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Biaryl substituted hydantoin compounds as TACE inhibitors

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ABSTRACT

We disclose further optimization of hydantoin TNF-α convertase enzyme (TACE) inhibitors. SAR with respect to the non-prime region of TACE active site was explored. A series of biaryl substituted hydantoin compounds was shown to have sub-nanomolar K_i, good rat PK, and good selectivity versus MMP-1, -2, -3, -7, -9, and -13.

Tumor necrosis factor-α (TNF-α) is a key cytokine in innate immune response. Overproduction of TNF-α mediates a variety of autoimmune diseases including rheumatoid arthritis, psoriasis, and Crohn's disease.[1] The reduction of circulating TNF-α levels by biologic drugs, such as Enbrel® and Remicade®, is a successful treatment for several inflammatory diseases. As a result, discovery of a cost-effective, orally active small molecule drug that could modulate TNF-α levels is of high interest.

An approach amenable to small molecule discovery is the regulation of TNF-α levels via the inhibition of TNF-α converting enzyme (TACE). TACE converts the 26-kDa transmembrane bound pro-TNF-α to the mature 17-kDa soluble form of TNF.[2,3] TACE inhibitors are generally classified as hydroxamates[4] or non-hydroxamates.[5] Our program has been focused on the non-hydroxamate class of TACE inhibitors. We recently disclosed a series of tartaric acid based TACE inhibitors[6] and a series of hydantoin-based TACE inhibitors (Fig. 1).[7] Herein we report further optimization of the hydantoin TACE inhibitors by the introduction of biaryl groups to occupy the non-prime region of the TACE active site.

The X-ray structure of **1** suggests that the non-prime region of the protein is pretty open and could tolerate other substitutions (Fig. 2). To explore this idea, a set of compounds with additional substitution on the phenyl group was prepared as described in Scheme 1. Compound **3** was converted to the desired amine **4** through sequential Boc protection, hydantoin formation, and Boc deprotection. Compound **7** was prepared from **5** by sequential methylation and bromination. Alkylation of amine **4** with benzyl

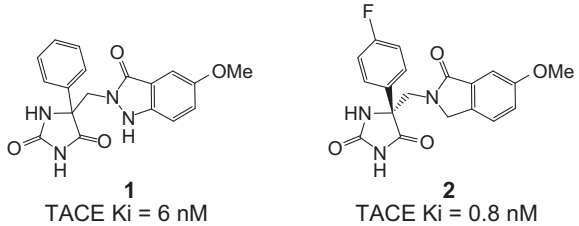

Figure 1. Hydantoin-based TACE inhibitors **1** and **2**.

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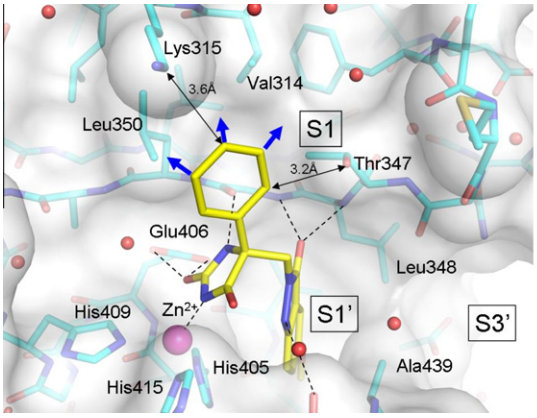
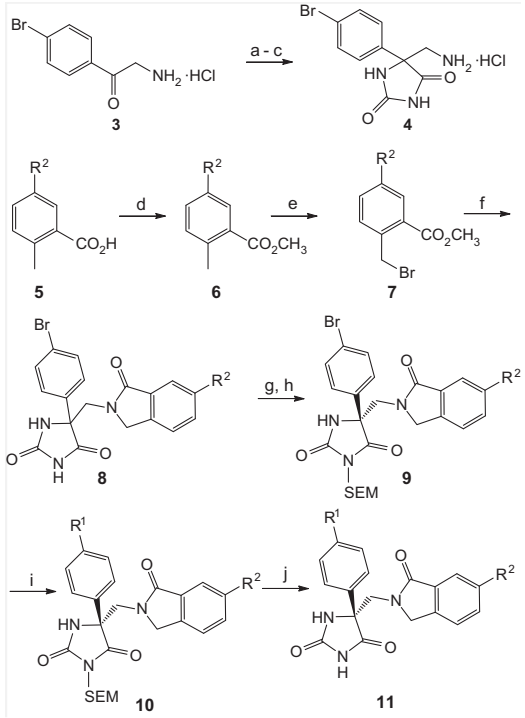
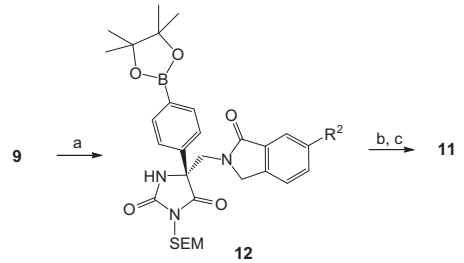


