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Discovery and SAR of hydantoin TACE inhibitors

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ABSTRACT

We disclose inhibitors of TNF-α converting enzyme (TACE) designed around a hydantoin zinc binding moiety. Crystal structures of inhibitors bound to TACE revealed monodentate coordination of the hydantoin to the zinc. SAR, X-ray, and modeling designs are described. To our knowledge, these are the first reported X-ray structures of TACE with a hydantoin zinc ligand.

Tumor necrosis factor-α (TNF-α) is a key cytokine for innate immune response. Dysregulation and, in particular, overproduction of TNF-α have been implicated in a variety of autoimmune diseases such as rheumatoid arthritis, Crohn's disease, and psoriasis.[1,2] Current treatments include injectable anti-TNF biologics such as Enbrel® and Remicade®. However, the advantages of an orally active drug, such as patient convenience and cost reduction, make a small molecule drug highly desirable.

TNF-α is released from membrane-bound pro-TNF-α through proteolytic cleavage by the TNF-α converting enzyme (TACE).[3] There has been significant interest in the development of TACE inhibitors to modulate the level of TNF-α which has long been viewed as having potential to treat related inflammatory diseases.[4,5]

The majority of known TACE inhibitors incorporate a hydroxamic acid as the zinc chelating group.[6] Non-hydroxamic acid TACE inhibitors, including tartrates and hydantoins, have also been reported.[7,8] In the course of our program, we aimed to identify non-hydroxamic acid TACE inhibitors. Previously we reported tartaric acid based TACE inhibitors and carboxylic acid based TACE inhibitors.[8,9] Herein, we report a new series of hydantoin based TACE inhibitors.

Several hydantoin containing compounds were identified as weak inhibitors, such as **1** (K_i = 6 μM), from our screening collection. Soaking experiments of these hydantoin compounds into crystals of the catalytic domain of TACE (V353G)[10] resulted in the X-ray crystal structure of **2** shown in Figure 2. The structure revealed two molecules of **2** coexisting in the active site, but occupying different subsites (Fig. 2A). The first molecule of **2** occupies the S1′ pocket whereas the second molecule of **2** binds to the S1 region. Unlike hydroxamates and tartrates which exhibit bidentate and tridentate zinc binding, respectively,[8,11] monodentate zinc coordination was observed with the S1 hydantoin nitrogen.[7b,12] The S1 hydantoin also forms multiple hydrogen bonds with the protein as indicated in Figure 2B. The amide nitrogen of the hydantoin interacts with the carbonyl oxygen of Gly349 and the oxygen of the adjacent carbonyl forms a bidentate hydrogen bond to the Glu406 side chain. In addition, the phenyl group occupies the hydrophobic non-prime site defined by the side chains of Val314,

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Thr347, Leu350, and Lys315 (Fig. 2A). The molecule of **2** in the S1′ site revealed hydrogen bond interactions between the hydantoin carbonyl and the backbone NH of Leu348 and Gly349. The phenylacetamide group is embedded in the S1′ pocket.

This crystal structure served as a starting point in our structure-based discovery of potent hydantoin TACE inhibitors. Our strategy was to design a scaffold based on the binding modes shown in Figure 2B, which would maintain the zinc binding of the hydantoin, and at the same time capture other key interactions, namely, hydrogen bonding to the backbone NH of Leu348, hydrogen bonding to Gly349, and filling the S1′ pocket.

Scaffolds containing these key features were evaluated using molecular modeling techniques. The results indicated that 1*H*-indazol-3(2*H*)-one scaffold **3** (Fig. 1) would best satisfy the above criteria. Specifically, the hydantoin could maintain all the interactions near the catalytic zinc as observed in **2**. The carbonyl oxygen of the indazolinone moiety would make hydrogen bonds with the backbone NH of Leu348 and Gly349; the methylene linker would ensure proper orientation of the scaffold for interactions with the S1′ pocket. Furthermore, substituents on the benzene ring would reach further into the S1′/S3′ pocket to establish additional interactions with the protein. The indazole NH could make a hydrogen bond with the carbonyl of Pro437. The methyl group on the hydantoin points into the non-prime side, into an area open for further substitutions.

