Bioorganic & Medicinal Chemistry Letters 21 (2011) 2823–2825

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

MMP-13 selective alpha-sulfone hydroxamates: Identification of selective P1′ amides

Yvette M. Fobian [a], John N. Freskos [a], Thomas E. Barta [b,*], Louis J. Bedell [b], Robert Heintz [a], Darren J. Kassab [a], James R. Kiefer [a], Brent V. Mischke [a], John M. Molyneaux [a], Patrick Mullins [a], Grace E. Munie [a], Daniel P. Becker [b]

[a] Departments of Medicinal Chemistry and Pharmacology, Pfizer Research & Development, 700 Chesterfield Village Parkway, St. Louis, MO 63198, USA
[b] Departments of Medicinal Chemistry and Pharmacology, Pfizer Research & Development, 4901 Searle Parkway, Skokie, IL 60077, USA

ARTICLE INFO

Article history:
Received 10 February 2011
Revised 23 March 2011
Accepted 24 March 2011
Available online 1 April 2011

Keywords:
MMP
Matrix metalloproteinases
MMP-13
Arthritis inflammation
Hydroxamic acids

ABSTRACT

Continuing our interest in designing compounds preferentially potent and selective for MMP-13, we report on a series of hydroxamic acids with a flexible amide P1′ substituents. We identify an amide which spares both MMP-1 and -14, and shows >500 fold selectivity for MMP-13 versus MMP-2 and -8.

Matrix metalloproteinases (MMPs) are a family of about 27 zinc-dependent enzymes responsible for the turnover of collagen in connective tissue. There are a variety of disease states where degradation of collagen contributes to the pathology, specifically in osteo- and rheumatoid arthritis; in tumor angiogenesis and metastasis; and in post-MI cardiovascular remodeling.[1] In spite of the promise that modulation of MMP activity offers, the delivery of a suitable MMP inhibitor to pharmacy shelves has not been realized. Clinical compounds often induce a dose-limiting joint-stiffening referred to as musculoskeletal syndrome (MSS) thus limiting their utility.

It has been hypothesized that inhibition by drug candidates of MMP-1, a constitutive enzyme involved in the turnover of type II collagen, contributes to MSS.[2a] Sparing MMP-1 may not be sufficient. In our earlier research we saw that dosing with the MMP-1 sparing hydroxamate **1** (**SC-276**, Fig. 1) eventually led to joint stiffening in animal models.[2b] MT1-MMP (MMP-14) may also play a role in MSS, since it has been observed that MMP-14 knockout mice suffer from joint lesions reminiscent of the changes in MSS.[3] The actual situation may be even more complex; MMP inhibitors, even those that spare both MMP-1 and -14, may bind to members of the structurally-related ADAMs family (A Disintegrin and Metalloprotease),[4] leading to undesired joint effects.

An alternative approach toward realizing efficacious MMP inhibitors with reduced side effects is to focus on optimizing the inhibition of the single MMP isozymes that should confer the most therapeutic benefit, reducing the probability of off-target protease inhibition. MMP-13 is an attractive isozyme to pursue; MMP-13 rapidly degrades type II collagen and is associated with pathology. The isozyme is upregulated in osteoarthritic joints and in cancer.[5] Structural studies show that MMP-13 differs from other MMP's in the depth of its S1′ pocket, suggesting that lengthier inhibitors may confer selectivity over other isozymes.

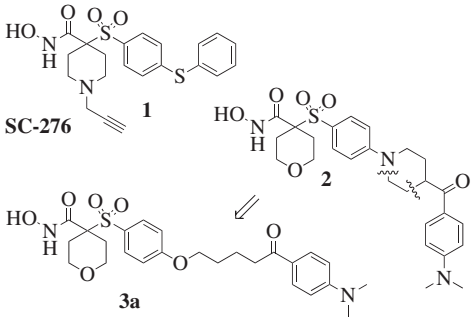
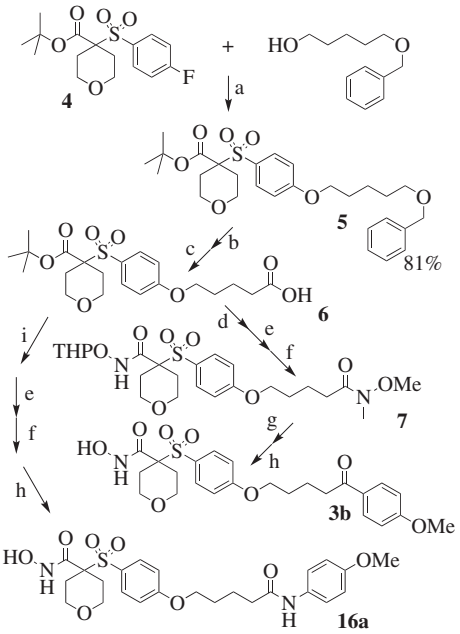


