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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

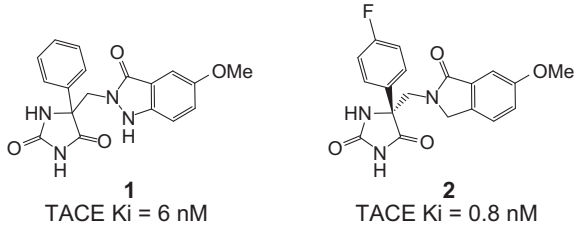

Figure 1. Hydantoin-based TACE inhibitors **1** and **2**.

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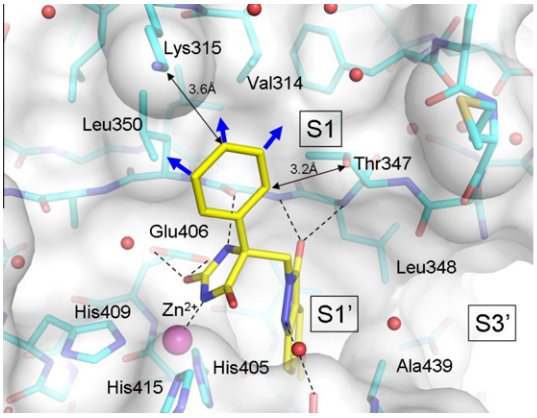
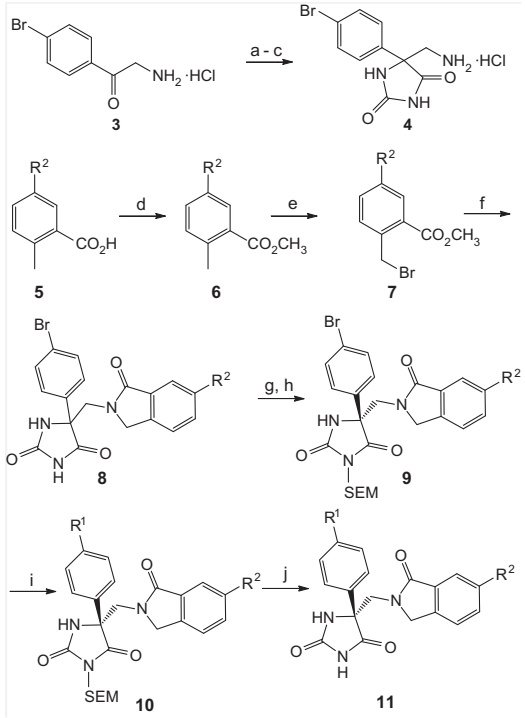
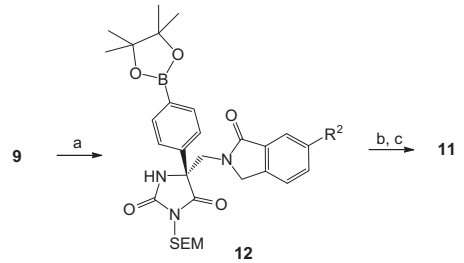


Figure 2. X-ray structure of **1** (3LE9) bound to the active site of TACE.

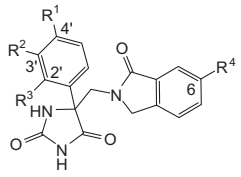


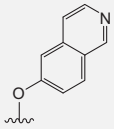
Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, DCM, Et_3N, rt, 16 h, 100%; (b) KCN, $(NH_4)_2CO_3$, EtOH/H_2O (1:1), 70 °C, 24 h, 86%; (c) HCl, MeOH, 16 h, 90%; (d) MeI, Cs_2CO_3, DMF, rt, 16 h, 99%; (e) NBS, benzoyl peroxide, CCl_4, 80 °C, 4 h, 99%; (f) **4**, DIPEA, DMF, rt, 16 h, 68%; (g) SEMCl, 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