Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 1408–1412
Bioorganic & Medicinal Chemistry Letters

A molecular modeling analysis of novel non-hydroxamate inhibitors of TACE

James E. Sheppeck, II,* Andrew Tebben,* John L. Gilmore, Anle Yang, Zelda R. Wasserman, Carl P. Decicco and James J.-W. Duan

Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 4000, Princeton, NJ 08543-4000, USA

Received 14 September 2006; revised 21 November 2006; accepted 30 November 2006
Available online 3 December 2006

Presented at the 228th National ACS Meeting, Philadelphia, PA Aug. 2004, MEDI-274.

Abstract—Recently, an X-ray co-crystal structure of our hydroxamate inhibitor IK682 and TACE [Niu, X.; Umland, S.; Ingram, R.; Beyer, B. M.; Liu, Y.-H.; Sun, J.; Lundell, D.; Orth, P. *Arch. Biochem. Biophys.* **2006**, *451*, 43–50] was published that explicitly shows the orientation of the hydroxamate and the TACE-selective 4-[(2-methyl-4-quinolinyl)methoxy]phenyl P1′ group in the S1′ and S3′ sites. The preceding paper described a novel series of potent and TACE-selective hydantoins and we previously described pyrimidinetrione (barbiturate) inhibitors of TACE, both of which contain the same P1′ group as IK682. Using this TACE-selective P1′ group as an anchor, stereochemical and conformational constraints in the inhibitors, and restrictions to the active site Zn coordination geometry, we developed a highly plausible and predictive pharmacophore model that rationalizes the observed TACE activity of all three inhibitors.
© 2006 Elsevier Ltd. All rights reserved.

Matrix metalloproteases are a family of zinc endopeptidases that are responsible for the proteolytic breakdown of extracellular matrix during normal tissue homeostasis. Of the close to 30 MMPs discovered to date, the aberrant activity of several members of this class has been linked to numerous disease states such as rheumatoid arthritis, osteoarthritis, metastasis, angiogenesis, and autoimmune disorders.[1] Beyond MMPs, there has been considerable effort directed at finding selective small molecule inhibitors for the zinc-dependent metalloprotease TACE, which is responsible for processing pro-TNF-α into its soluble, inflammatory form.[2] The clinical success of Remicade®, Enbrel®, and Humira® (biologics that sequester TNF-α) in treating RA, IBD, and psoriasis proves that attenuating the effects of TNF-α can mitigate the severity of numerous autoimmune diseases.[3]

The catalytic domain of zinc metalloproteases possesses a conserved HEXXHXXGXXH zinc ligating sequence that forms an active site zinc coordinatively saturated by a water molecule that catalyzes the hydrolysis of amide bonds in protein substrates. Inhibitors of MMPs typically consist of a zinc binding group (ZBG, e.g., hydroxamates) appended to a large P1′ substituent that binds in the large hydrophobic S1′ pocket. Much of the MMP selectivity of these inhibitors comes from taking advantage of the structural differences found in the S1′ subsite.[1]

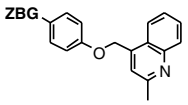
To date, several crystal structures of TACE in complex with inhibitors containing the hydroxamic acid Zn ligating group have been reported.[4] The preceding manuscript[5a] described the chemistry and structure–activity relationships of a new class of potent hydantoin TACE inhibitors. In addition, the 4-[(2-methyl-4-quinolinyl)methoxy]phenyl group was found to broadly confer excellent TACE-selectivity to our hydantoin, barbiturate and hydroxamate inhibitors.[5] The goal of this modeling study was to compare the interactions that hydroxamate and non-hydroxamate ZBGs (that all bear the same P1′ group) make with the active site of TACE and rationalize their observed activity and orientation in TACE. Such models might also be used to improve or expand upon the design of these and other non-hydroxamate zinc metalloprotease inhibitors.

