10**) gradually improved the Caco-2 permeability, but compromised WBA activity. A propargyl group or a 2-butynyl group on the pyrrolidine nitrogen provided analogs **11** and **12**, which demonstrated potent WBA activity and acceptable cell permeability. Analogs with a pivaloyl (**13**), a 1-butanesulfonyl (**14**) or a methoxycarbonyl (**15**) substituent on the pyrrolidine nitrogen retained potency in the WBA, but exhibited poor cell permeability. The potent WBA activities and the acceptable cell permeability of **11** and **12** prompted us to evaluate these two compounds in rat N-in-1 PK studies (N compounds in one dosage)[18] (Table 3). Although both of these compounds showed similar oral bioavailability (F_{po} 19–20%), **11** exhibited a much shorter half-life and lower oral drug exposure compared to **12**, which is attributed to the relatively higher clearance associated with **11**.

Next, we examined the effectiveness of incorporating the 4-(2-methylquinolin-4-ylmethyl)phenyl P1′ group onto other carbocycle or heterocycle cores.[15] As shown in Table 4, all of the compounds except **16** were potent against p-TACE. **16** was a weak inhibitor of p-TACE and completely inactive up to 3 μM in the WBA. A comparison of the two five-membered cyclic compounds **17** and **19** revealed that the more polar tetrahydrofuran ring was superior to the less polar cyclopentane ring in terms of WBA activity. **17**, however, was inferior to **19** in the Caco-2 permeability assay. The six-membered tetrahydropyran ring provided potent WBA activity and acceptable Caco-2 permeability. Compound **18** also demonstrated favorable PK properties with high oral drug exposure and good oral bioavailability in rat and dog (Table 5).

Because of the most favorable in vitro potencies and PK properties of **18**, we examined its selectivity profile against a panel of MMPs (Table 6). Compound **18** was selective against the MMPs in the panel.

In an attempt to improve the profile of **18**, we investigated the effect of substitution on the quinoline ring. With

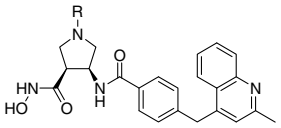
Table 1. Biological evaluation of analogs with an oxygen and methylene linker

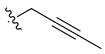
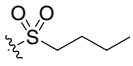


Compound	R	X	p-TACE[a] IC_{50} (nM)	WBA[b] IC_{50} (nM)
1	H	$–OCH_2–$	6.3 ± 1.6	75 ± 22
4	$–CO_2$-*t*-Bu	–O–	1.3 ± 0.3	750 ± 180
5	H	–O–	3.5 ± 1.1	920 ±180
6	$–CO_2$-*t*-Bu	$–CH_2–$	<1	96 ± 14
7	H	$–CH_2–$	<1	67 ± 17

[a] (n = 2–6).
[b] (n = 3–12).

Table 2. SAR on the 4-amino-pyrrolidine 3-carbohydroxamic acid series[a]



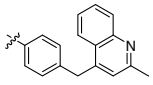
Compound	R	p-TACE[b] IC_{50} (nM)	WBA[c] IC_{50} (nM)	Caco-2 $X10^{-6}$ cm/s
8		2.5 ± 0.6	96 ± 14	0.3
9		1.6 ± 0.4	220 ± 69	1.5
10		1.6 ± 0.3	700 ± 94	9.3
11		4.3 ± 1.1	86 ± 25	0.7
12		1.0 ± 0.2	110 ± 35	1.9
13		1.5 ± 0.3	95 ± 24	0
14		1.1 ± 0.3	120 ± 45	0.3
15		3.3 ± 1.0	50 ± 15	0.1

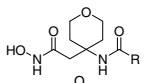
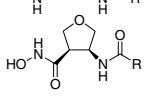
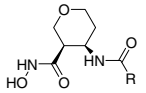
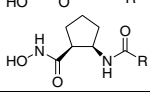
[a] All of the compounds were selective over MMP-1 (>5.0 μM), MMP-2 (>3.0 μM), MMP-9 (>2.0 μM) and MMP-13 (>5.0 μM).
[b] (n = 2–6).
[c] (n = 3–12).

