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Rational Design, Synthesis and Structure–Activity Relationships of a Cyclic Succinate Series of TNF-α Converting Enzyme Inhibitors. Part 2: Lead Optimization

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Abstract—Modifications of the lead TACE inhibitor **1** (*N*-hydroxy-*trans*-2-{[4-(4-quinolinyloxymethyl)anilinyl]carbonyl}-1-cyclohexanecarboxamide) at the cyclohexyl ring and the quinoline moiety led to the identification of a series of piperidine containing TACE inhibitors with potent activity in the inhibition of TNF-α release in the whole blood assay (WBA). The most potent analogue IM491 [*N*-hydroxy-(5*S*,6*S*)-1-methyl-6-{[4-(2-methyl-4-quinolinylmethoxy)anilinyl]carbonyl}-5-piperidinecarboxamide] exhibited an IC_{50} value of 20 nM in WBA with excellent selectivity over MMP-1, -2 and -9 and is orally bioavailable with an *F* value of 43% in beagle dogs.

Tumor necrosis factor-α (TNF-α)[1] is a key proinflammatory cytokine that plays a pivotal role in a number of autoimmune diseases such as rheumatoid arthritis (RA).[2] Over-expression of TNF-α has been shown in the joint of RA patients.[3] The clinic success of anti-TNF-α biologics, which neutralize TNF-α activity by forming biologically inactive complex with the cytokine,[4] has validated TNF-α as a target for the treatment of RA and stimulated considerable interest in small molecule TNF-α converting enzyme (TACE) inhibitors recently.[5] TACE[6] is responsible for the processing of inactive membrane-anchored proform of TNF-α to its active soluble form. It is believed that inhibition of TNF-α through inhibition of TACE may represent a new potential therapeutic target for the treatment of RA.[7]

In the preceding communication,[8] we described the rational design of TACE inhibitors based on the Ciba-Geigy's sulfonamide CGS 27023A,[9] which led to the identification of a novel series of TACE inhibitors as exemplified by compound **1** (Fig. 1). Compound **1** is a six-membered cyclic succinate derivative with 4-[(4-quinolinyl)oxymethyl]aniline as a P1′ residue and as a racemic mixture, showed potent porcine TACE (pTACE) activity with an IC_{50} of 8 nM and excellent selectivity over MMP-1, -2, -9 and aggrecanase. Unfortunately, compound **1** is ineffective in the inhibition of TNF-α release in the cellular assay. In this communication, we report that optimization at the six-membered carbocycle and the quinoline moiety led to the identification of a new series of selective TACE inhibitors with potent anti-TNF-α activity in the cellular assay as represented by **4b** (IM491, Fig. 1).

Synthesis

Compounds **2a–v** were synthesized using the procedures described in Scheme 1. Optically pure (3*R*,4*S*)-4-(*tert*-butoxycarbonyl)-3-piperidinecarboxylic acid (**5**), which was prepared as described in the literature,[10] was reacted with allyl chloroformate in a mixed solvent of water and THF using *N*-methylmorpholine as a base to provide the *N*-allyloxycarbonyl intermediate **6** in 75% yield. Alkylation of **6** with allyl bromide in the presence