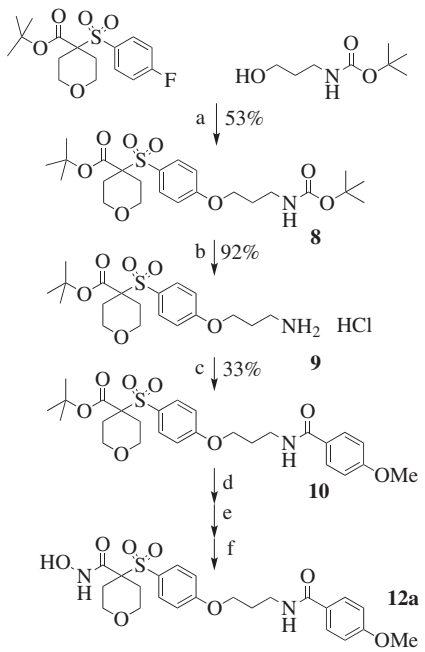
Figure 1. MMP inhibitors. Compound **1** spares MMP-1; Compounds **2** and **3a** are MMP-13 selective.

* Corresponding author.
E-mail address: thomas_e_barta@yahoo.com (T.E. Barta).

0960-894X/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2011.03.095



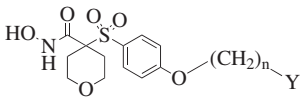
Scheme 1. Reagents and Conditions: (a) BnO(CH2)5OH (1.05 equiv), NaH 1.2 (equiv), 0 °C–rt, 4 h; (b) 5% Pd/C (wet), 80 psi, THF, 1.5 h; (c) 2.5% RuCl3, NaIO4 (3 equiv), CCl4, water; (d) triethylamine (6.0 eq), N-hydroxybenzotriazole (1.5 eq), HN(Me)OMe (3.0 equiv), EDC (1.4), DMF, 16 h (e) trifluoroacetic acid, triturate; (f) triethylamine (2.1 equiv), HOBT (3.0 equiv), THPONH2 (3.0 equiv), EDC (1.2 equiv), DMF, 3.5 h 40 °C, rt 16 h; (g) 4-(MeO)PhMgBr (5 equiv), THF, 0 °C–rt overnight, then NH4Cl; (h) 4 N HCl, dioxane, MeOH, triturate.

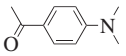
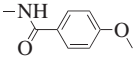
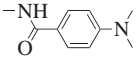
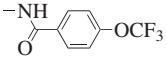
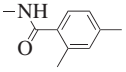
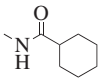
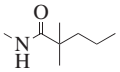
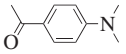
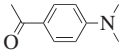
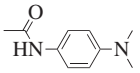
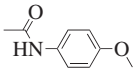
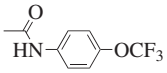
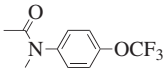
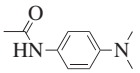
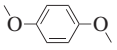


Scheme 2. Reagents and Conditions: (a) *tert*-butyl N-(3-hydroxypropyl)carbamate (1.1 equiv), NaH (1.2 equiv), DMF, 0 °C, 18 h; (b) 4 N HCl/dioxane, 1 h; (c) DMF, triethylamine (1.2 equiv), anisoyl chloride (1.2 equiv); (d) trifluoroacetic acid, 3 h, concd at 50 °C; (e) Nmethylmorpholine (2.1 equiv), N-hydroxybenzotriazole (1.2 equiv), THPONH2 (1.5 equiv), EDC (1.5 equiv), DMF, 3 days; (f) 4 N HCl. dioxane, MeOH, 1 h, concd, triturate.

With this in mind, we previously reported a series of rigid piperidino-ketones (compound **2**, Fig. 1) with lengthier P1′ subunits and, with optimization, we achieved significant selectivity for MMP-13 versus other MMP isoforms.[6,7] Although potent and selective, ketones like **2** exhibited poor PK, so we endeavored to improve their ADME properties, in part, though reduction of molecular weight. Conceptually dissecting the piperidine ring in compound **2** led to acyclic-chain analogs such as ketone **3a** (Fig. 1).