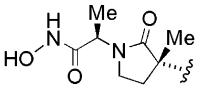
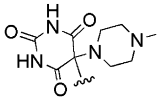
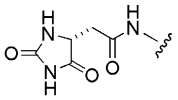
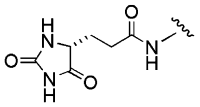
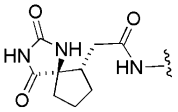
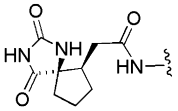
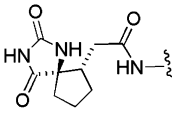
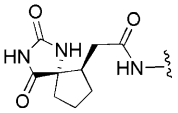
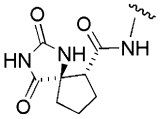
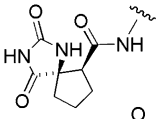
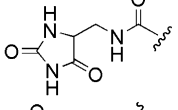
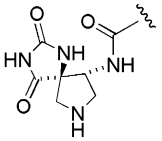
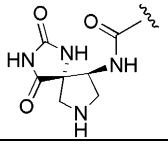
Keywords: TACE; TACE inhibitor; Modeling; Hydantoin; Barbiturate; Hydroxamate; MMP; Metalloprotease; Metalloproteinase; TNF; Non-hydroxamate.
* Corresponding authors. Tel.: +1 609 252 3211; fax: +1 609 252 3993(J.E.S.); e-mail: jim.sheppeck@bms.com

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.11.082

Several of the compounds in Table 1 were modeled in chain A of the TACE crystal structure 2fv5.[3c] The TACE/IK682 complex was minimized and the resulting coordinates used as the starting structure for model building. Each non-hydroxamate ZBG was then built manually onto the shared 4-[(2-methyl-4-quinolinyl)methoxy]phenyl P1′ group and the resulting complex was then fully minimized.[6] Figure 1 shows the modeling results of conformationally constrained hydantoins and barbiturates in TACE compared to the IK682–TACE and barbiturate–MMP-8 crystal structures.

Table 1. In vitro potency of various inhibitors of pTACE



Compound	Zinc binding group (ZBG)	Stereochem	pTACE IC_{50} (nM)
IK682		(2*R*, 3′*S*)	<1
2		(rac)	91
3		(5*R*)	170
4		(5*R*)	150
5a		(rac)-trans	17
5b		(rac)-cis	7400
5c		(5*R*,6*S*)-trans	11
5d		(5*S*,6*R*)-trans	900
6a		(rac)-trans	230
6b		(rac)-cis	64
7		(rac)	98
8a		(5*R*,6*S*)-trans	25
8b		(5*S*,6*R*)-trans	900

The position of the metal ligating group is largely determined by a set of hydrogen bonds observed crystallographically and in the models of the hydantoin containing inhibitors. A subset of these interactions are observed between the protein and the hydroxamic acid moiety in the TACE crystal structure 2fv5 (Fig. 1B). The hydroxamic acid is anchored in the active site by four interactions: two hydrogen bonds via the hydroxyl in contact with E406 and the hydroxamate NH interacting with the backbone carbonyl of G349, and a bidentate ligation of the hydroxyl and carbonyl oxygens to the zinc atom.

The interactions of the non-hydroxamate ZBGs with the TACE active site differ from those of the hydroxamate because they ligate Zn in monodentate fashion and hydrogen bond the same residues but in a fundamentally different way. In the pyrimidinetriones (Fig. 1A), one such interaction is the hydrogen bond between the backbone NH of L348 and the carbonyl at the 4-position of the pyrimidinetrione present in both the MMP-8 (human neutrophil elastase) crystal structure[7] and our model of compound **2**.[5e] Another hydrogen bond is observed between the E406 acid and the C2 carbonyl of the pyrimidinetrione (which in turn coordinates the Zn in monodentate fashion) via the enol tautomer of the heterocycle. The MMP-8 X-ray structure shows a bidentate pyrimidinetrione Zn interaction while our model of compound **2** was consistently monodentate. The difference between the two appears to arise from the highly optimized P1′ group in **2** that will not allow the pyrimidinetrione to shift into the bidentate orientation observed in MMP-8. An additional hydrogen bond between the amide NH and the backbone carbonyl of P437 (observed in several MMP/hydroxamate crystal structures) is sometimes observed, but not strictly conserved.

Models of the hydantoins show a similar hydrogen bonding pattern to the pyrimidinetriones with some important differences (Figs. 1B–D). On the surface, the modeling suggests that the key metal interaction may be bidentate as both the oxygen and nitrogen atom are consistently observed within ~2.0 Å of the zinc. However, while the hydantoin nitrogen is in close proximity to the zinc, its lone pair is not properly oriented to form a direct interaction because it is directed away from the zinc. This suggests that, unlike the hydroxamates, the hydantoins form only a monodentate interaction with the zinc through the C2 carbonyl. Based on the models, we predict that the hydantoin has been ionized by the active site E406 general base in what resembles an enol tautomeric form stabilized by hydrogen bonding to

Download English Version:

https://daneshyari.com/en/article/1378027

Download Persian Version:

https://daneshyari.com/article/1378027

Daneshyari.com