Figure 2. X-ray structure of **1** (3LE9) bound to the active site of TACE.

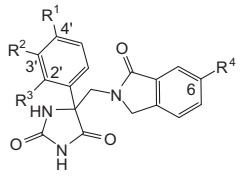


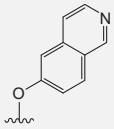
Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, DCM, Et_3N, rt, 16 h, 100%; (b) KCN, $(NH_4)_2CO_3$, EtOH/H_2O (1:1), 70 °C, 24 h, 86%; (c) HCl, MeOH, 16 h, 90%; (d) MeI, Cs_2CO_3, DMF, rt, 16 h, 99%; (e) NBS, benzoyl peroxide, CCl_4, 80 °C, 4 h, 99%; (f) **4**, DIPEA, DMF, rt, 16 h, 68%; (g) SEMCl, DIPEA, DMF, rt, 5 h, 85%; (h) HPLC separation; (i) $R^1B(OH)_2$, $Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$, K_2CO_3, CH_3CN, H_2O, 50–90%, or R^1OH, CuI, Cs_2CO_3, 2,2,6,6-tetramethyl-3,5-heptanedione, NMP, 140 °C, 15 h, 20–80%; or pyrrolidin-2-one, $Pd(dba)_2$, Xantphos, Cs_2CO_3, dioxane, 100 °C, 16 h, 70%; (j) HCl, MeOH, 90 °C, 16 h, then TEA, 46–80%.



Scheme 2. Reagents and conditions: (a) Bis(pinacolato)diboron, $Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$, KOAc, dioxane, 125 °C, 2 h; (b) RBr or RI, $Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$, K_2CO_3, CH_3CN, H_2O; (c) HCl, MeOH, 90 °C, 16 h, then TEA.

Table 1
TACE K_i of hydantoin TACE inhibitors



Compd	R^1	R^2	R^3	R^4	TACE K_i[a] (nM)
(*R*)-**13**		H	H	OMe	3
(*R*)-**14**		H	H	OMe	7
(*R*)-**15**		H	H	OMe	8
(*R*)-**16**		H	H	OMe	6
(*R*)-**17**		H	H	F	8
(*R*)-**18**		H	H	OMe	6
(±)-**19**	H	H	OPh	F	29
(±)-**20**	H	OPh	H	F	27

[a] The compounds were tested for their inhibition of the cleavage of a pro-TNF-α peptide catalyzed by TACE.[9]

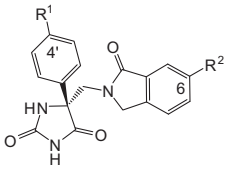
bromide **7** gave **8** in moderate yield. Compound **8** was protected as a SEM ether and the enantiomers were separated by HPLC on a Chiralpak AD column.[8] The desired (*R*)-enantiomer **9** was coupled with $R^1B(OH)_2$, R^1OH, amines, or amides under various coupling conditions to give **10** in moderate to good yield. The SEM group was deprotected by sequential treatment with HCl in MeOH, then triethylamine to give **11** in moderate yield.