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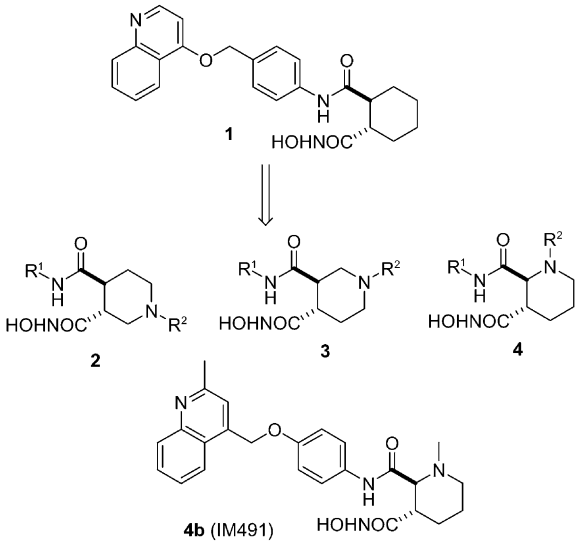
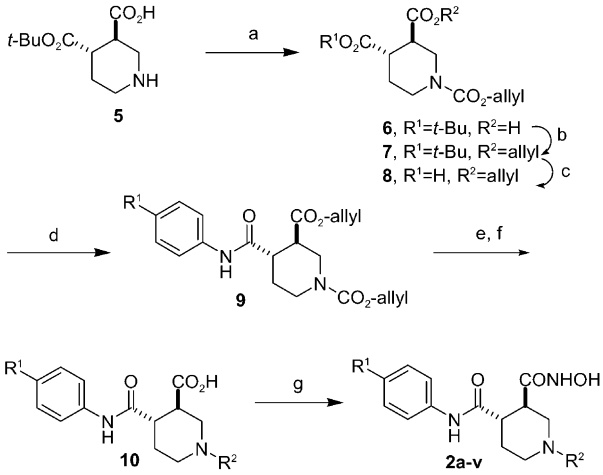
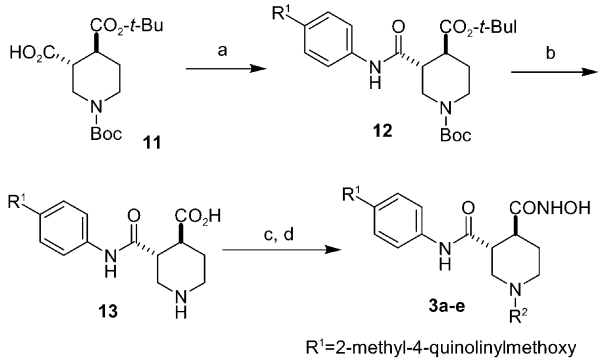


Figure 1.



Scheme 1. Reagents and conditions: (a) allyl chloroformate, NMM, THF, H_2O, 0 °C, 75%; (b) allyl bromide, K_2CO_3, acetone, reflux, 85%; (c) TFA, CH_2Cl_2, 100%; (d) an aniline derivative, BOP, DIEA, DMF; (e) tetrakis(triphenylphosphine)palladium, pyrrolidine, THF; (f) aldehyde, $Na(OAc)_3BH$, DIEA, THF or chloroformate, NMM, THF, H_2O or acid chloride, NMM, THF, H_2O or sulfonyl chloride, NMM, THF, H_2O or isocyanate, DIEA, THF; (g) hydroxylamine hydrochloride, BOP, DIEA, DMF.

of K_2CO_3 provided the diester **7** which was treated with TFA to give the carboxylic acid **8**. Coupling of the carboxylic acid **8** with an aniline derivative using BOP gave rise to the anilide product **9**. After removal of the allyloxycarbonyl and allyl groups by treatment with pyrrolidine/tetrakis(triphenylphosphine)palladium, the resulting amine was subjected to a reductive amination, acylation, sulfonylation, reaction with a chloroformate or an isocyanate to give the intermediate **10**. Conversion of the carboxylic acid to a hydroxamic acid by coupling with hydroxylamine hydrochloride using BOP afforded the final products **2a–v**.



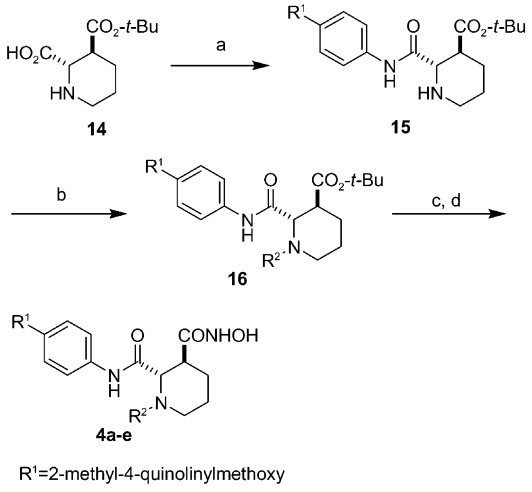
Scheme 2. Reagents and conditions: (a) 4-[(2-methyl-4-quinolinyl)methoxy]aniline, BOP, DIEA, DMF, 78%; (b) TFA, CH_2Cl_2, 100%; (c) an aldehyde, $Na(OAc)_3BH$, DIEA, THF or 2-furoyl chloride, NMM, THF, H_2O; (d) hydroxylamine hydrochloride, DIEA, BOP, DMF.