Table 1
MMP selectivity of studied compounds



#	*n*	Y	hMMP IC_{50}[a] (nM)			
			-2	-8	-9	-13
1	—	—	0.33	1.8	1.5	<1.0
2	—	—	4000	>10k	>10k	8.0
3a	4		35	140	1100	0.4
12a	3		550	900	NT	1.6
12b	3		1100	1100	NT	1.6
12c	3		360	140	2200	0.66
12d	3		940	700	NT	8.0
12e	3		650	3100	NT	8.2
12f	3		450	1200	NT	8.2
13	2		16	120	NT	0.9
14	3		18	170	930	0.2
15a	3		10	100	960	1.7
15b	3		2.5	31	23	0.3
15c	3		11	6.7	180	0.2
15d	3		270	49	380	3.3
15e	3		170	800	670	1.2
16	4		1.8	2.6	500	1.8
17	4		6.6	67	NT	0.9

[a] For each compound, MMP-1 and MT1-MMP >5000, except for **1**, where MT1-MMP = 8 nM.

The synthesis of ketone **3a** and related ketones (e.g., **3b**, Scheme 1) proceeded from aryl fluoride **4**,[8] which was reacted with an omega benzyloxy 1-alkanol. The benzyl ether could be cleaved by hydrogenation and the resulting alcohol oxidized to carboxylic acid **6**. Acid **6** was converted using EDC coupling to a Weinreb amide[9], the t-butyl ester was cleaved with TFA affording acid **7**, and this acid was coupled with $THPONH_2$. Excess aryl Grignard and subsequent treatment with HCl led to the final product, **3b**. Similar

straightforward chemistry could be used to arrive at amides including **16a**.

Isomeric amides such as **12a** (Scheme 2) could be obtained using, for example, *tert*-butyl N-(3-hydroxypropyl)carbamate, which could be carried on to amine **9**. Amine **9** was converted to amide analogs **10**, and on to final hydroxamic acids **12a**.

We synthesized over 500 extended chain amides and ketones in our MMP-13 program and the findings for selected analogs are summarized in Table 1. Isonipecotate **2** demonstrates excellent selectivity for MMP-13 versus the other MMP isoforms tested. The direct open-chain analogs of **2**, ketones **13**, **14**, and **3a**, which differ only in connecting chain length, are each more potent toward MMP-13 than isonipecotate **2**. Compounds **14** and **3a** achieve encouraging selectivity ratios for MMP-13 versus MMP-8, -9, -1, and -14, but exhibit poor selectivity with respect to MMP-2.

We explored a variety of different linkers. Ether-linked compounds including **17** lacked MMP-13/-2 selectivity. Amide analogs made according to Scheme 1, such as **15a** and **16**, showed disappointing selectivity, with **16** being essentially equipotent for MMP-2, -8, and -13. N-Methylation, to alter the steric environment, did not improve the ratios, as can be seen from **15c** and **15d**. However, the isomeric benzamides (Scheme 2) look significantly more attractive.

For example, compound **12b** is potent for MMP-13, but unlike its direct amide isomer, **15a**, spares MMP-2 and -8. Conjugation of the amide pi system into the aryl ring may diminish the conformational mobility of these amides versus the amides of Scheme 1 (e.g., **12c** vs **15c**; **12a** vs **15a**) and this might account for the improved selectivity of the latter series. Further exploration in the series has shown the electronics of ring substitution did not have a pronounced effect on potency/selectivity, although more hindered analogs, such as **12d**, saw a drop off in activity. Additionally, saturated amides, including **12e** and **12f** exhibit reduced potency and/or selectivity.

Benzamides like **12a** and **12c** became the focus of further study, and, while we achieved meaningful levels of MMP-13 selectivity, we did not find amides that had both high potency and acceptable PK properties. Compound **12a** had a half-life in rats of only 0.58 h (BA 1.5%), presumably due to in vivo amide hydrolysis, and that was typical of the series. To address this issue, non-hydrolyzable bioisosteric replacements for the amide linkage were sought, as reported in the following Letter.

