Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 1807–1810
Bioorganic & Medicinal Chemistry Letters

Potent pyrimidinetrione-based inhibitors of MMP-13 with enhanced selectivity over MMP-14

Julian A. Blagg, Mark C. Noe, Lilli A. Wolf-Gouveia, Lawrence A. Reiter,* Ellen R. Laird, Shang-Poa P. Chang, Dennis E. Danley, James T. Downs, Nancy C. Elliott, James D. Eskra, Richard J. Griffiths, Joel R. Hardink, Amber I. Haugeto, Christopher S. Jones, Jennifer L. Liras, Lori L. Lopresti-Morrow, Peter G. Mitchell, Jayvardhan Pandit, Ralph P. Robinson, Chakrapani Subramanyam, Marcie L. Vaughn-Bowser and Sue A. Yocum

Pfizer Global Research and Development, Groton Laboratories, MS8220-2471, Eastern Point Road, Groton, CT 06340, USA

Received 13 December 2004; revised 9 February 2005; accepted 14 February 2005

Abstract—Through the use of computational modeling, a series of pyrimidinetrione-based inhibitors of MMP-13 was designed based on a lead inhibitor identified through file screening. Incorporation of a biaryl ether moiety at the C-5 position of the pyrimidinetrione ring resulted in a dramatic enhancement of MMP-13 potency. Protein crystallography revealed that this moiety binds in the S_1' pocket of the enzyme. Optimization of the C-4 substituent of the terminal aromatic ring led to incorporation of selectivity versus MMP-14 (MT-1 MMP). Structure activity relationships of the biaryl ether substituent are presented as is pharmacokinetic data for a compound that meets our in vitro potency and selectivity goals.

Owing to their likely role in the pathology of various diseases (e.g., osteoarthritis and cancer) therapeutically useful MMP inhibitors have been sought for many years.[1,2] A number of compounds have been advanced into clinical trials. However, these relatively nonselective MMP inhibitors have exhibited musculoskeletal side effects (MSS) characterized by joint stiffness and pain, particularly in the hands and shoulders.[3] In rodents, many of these compounds induce joint fibroplasia and accumulation of type-I collagen.[4] An hypothesis that these effects are caused by inhibition of MMP-1 has recently been discounted through the clinical study of an MMP-13 inhibitor that spares MMP-1.[1] Thus, the pharmacological basis for this side effect remains unknown, but still presumably involves the indiscriminate inhibition of MMPs other than MMP-1. In an effort to determine the role of the various MMPs in disease and to help identify, which MMP(s) is responsible for MSS, a number of murine MMP knock-outs has been produced. Of these, the MMP-14 (MT-1 MMP) knock-out displays a phenotype reminiscent of the histopathology produced in rats by nonselective inhibitors.[5] This observation, combined with the evidence that MMP-13 plays a critical role in the pathology of osteoarthritis (OA),[6] suggests that an MMP-13 inhibitor that spares MMP-14 may reduce articular cartilage degradation while avoiding the MSS side effect, thereby providing an effective therapy for OA.

A component of our program to discover therapeutically useful MMP-13 inhibitors involved identifying compounds that possess a zinc binding group other than the ubiquitous, and generally metabolically labile, hydroxamic acid. File screening revealed pyrimidinetrione **1** as a weak MMP-13 inhibitor (Fig. 1). The utility of pyrimidinetriones for the inhibition of MMPs has also been reported by the Boehringer Mannheim/Hoffman La Roche group,[7] and, very recently, by Bristol Meyers Squibb.[8] Molecular modeling suggested that the pendant aryl ether of **1** would occupy the S_1' pocket, while the methyl group would project into a largely solvent exposed region. If this were so, then replacing the 4-chloro substituent of **1** with an aryloxyaryl ether, to take

Keywords: MMP-13; Matrix metalloproteinase; Osteoarthritis.
* Corresponding author. Tel.: +1 860 441 3681; fax: +1 860 686 1176; e-mail: lawrence.a.reiter@pfizer.com

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.02.038

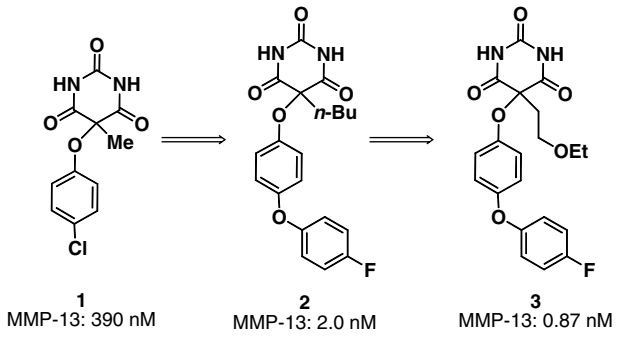


Figure 1. File lead and its initial development.