Compounds **3a–e** were synthesized using the protocols outlined in Scheme 2. Optically pure (3*R*,4*S*)-1,4-bis-(*tert*-butoxycarbonyl)-3-piperidinecarboxylic acid (**11**), which was synthesized as described in the literature,[10] was condensed with 4-[(2-methyl-4-quinolinyl)methoxy] aniline[11] using BOP to provide the anilide **12** in 78% yield. Treatment of **12** with TFA removed the Boc and *tert*-butyl groups. The final products **3a–e** were obtained by reductive amination of the resulting amine with an aldehyde or by acylation with 2-furoyl chloride followed by coupling of the resulting carboxylic acids with hydroxylamine using BOP.

Compounds **4a–e** were synthesized using the sequence depicted in Scheme 3. Without protection of the secondary piperidne amine, the enantiopure (2*S*,3*S*)-3-(*tert*-butoxycarbonyl)-2-piperidinecarboxylic acid (**14**), which was prepared as described in the literature,[10] was coupled with 4-[(2-methyl-4-quinolinyl)methoxy]aniline using BOP to give the anilide **15** in 68% yield. Reductive amination of **15** with an aldehyde using $Na(OAc)_3BH$ provided the tertiary amine **16**. Following removal of the *tert*-butyl group using TFA, the resulting carboxylic acid was converted to a hydroxamic acid as described above.

Results and Discussion

Since compound **1** had high affinity for pTACE[12] ($IC_{50}=8$ nM), we reasoned that the poor inhibition of TNF-α release in WBA ($IC_{50}>50$ μM) might be caused by the lipophilicity of the cyclohexyl ring which could make the molecule highly protein-bound. Thus the cyclohexyl ring in **1** was replaced with a piperidine ring to provide a new series of 3,4-piperidinedicarboxamide derivatives (Table 1). With a cyclopropanecarbonyl group on the piperidine nitrogen, analogue **2a** showed 4-fold improvement in pTACE activity relative to **1** with maintenance of selectivity profile over MMP-1, -2 and -9. More importantly, this modification significantly boosted the cellular potency: **2a** displayed an IC_{50} value of 0.71 μM in WBA, which is >70-fold improvement



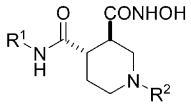
Scheme 3. Reagents and conditions: (a) 4-[(2-methyl-4-quinolinyl)methoxy]aniline, BOP, DIEA, DMF, 68%; (b) aldehyde, $Na(OAc)_3BH$, DIEA, THF; (c) TFA, CH_2Cl_2; (d) hydroxylamine hydrochloride, BOP, DIEA, DMF.

over compound **1**. To optimize the P1′ residue, several quinoline-containing P1′ groups were investigated using the piperidine template of **2a**. While exchanging the positions of the oxygen and methylene between the quinoline and aniline in **2a** basically maintained the potency and selectivity profile (**2b**), removal of the methylene residue at that position resulted in complete loss in pTACE and cellular activity as seen in **2c**, suggesting the importance of the methylene for the orientation of the quinoline residue in the S1′ pocket.[13] Comparisons in pTACE and WBA potency between **2d** and **2e** and between **2f** and **2g** indicate that substitution at the 7-position with trifluoromethyl or at the 2-position with methyl on the quinoline is detrimental to pTACE and cellular activities. However, exchanging the positions of the oxygen and methylene between the quinoline and aniline in **2g** afforded a potent analogue **2h**, which exhibited IC_{50} values of 66 picomolar and 170 nM in pTACE and whole blood assays, respectively. Although analogue **2h** displayed a submicromolar potency for MMP-9, it is still >7000-fold selective for pTACE versus MMP-9. Unfortunately, analogue **2h** had a low water solubility (0.01 mg/mL), low Caco-2 permeability ($P_{app} = 0.1 \times 10^{-6}$ cm/s) and low oral bioavailability (5%) when dosed to beagle dogs (Table 2).