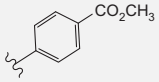
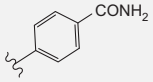
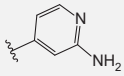
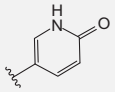
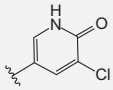
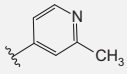
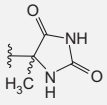
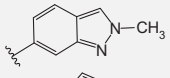
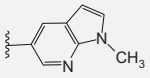
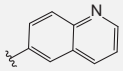
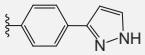
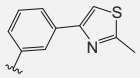
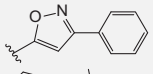
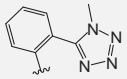
An alternative way to prepare **11** is shown in Scheme 2. Compound **9** was converted to boronate **12** via Pd-catalyzed reaction with bis(pinacolato)diboron. Compound **11** was obtained via various coupling reactions of **12** with R^1Br or R^1I followed by deprotection of the SEM group.

The TACE activities of some compounds prepared following Scheme 1 or Scheme 2 are shown in Table 1. The 4′-cyclopentoxy analog **13** showed single-digit nanomolar activity. Replacement of cyclopentyl by pyridyl **14** retained the activity. When a large group such as isoquinolin-6-yloxy **15** was incorporated, TACE activity was maintained relative to **14**. N-linked substitution, such as found in the 4′-morpholinyl analog **16** and the γ-lactam **17**, was also tolerated. Likewise, the carbonyl-linked tertiary amide **18** possessed similar activity. These results suggest that a wide variety of substituents differing in size and linker atom is permissible at C4′. By contrast, two analogs bearing phenoxy substitution at either C2′ (**19**) or C3′ (**20**) showed slightly reduced activity relative to the preceding compounds.

Thus it seems that C4′ substitutions can offer potent TACE inhibitors. Examination of the X-ray structure of **1** suggested that the substituent at the C4′ position may interact with the methylene chain of Lys315. To further test this hypothesis, more C4′-substituted analogs with linear biaryl groups were prepared (Table 2). The linear arrangement of the biaryl groups can maximize the

Table 2
TACE K_i of biaryl substituted hydantoin TACE inhibitors



Compd	R^1	R^2	TACE K_i (nM)
21	4-Cl-phenyl	OMe	2
22	2,4-Di-F-phenyl	F	2
23	4-CF_3-phenyl	F	18
24		OMe	9
25		OMe	3
26	2-Pyridinyl	OMe	0.5
27	3-Pyridinyl	OMe	0.8
28	4-Pyridinyl	OMe	0.6
29		OMe	1.4
30		F	0.2
31		F	0.1
32	5-Pyrimidinyl	OMe	0.9
33	2-Thiazolyl	OMe	0.6
34	2-Pyrazinyl	OMe	1.2
35	3-Pyridinyl	F	1.0
36		F	0.5
37		OMe	2.0
38		OMe	0.5
39		OMe	2.6
40		OMe	2.0
41		OMe	3.0
42		F	0.8
43		OMe	2.0
44		OMe	31
45		OMe	28
46		F	10

interaction with Lys315 side chain. Halogenated phenyl analogs **21** and **22** gave single-digit nanomolar activity. The 4′-CF_3-phenyl analog **23** is less active. The 4′-methyl benzoate analog **24** is less active than the corresponding amide analog **25**. Since the biphenyl group occupies the non-prime S1 pocket which is mostly solvent-exposed, a more hydrophilic substitution might be preferred. Pyridyl analogs (**26**–**28**) were prepared and they are 3- to 4-fold more potent than the biphenyl analogs **21** and **22**. The X-ray structure of **27** bound to the TACE active site (Fig. 3) shows that the phenyl–pyridyl group occupies the shallow S1 pocket and forms hydrophobic contacts to residues Val314, Lys315, Thr347, and Leu350. 2-Aminopyridine analog **29** is slightly less active than the 4′-pyridyl analog **28**. Pyridone analogs **30** and **31** are more potent than the 3′-pyridyl analog **27**. Other heterocyclic substitutions (e.g., R^1 = 5′-pyrimidinyl (**32**), 2′-thiazolyl (**33**), and 2′-pyrazinyl (**34**)) all show good potency. 6-F analogs **35** and **36** show good potency as well. Addition of one or two methyl groups to the heteroaryl groups are well tolerated (**36**–**38**). A hydantoin analog **39** also has good TACE activity.