Table 3. Pharmacokinetic parameters of **11** and **12** in rat N-in-1 study (N compounds in one dosage study)

iv	Dose (mg/kg)	$t_{1/2}$ (h)	Cl (L/h/kg)	V_{ss} (L/kg)	AUC (nM h)
11	5.0	0.6	2.2	0.8	5100
12	5.0	2.9	0.3	0.1	27,000
po	Dose (mg/kg)	t_{max} (h)	AUC (nM h)	F (%)	
11	5.0	0.25	962	19	
12	5.0	0.25	5270	20	

Table 4. The effectiveness of the new P1′ group on different cores[a]

R= 

Compound	Structure	p-TACE[b] IC_{50} (nM)	WBA[c] IC_{50} (nM)	Caco-2 × 10^{-6} cm/s
16		97 ± 24	>3000	
17		2.0 ± 0.5	130 ± 36	0.1
18		1.0 ± 0.3	130 ± 24	0.6
19		1.8 ± 0.4	560 ± 130	1.2

[a] All of the compounds were selective over MMP-1 (>5.0 μM), MMP-2 (>3.0 μM), MMP-9 (>2.0 μM), and MMP-13 (>5.0 μM).
[b] (n = 2–6).
[c] (n = 3–12).

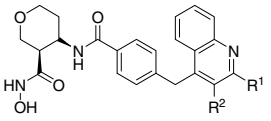
Table 5. Pharmacokinetic parameters of **18** in rat and dog

iv	Dose (mg/kg)	$t_{1/2}$ (h)	Cl (L/h/kg)	V_{ss} (L/kg)	AUC (nM h)
Rat	4.0	1.7	0.5	0.5	19000
Dog	2.0	3.7	2.1	7.1	2300
po	Dose (mg/kg)	t_{max} (h)	AUC (nM h)	F (%)	
Rat	8.0	3.0	15000	39	
Dog	8.0	9.5	5900	64	

Table 6. Selectivity profile of **18**

Enzyme	IC_{50} (nM)	Enzyme	IC_{50} (nM)
MMP-1	>5000	MMP-9	>2000
MMP-2	>3000	MMP-10	2400
MMP-3	1800	MMP-13	>5000
MMP-7	1700	MMP-14	>5000
MMP-8	>3000	MMP-15	>7000

Table 7. SAR on quinoline with 4-aminotetrahydropyran 3-carbohydroxamic acid core



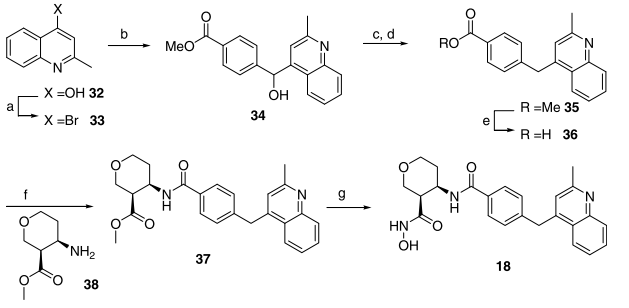
Compound	R^1	R^2	p-TACE[a] IC_{50} (nM)	WBA[b] IC_{50} (nM)
20	CF_3	H	2.2 ± 0.4	260 ± 78
21	Et	H	1.7 ± 0.4	78 ± 27
22	*i*-Pr	H	<1.0	420 ± 72
23	Morpholinyl	H	1.6 ± 0.1	720 ± 190
24	Me_2N	H	1.2 ± 0.4	460 ± 150
25	Cyclopropyl	H	1.3 ± 0.3	230 ± 58
26	H	Me	1.5 ± 0.5	98 ± 22
27	Me	Me	1.2 ± 0.4	85 ± 17
28	Me	Et	7.8 ± 2.6	1200 ± 400
29			1.0 ± 0.2	72 ± 10
30			2.6 ± 0.7	87 ± 26
31			1.3 ± 0.1	77 ± 27

[a] (n = 2–6).
[b] (n = 3–12).