To improve the water solubility, Caco-2 permeability and oral bioavailability of **2h**, a variety of substituents on the piperidine nitrogen were examined while keeping the 4-[(2-methyl-4-quinolinyl)methoxy]anilinyl at P1′ constant (Table 2). The *N*-acyl analogues **2i–k**, urea analogue **2l** and carbamate analogues **2o–s** all showed WBA potency comparable to **2h** but no improvement in permeability, solubility and oral biavailability over **2h**, whereas a slight loss in cellular potency was observed with the sulfonamide analogues **2m–n** and the secondary and tertiary amino analogues **2t–v**. Comparison in water solubility of analogues **2t–v** with other analogues in Table 2 indicates that the basic piperidine nitrogen in the molecule in **2t–v** significantly improved water solubility (>10 mg/mL), which prompted us to explore new analogues bearing a basic piperidine nitrogen (vide infra).

We next carried out SAR studies by moving the piperidine nitrogen one atom away from the hydroxamic acid in **2h** to provide a new series of 4,5-piperidinedicarboxamide derivatives (Table 3). In contrast to the 3,4-piperidinedicarboxamide series in which the 2-furoyl analogue **2h** is much more potent than analogues **2t–v** with a basic piperidine nitrogen (Table 2), analogues **3b–e** with a basic piperidine nitrogen in this series exhibited better WBA potency than the 2-furoyl analogue **3a** (Table 3). Of particular note in this series is that the N-methyl analogue **3c** is very potent in the inhibition of TNF-α release, with an IC_{50} value of 100 nM in the cellular assay. Despite its good water solubility, **3c** showed low Caco-2 permeability and low oral bioavailability (9%) when dosed to beagle dogs. Attempts to improve the Caco-2 permeability and oral bioavailability by increasing the size of the substituent on the piperidine nitrogen resulted in a slight loss in WBA potency as seen in the cyclopropylmethyl and 2-thiazolemethyl analogues **3d** and **3e**.

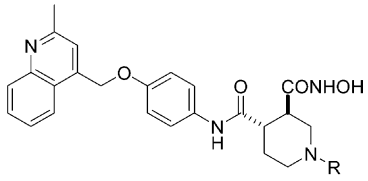
Table 1. (3*R*,4*S*)-N^3-Hydroxy-3,4-piperidinedicarboxamide derivatives with different P1′ residues[a–c]



Compd	R^1	R^2	PTACE IC_{50}, nM	WBA IC_{50}, μM	MMP-1 K_i, nM	MMP-2 K_i, nM	MMP-9 K_i, nM
1			8.0	>50	>4949	>3333	>2128
2a	4-[(4-Quinolinyl)oxymethyl]phenyl	Cyclopropanecarbonyl	2.0	0.71	>4949	>3333	>2128
2b	4-[(4-Quinolinyl)methoxy]phenyl	Cyclopropanecarbonyl	1.0	1.3	>4949	>3333	>2128
2c	4-[(4-Quinolinyl)oxy]phenyl	Cyclopropanecarbonyl	>1000	>50	>4949	>3333	>2128
2d	4-[(4-Quinolinyl)oxymethyl]phenyl	Acetyl	1.0	0.56	>4949	>3333	>2128
2e	4-[(7-Trifluoromethyl-4-Quinolinyl)oxymethyl]phenyl	Acetyl	3.2	2.6	>4949	>3333	>2128
2f	4-[(4-Quinolinyl)oxymethyl]phenyl	2-Furoyl	0.80	0.70	>4949	>3333	>2128
2g	4-[(2-Methyl-4-Quinolinyl)oxymethyl]phenyl	2-Furoyl	3.0	3.4	>4949	>3333	>2128
2h	4-[(2-Methyl-4-Quinolinyl)methoxy]phenyl	2-Furoyl	0.066	0.17	>4949	1011	465

[a]See ref 12 for pTACE, WBA and MMP assay protocols.
[b]pTACE IC_{50} and MMP K_i values are from single determination.
[c]Inhibition of TNF-α release in whole blood assay (WBA) was determined with three donors.