The synthetic route to **3** is illustrated in Scheme 1 and was used for the synthesis of analogs. Compound **4** was treated with diben-

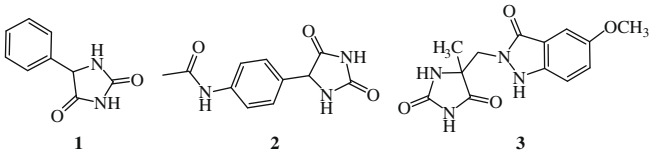


Figure 1. Hydantoin based TACE inhibitors

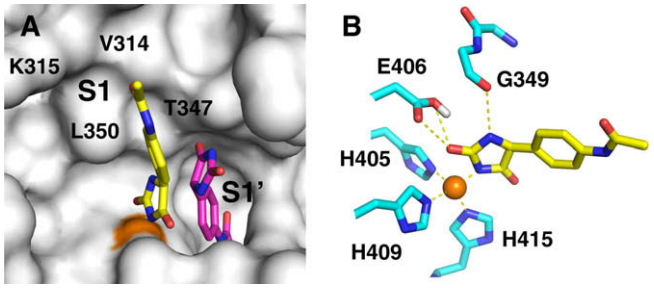
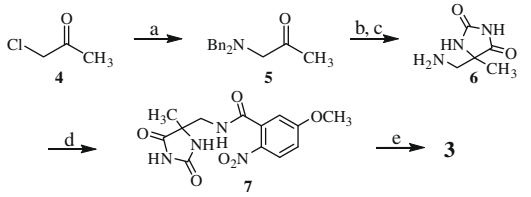


Figure 2. Modes of binding of compound **2** to the active site of TACE. (A) Two binding modes (cyan and yellow carbons, respectively) of **2** to the active site of TACE (shown as surface with zinc colored orange, PDB code: 3L0T). The S1 and S1′ subsites are also indicated. (B) Stick representation showing the zinc binding of **2** and hydrogen bonding interactions (dashed lines).



Scheme 1. Reagents and conditions: (a) Bn_2NH, Et_3N, THF, rt, 3 days, 89%; (b) KCN, $(NH_4)_2CO_3$, EtOH/H_2O (1:1), 70 °C 8 h, 86%; (c) H_2, 50 psi, Pd(OH)$_2$/C, EtOH/MeOH (5:1), rt, 48 h, 95%; (d) 5-methoxy-2-nitrobenzoic acid, EDCI, HOBT, NMM, DMF, rt, 16 h, 85%; (e) Zn, NaOH, MeOH/H_2O (1:1), 75 °C, 20 h, 14–69%.

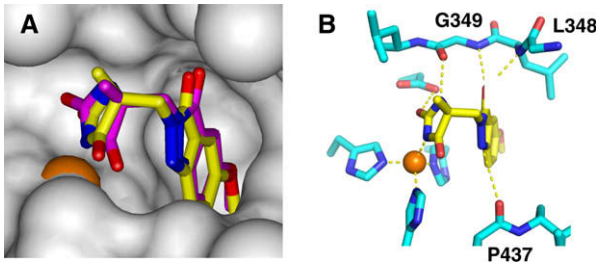
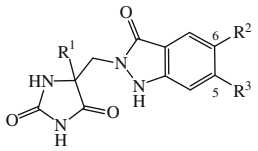


Figure 3. (A) Docked model of **3** (magenta) in the TACE active site (surface). The X-ray structure is shown in yellow (PDB code: 3L0V). (B) Stick representations showing the detailed interactions of **3** with the TACE active site observed in the X-ray.

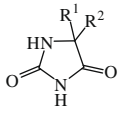
Table 1
TACE K_i of 1*H*-indazol-3(2*H*)-ones analogs (±)

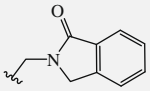
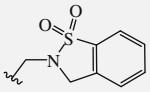
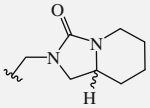
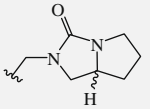
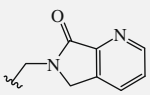
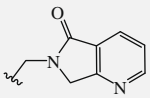
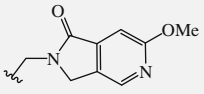


Compound	R^1	R^2	R^3	TACE K_i[a] (nM)
3	Me	MeO	H	23
8	Me	H	MeO	28
9	Me	EtO	H	209
10	Me	BnO	H	391
11	Me	H	BnO	100
12	Ph	MeO	MeO	53
13	Ph	MeO	H	6

[a] The compounds were tested in a FRET assay using the catalytic domain of TACE.

Table 2
TACE K_i of analogs with different ring system



Compound	R^1	R^2	TACE K_i[a] (nM)
(±)-**17**	4-F-Ph		4
(±)-**18**	4-F-Ph		1048
(±)-**19**	4-F-Ph		2729
(±)-**20**	4-F-Ph		>50,000
(±)-**21**	Me		4818
(±)-**22**	Me		24,900
(±)-**23**	4-F-Ph		5

[a] The compounds were tested in a FRET assay using the catalytic domain of TACE.