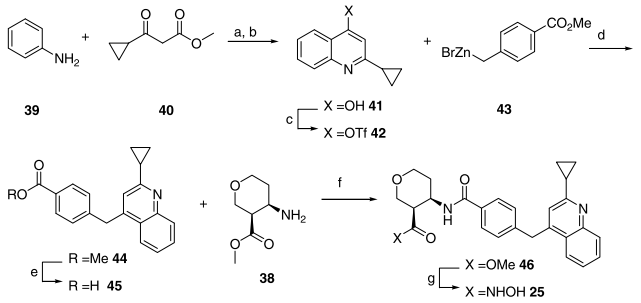
the tetrahydropyran core (Table 7), substitutions on the R^1 and R^2 positions were generally tolerated for p-TACE activity, regardless of the electronic-nature and the bulk of the substituents. However, the WBA potency was highly dependent on the nature of the groups. While the electronic-deficient group (CF_3), electronic-rich groups (NMe_2, morpholinyl), and bulky groups (*i*-Pr and *c*-Pr) decreased the WBA potency, 2-ethyl (**21**), 3-methyl (**26**), and 2,3-dimethyl (**27**) substituents on the quinoline retained the activity. When the 2-position on the quinoline was substituted with a methyl group, a slightly longer alkyl substituent (i.e., an ethyl) than a methyl group at the 3-position was detrimental to p-TACE and especially to WBA as seen with **28**. When the methyl and ethyl groups in **28** were tethered into a five-membered cycle (i.e., **29**), potent p-TACE and WBA activities were observed. Introducing an oxygen atom in the tricyclic portion of **29** (i.e., **30** and **31**) had little effect on the potency of both p-TACE and WBA.

The synthesis of compound **18** started from the commercially available 4-hydroxy-2-methylquinoline (**32**), as illustrated in Scheme 1. Compound **32** was treated with phosphorus oxytribromide to give the corresponding bromide **33**. Treatment of the resulting bromide with *n*-BuLi at −78 °C in THF, followed by the addition of a solution of methyl 4-formylbenzoate, afforded the carbinol **34**. Deoxygenation of **34** was achieved using a two-step procedure. First, **34** was treated with MsCl and triethylamine in dichloromethane. Second, hydrogenation of the resulting mesylate under 1 atm of H_2 in the presence of 10 % Pd/C in MeOH led to **35**. Hydrolysis of **35** was achieved under basic conditions to afford the corresponding acid **36**, which was coupled with (3*R*,4*R*)-methyl 4-aminotetrahydro-2*H*-pyran-3-carboxylate **38**[15a] to give intermediate **37**. Conversion of **37** to the corresponding hydroxamic acid **18** was carried out with hydroxylamine under basic conditions.

A more concise synthetic strategy utilizing 4-methoxycarbonylbenzyl zinc bromide[19] was developed for the synthesis of compound **25** (Scheme 2). Using the Conrad–Limpach quinoline synthesis,[20] 2-cyclopropyl-4-hydroxyquinoline (**41**) was assembled from aniline **39** and β-ketoester **40** in two steps. Compound **41** was converted to the triflate **42** upon treatment with LHMDS and *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoro-*N*-(trifluoromethylsulfonyl)methanesulfonamide. Intermediate **42** was reacted with zinc reagent **43**[19] to provide compound **44**. Hydrolysis of **44** under basic conditions,



Scheme 1. Reagents and conditions: (a) $POBr_3$, 160 °C, 12 h, 40%; (b) *n*-BuLi, THF, −78 °C, then methyl 4-formylbenzoate, 65%; (c) MsCl, TEA, DCM; (d) 10% Pd/C, H_2, MeOH, >95% over two steps; (e) 1 N NaOH, MeOH, 60 °C, >95%; (f) BOP, DIEA, DCM, 97%; (g) $NH_2OH{\cdot}HCl$, NaOMe, MeOH, 55%.



Scheme 2. Reagents and conditions: (a) *p*-TsOH·H_2O, PhH; (b) Ph_2O, 250 °C, 27% over two steps; (c) LHMDS, *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoro-*N*-(trifluoromethyl sulfonyl)methanesulfonamide, THF, 79%; (d) LiCl, $Pd(PPh_3)_4$, DMF, 45%; (e) 1 N NaOH, MeOH, 84%; (f) BOP, DIEA, DCM, 92%; (g) NH_2OH·HCl, NaOMe, MeOH, 50%.

followed by coupling with β-amino ester **38**, gave rise to the product **46**. Treatment of **46** with hydroxylamine under basic conditions provided the corresponding hydroxamic acid **25**. The compounds disclosed in Tables 1, 2, 4, and 7 were synthesized in a similar manner as described in Schemes 1 and 2, substituting **38** with different cyclic β-amino ester.[21]

In conclusion, we have successfully identified 4-(2-methylquinolin-4-ylmethyl)phenyl as an effective P1′ group for TACE inhibitors by eliminating the oxygen atom in the linker of the original 4-(2-methylquinolin-4-ylmethoxy)phenyl P1′ group. Incorporating the new P1′ group onto different β-aminohydroxamic acid cores provided a new series of TACE inhibitors with potent WBA activity. Among them, compound **18** was identified to have good PK properties and an excellent selectivity profile over the MMPs.

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