advantage of the deep S_1' pocket of MMP-13,[9] was expected to improve MMP-13 inhibition potency. This change and concomitant extension of the C-5 substituent to a butyl residue (**2**) did lead to substantial improvement in potency. The overall lipophilicity could be reduced by replacement of the butyl group with an ethoxyethyl group (**3**) (*c*log *P* **2**: 5.05, **3**: 3.11). The X-ray crystal structure of **3** bound to MMP-13 (Fig. 2)[10] confirmed the modeling predictions with the aryloxyaryl ether residing in the S_1' pocket. Other observations include the binding of the pyrimidinetrione to the active site zinc in an enolic form and the apparent displacement of an ordered water by the ether oxygen in the C-5 side chain. The latter could account for the modest increase in potency of **3** over **2**. Unfortunately, none of the above analogs possessed high selectivity (>100-fold) versus MMP-14. We did not anticipate that altering the solvent exposed C-5 side chain or the pyrimidinetrione core would lead to any improvement in selectivity. Thus, our efforts focused on exploring the effect that substitution of the biaryl ether has on MMP-13 potency and selectivity. Such analogs of **3** were prepared using the route outlined in the Scheme 1.

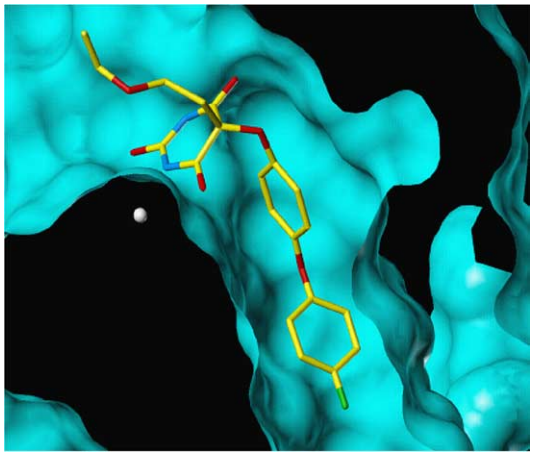
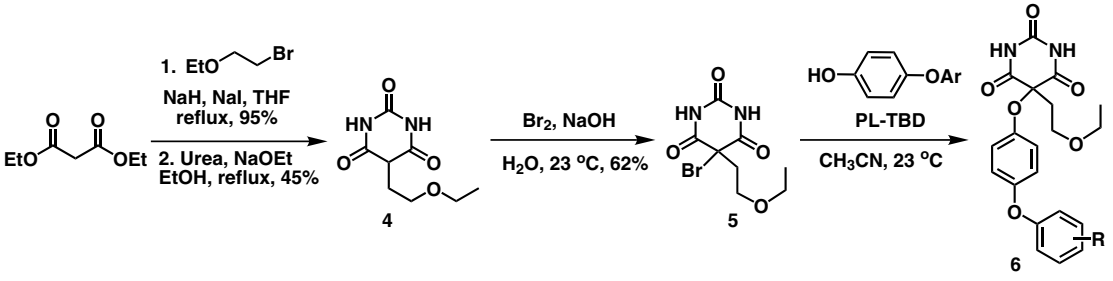


Figure 2. X-ray crystal structure of **3** bound to MMP-13.

Alkylation of diethylmalonate with ethyl 2-bromoethyl ether followed by reaction with urea afforded the monosubstituted pyrimidinetrione **4**. Subsequent bromination of **4** gave bromopyrimidinetrione **5**. Analogs of **3** could be rapidly prepared by treatment of **5** with the appropriate phenol and the polymer bound base PL-TBD[11] in acetonitrile. Aqueous acid workup and silica gel chromatography gave good to excellent yields of the target pyrimidinetriones **6**.

The biological activity of our initial set of substituted biaryl ether derivatives containing C-4, C-3, and C-2 fluoro, chloro, or methyl substituents on the terminal aryl ring (compounds **3** and **7**–**14**, Table 1) demonstrated that C-4 was a promising position for exploration. Thus, the C-4 substituted compounds, **3**, **9**, and **12**, are potent inhibitors and display some selectivity. In contrast, the C-3 analogs, **7**, **10**, and **13**, display only moderate MMP-13 potency and little selectivity. While the C-2 chloro analog **11** is only a weak inhibitor, the C-2 fluoro and methyl analogs, **8** and **14**, display reasonably potent MMP-13 inhibition with the latter also being moderately selective. Nevertheless, the X-ray of **3** co-crystallized with MMP-13 indicated that the opportunity to make significant modifications in this region of the molecule was likely to be limited. We therefore focused our efforts on examining substituents at C-4. The presence of a hydrophobic group at C-4 appears to be beneficial—the halide and methyl analogs (**3**, **9**, **12**, and **15**) are all quite potent MMP-13 inhibitors. There does, however, appear to be a steric limit to the size of the C-4 substituent indicating that the S_1' pocket is deep but narrow. Thus, the trifluoromethyl analog **16** is slightly less potent than the halides and the *tert*-butyl derivative **17** is substantially less so. In contrast, the phenyl derivative **18**, having a large but flat hydrophobic group at C-4, is still very potent. Consistent with this region of the S_1' pocket being hydrophobic, incorporation of hydrophilic groups leads to decreases in MMP-13 potency (compounds **19**–**25**). The compound containing the hydrophilic carboxy (**25**) group loses the most potency.



Scheme 1. Synthesis of pyrimidinetrione analogs **6** from diethylmalonate.