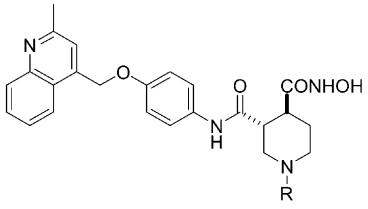
Table 2. (3*R*,4*S*)-N^3-Hydroxy-3,4-piperidinedicarboxamide derivatives with 4-[(2-methyl-4-quinolinyl)methoxy]anilide at P1′[a–c]



Compd	R	PTACE IC_{50}, nM	WBA IC_{50}, μM	MMP-1 K_i, nM	MMP-2 K_i, nM	MMP-9 K_i, nM	Caco-2 *P*app ($\times 10^{-6}$ cm/s)	Solubility mg/mL	Dog PK *F*%
2h	2-Furoyl	0.066	0.17	>4949	1011	465	0.1	0.01	5
2i	Cyclopropanecarbonyl	0.45	0.39	>4949	2454	1656	0.2	0.05	8
2j	Butyryl	0.26	0.33	>4949	>3333	>2128			
2k	2-Methylpropionyl	0.22	0.27	>4949	>3333	>2128	0.3	0.03	9
2l	*tert*-Butylaminocarbonyl	0.41	0.56	>4949	>3333	>2128	0.7	<0.01	5
2m	Methanesulfonyl	0.48	1.36	>4949	656	306	0.2	<0.01	7
2n	1-Methyl-4-imidazolesulfonyl	0.31	1.5	>4949	1002	366			
2o	Methoxycarbonyl	0.28	0.57	>4949	1111	767			
2p	Isopropyloxycarbonyl	0.44	0.21	>4949	771	252			
2q	Cyclopropyloxycarbonyl	0.83	0.70	>4949	642	209	0.2	<0.01	8
2r	2-Thiazolemethoxycarbonyl	<0.3	0.45	>4949	1537	768	0.1	<0.01	3
2s	4-Thiazolemethoxycarbonyl	<0.3	0.53	>4949	476	296			
2t	H	1.5	4.3	>4949	>3333	>2128		>10	
2u	Isopropyl	1.2	1.2	>4949	>3333	>2128		>10	
2v	Cyclobutyl	1.6	1.1	>4949	>3333	>2128		>10	

[a]pTACE IC_{50} and MMP K_i values are from single determination.
[b]Inhibition of TNF-α release in whole blood assay (WBA) was determined with three donors.
[c]Oral bioavailability (*F*%) from dog pharmacokinetics studies.

Table 3. (4*S*,5*S*)-N^4-Hydroxy-4,5-piperidinedicarboxamide derivatives with 4-[(2-methyl-4-quinolinyl)methoxy]anilide at P1′[a–c]

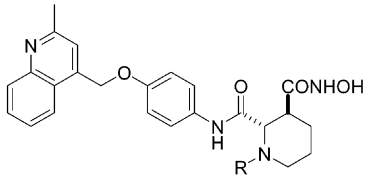


Compd	R	PTACE IC_{50}, nM	WBA IC_{50}, μM	MMP-1 K_i, nM	MMP-2 K_i, nM	MMP-9 K_i, nM	Caco-2 *P*app ($\times 10^{-6}$ cm/s)	Solubility mg/mL	Dog PK *F*%
3a	2-Furoyl	<0.3	1.3	>4949	>3333	>2128	0.2	<0.1	
3b	H	3.0	0.53	>4949	>3333	>2128		>10	
3c	Me	5.0	0.10	>4949	>3333	>2128	0.1	>10	9
3d	Cyclopropylmethyl	1.0	0.30	>4949	>3333	>2128		>10	
3e	2-Thiazolemethyl	0.80	0.56	>4949	>3333	>2128			

[a]pTACE IC_{50} and MMP K_i values are from single determination.
[b]Inhibition of TNF-α release in whole blood assay (WBA) was determined with three donors.
[c]Oral bioavailability (*F*%) from dog pharmacokinetics studies.