References and notes

1. *Inhibition of Matrix Metalloproteinases: Therapeutic Applications*; Greenwald, R. A., Zucker, S., Golub, L. M., Eds.; New York Academy of Sciences: New York, 1999.
2. (a) Becker, D. P.; Villamil, C. I.; Barta, T. E.; Bedell, L. J.; Boehm, T. L.; Decrescenzo, G. A.; Freskos, J. N.; Getman, D. P.; Hockerman, S. L.; Heintz, R.; Howard, S. C.; Li, M. H.; McDonald, J. J.; Carron, C. P.; Funckes-Shippy, C. L.; Mehta, P. P.; Munie, G. E.; Swearingen, C. A. *J. Med. Chem.* **2005**, *48*, 6713; (b) Becker, D. P.; Barta, T. E.; Bedell, L. J.; Boehm, T. L.; Bond, B. R.; Carroll, J.; Carron, C. P.; DeCrescenzo, G. A.; Easton, A. M.; Freskos, J. N.; Funckes-Shippy, C. L.; Heron, M.; Hockerman, S. L.; Howard, C. P.; Kiefer, J. R.; Li, M. H.; Mathis, K. J.; McDonald, J. J.; Mehta, P. P.; Munie, G. E.; Sunyer, T.; Swearingen, C. A.; Villamil, C. I.; Welsch, D.; Williams, J. M.; Yu, Y.; Yao, J. *J. Med Chem.* **2010**, *53*, 6653.
3. (a) Holmbeck, K.; Bianco, P.; Caterina, J.; Yamada, S.; Kromer, M.; Kuznetsov, S. A.; Mankani, M.; Robey, P. G.; Poole, A. R.; Pidoux, I.; Ward, J. M.; Birkedal-Hansen, H. *Cell* **1999**, *99*, 81; (b) Zhou, Z.; Apte, S. S.; Soininen, R.; Cao, R.; Baaklini, G. Y.; Rauser, R. W.; Wang, J.; Cao, Y.; Tryggvason, K. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 4052.
4. Wasserman, Z. R. *Chem. Biol.* **2005**, *12*, 143.
5. (a) Johnson, A. R.; Pavlovsky, A. G.; Ortwine, D. F.; Prior, F.; Man, C. F.; Bornemeier, D. A.; Banotai, C. A.; Mueller, W. T.; McConnell, P.; Yan, C.; Baragi, V.; Lesch, C.; Roark, W. H.; Wilson, M.; Datta, K.; Guzman, R.; Han, H. K.; Dyer, R. D. *J. Biol Chem.* **2007**, *282*, 27781; (b) LaFleur, M. A.; Drew, A. F.; de Sousa, E. L.; Blick, T.; Bills, M.; Walker, E. C.; Williams, E. D.; Walthan, M.; Thompson, E. W. *Int. J. Cancer* **2005**, *114*, 544.
6. Kolodziej, S. A.; Hockerman, S. L.; DeCrescenzo, G. A.; McDonald, J. J.; Mischke, D. A.; Munie, G. E.; Fletcher, T. R.; Stehle, N.; Swearingen, C.; Becker, D. P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3561; See also: Kolodziej, S. A.; Hockerman, S. L.; Boehm, T. L.; DeCrescenzo, G. A.; McDonald, J. J.; Mischke, D. A.; Munie, G. E.; Fletcher, T. R.; Stehle, N.; Swearingen, C.; Becker, D. P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3557.
7. For other groups interested in MMP-13 selective inhibitors: (a) Wu, J.; Rush, T. S., III; Hotchandani, R.; Du, X.; Geck, M.; Collins, E.; Xu, Z. B.; Skotnicki, J.; Levin, J. I.; Lovering, F. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4105; (b) Nuti, E.; Casalini, F.; Avramova, S. I.; Santamaria, S.; Cercignani, G.; Marinelli, L.; La Pietra, V.; Novellino, E.; Orlandini, E.; Nencetti, S.; Tuccinardi, T.; Martinelli, A.; Lim, N.; Visse, R.; Nagase, H.; Rossello, A. *J. Med. Chem.* **2009**, *52*, 4757.
8. Freskos, J. N.; Fobian, Y. M.; Barta; T. E.; Becker, D. P.; Bedell, L. J.; Boehm, T. L.; Carroll, J. N.; DeCrescenzo, G. A.; Hockerman, S. L.; Kassab; D. J.; Kolodziej, S. A.; McDonald, J. J.; Mischke, D.A.; Norton, Monica B.; Rico, J. G.; Talley; J. J.; Villamil, C. I.; Wang, Lijuan J. U.S. Patent 6,890,928, 2005; *Chem. Abstr.* **1999**, *131*, 44740.
9. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.