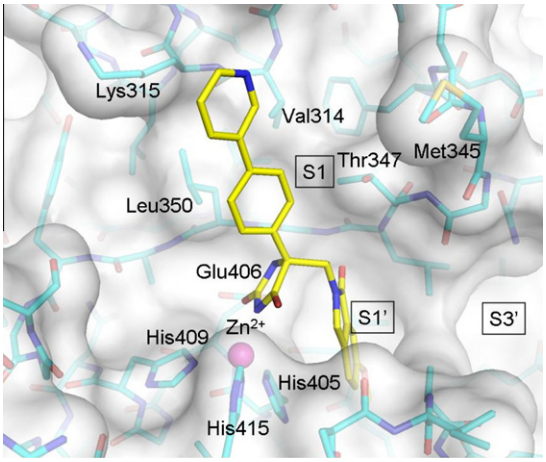


Figure 3. X-ray structure of **27** (3LEA) bound to the active site of TACE.

Table 3
Rat pharmacokinetic parameters of **27**, **37**, and **38**

		27	**37**	**38**
iv	Dose (mg/kg)	3	3	3
	AUC (μM h)	19.0	36.2	21.0
	$T_{1/2}$ (h)	4.3	4.4	4.4
	Cl (L/h/kg)	6.2	3.3	5.5
	V_{ss} (L/kg)	0.3	0.3	0.3
po	Dose (mg/kg)	10	10	10
	AUC (μM h)	9.1	22.2	13.0
	C_{max} (μM)	2.96	4.45	3.3
	T_{max} (h)	0.58	2.00	1.7
	F%	14.1	18.0	19.0

Table 4
Selectivity data of compounds **27**, **37**, and **38**[a]

Compounds	**27**	**37**	**38**
TACE (nM)	0.77	0.88	0.52
MMP-1 (nM)	655	718	1740
MMP-2 (nM)	—	24	86
MMP-3 (nM)	3.61	430	434
MMP-7 (nM)	17,400	>40,000	30,000
MMP-9 (nM)	124	122	212
MMP-13 (nM)	155	202	194
MMP-14 (nM)	25	19	36
ADAM10 (nM)	216	187	253

[a] The compounds were tested for their inhibition of the cleavage of peptide substrates catalyzed by various MMPs.

To further explore the substitution patterns that could be tolerated, compounds with larger substituents were prepared. 2-Methyl-2*H*-indazolyl (**40**) and 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridyl (**41**) analogs displayed single-digit nanomolar activity. The quinolinyl analog **42** as well as the non-fused, linear triaryl analog **43** were also potent. However, compounds **44**–**46**, which have a non-linear structure, are less potent since vander-Waals interactions to Asp313 and Lys315 are presumably disrupted.

The data shown in Table 2 shows that multiple heterocycles are well tolerated and a large number of compounds are found to have sub-nanomolar activity. The human whole blood activity of some of these compounds was tested.[10] They showed an improved IC_{50} compared with our earlier hydantoin TACE inhibitors.[7] For example, the human whole blood IC_{50} of **16**, **27**, **28**, **32**, and **39** ranged from 0.5 to 1.3 μM.

The rat pharmacokinetic parameters of **27**, **37**, and **38** were profiled. All were found to have excellent AUCs and moderate bioavailability as shown in Table 3.

The selectivity data of **27**, **37**, and **38** versus a group of MMP and ADAM enzymes are listed in Table 4. These compounds have good selectivity versus MMP-1, -3, -7, -9, -13, and ADAM10, but their selectivity versus MMP-1 and -14 was lower.

In summary, we have explored and optimized the SAR with respect to the non-prime region of the TACE active site. A series of biaryl hydantoin TACE inhibitors was found to have sub-nanomolar activity. Several members of this series also have good rat PK and good selectivity versus MMP-1, -3, -7, -9, -13, and ADAM10. The human whole blood activity of this series of TACE inhibitors is improved relative to our early hydantoin TACE leads.[7] Further optimization of the human whole blood activity of our lead hydantoin TACE inhibitors will be reported in future publications.

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10. Human whole blood is diluted 1:1 with serum free medium (RPMI, L-glutamine, Pen-Strep, HEPES) and incubated with a compound in a final volume of 360 μL for 1 h at 37 °C. Forty microliters of LPS (10 g/mL) is then added. Supernatant is collected after 3.5 h incubation and the concentration of TNF-α is determined by ELISA (R&D Systems).