To further improve the cellular potency and oral bioavailability, SAR studies were next conducted by moving the piperidine nitrogen next to the P1′ residue to provide a new series of 5,6-piperidinedicarboxamide derivatives (Table 4). With no substitution and a methyl substituent on the piperidine nitrogen, analogues **4a** and **4b** (IM491) showed 4- and 5-fold improvement over the 4,5-piperidinedicarboxamide counterparts **3b** and **3c**, respectively, in WBA potency. IM491 is the most potent TACE inhibitor identified so far in the inhibition of TNF-α release from cells, with an IC_{50} value of 20 nM in the whole blood assay. Accompanied by their excellent WBA potency were the good water solubility (>10 mg/mL), excellent selectivity over MMP-1, -2, and -9 and the decent Caco-2 permeability of these two analogues, with P_{app} values of 2.2×10^{-6} and 2.1×10^{-6} cm/s for **4a** and IM491, respectively. The improved Caco-2 permeability of IM491 over **3c** probably can be explained by the less basicity and more steric hindrance of the piperidine nitrogen in IM491 compared to **3c** as the piperidine nitrogen is at a position α to the carboxamide in IM491 but β to the carboxamide in **3c**. In parallel to their good permeability, analogues **4a** and IM491 exhibited good oral bioavailability in beagle dogs, with *F* values of 24% and 43% for **4a** and IM491, respectively. In addition to its good oral absorption, the favorable oral bioavailability of IM491 may also be contributed from its low clearance (0.6 L/h/kg). The lower oral bioavailability

Table 4. (5*S*,6*S*)-N^5-Hydroxy-5,6-piperidinedicarboxamide derivatives with 4-[(2-methyl-4-quinolinyl)methoxy]anilide at P1′[a–c]



Compd	R	PTACE IC_{50}, nM	WBA IC_{50}, μM	MMP-1 K_i, nM	MMP-2 K_i, nM	MMP-9 K_i, nM	Caco-2 *P*app ($\times 10^{-6}$ cm/s)	Solubility mg/mL	Dog PK *F*%
4a	H	1.0	0.12	>4949	>3333	>2128	2.2	>10	24
4b (IM491)	Me	6.2	0.020	>4949	>3333	>2128	2.1	>10	43
4c	Et	8.0	0.10	>4949	>3333	>2128		>10	
4d	Cyclopropylmethyl	1.0	0.40	>4949	>3333	>2128			
4e	2-Thiazolemethyl	1.0	1.4	>4949	>3333	>2128			

[a]pTACE IC_{50} and MMP K_i values are from single determination.
[b]Inhibition of TNF-α release in whole blood assay (WBA) was determined with three donors.
[c]Oral bioavailability (*F*%) from dog pharmacokinetics studies.

of **4a** relative to IM491 is probably caused by its relatively high clearance (1.2 L/h/kg).

A more considerable effect on WBA potency was observed in the 5,6-piperidinedicarboxamide series (Table 4) compared with 4,5-piperidinedicarboxamide series (Table 3) by the increase in size of the substituent on the piperidine nitrogen. Replacement of the methyl group on the piperidine nitrogen in IM491 with ethyl (**4c**), cyclopropylmethyl (**4d**) and 2-thiazolemethyl (**4e**) resulted in 5-, 20- and 70-fold loss in cellular activity.

In summary, to improve the cellular activity of the lead TACE compound **1**, modifications were carried out at the cyclohexyl ring and the quinoline P1′ residue. Replacement of a methylene residue of the cyclohexyl ring with a nitrogen at three different positions provided a new series of piperidinedicarboxamide analogues which significantly improved the WBA potency. With 4-[(2-methyl-4-quinolinyl)methoxy]anilinyl at the P1′ position, the 5,6-piperidinedicarboxamide analogue IM491 bearing a methyl group on the piperidine nitrogen was identified as the most potent TACE inhibitor in the inhibition of TNF-α release, with an IC_{50} value of 20 nM in the cellular assay. IM491 also showed excellent selectivity over MMP-1, -2 and -9, decent Caco-2 permeability, excellent water solubility and good oral bioavailability in beagle dogs.

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