Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 2481–2483

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Selective, Orally Active MMP Inhibitors with an Aryl Backbone

Thomas E. Barta,[a,*] Daniel P. Becker,[a] Louis J. Bedell,[a] Gary A. De Crescenzo,[b] Joseph J. McDonald,[b] Pramod Mehta,[b] Grace E. Munie[b] and Clara I. Villamil[a]

[a]*Pharmacia, Department of Medicinal Chemistry, 4901 Searle Parkway, Skokie, IL 60077, USA*
[b]*Pharmacia, Department of Medicinal Chemistry, 700 North Chesterfield Parkway, St. Louis, MO 63198, USA*

Received 9 May 2001; accepted 2 July 2001

Abstract—This letter describes SAR exploration and rat PK optimization of a series of novel, MMP-1 sparing aryl hydroxamate sulfonamides with activity against MMP-2 and MMP-13.

There are over 20 known human matrix metalloproteinases (MMPs). MMPs play a crucial role in development and in tissue growth and repair.[1] In certain pathologies, including cancer metastasis,[2] arthritis,[3] and congestive heart failure,[4] elevated MMP levels may exacerbate the disease. Thus, there has been considerable effort in the drug industry (Fig. 1) directed towards identifying small molecule inhibitors and several MMPIs are in clinical trials. Prolonged administration of broad spectrum inhibitors, such as marimistat, has been associated with a progressive, albeit reversible, musculoskeletal syndrome (MSS) involving pain and stiffening in the joints.[5] For this reason, researchers are interested in identifying selectivity profiles that avoid MSS. Our paradigm has been to design compounds that inhibit those MMPs implicated in disease pathology while sparing the ubiquitous MMP-1.[6]

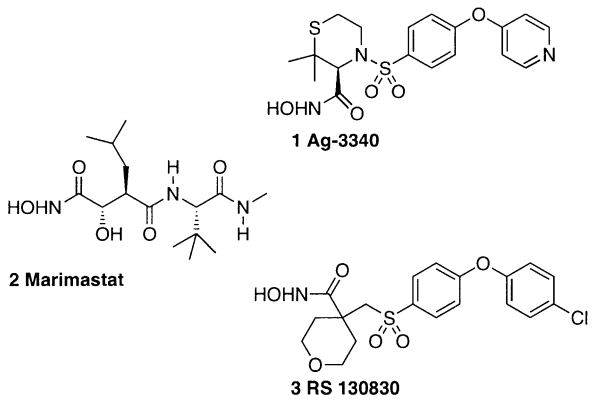
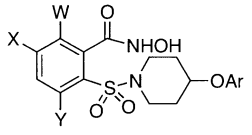


Figure 1. Some reported MMPIs.

In our previous paper,[7,8] we described our early work in a series of aryl-backbone, MMP-1 sparing hydroxamates.[9] Our aryl analogues were dosed in rat and found to be orally bioavailable (e.g., **4a**, Fig. 2: C_{max} 1230 ng/mL @ 20 MPK; $t_{1/2} = 0.8$ h). Subsequent analogues were designed to improve both exposure and half-life in the rat.

Specifically, it occurred to us that we might improve the C_{max} values the compounds could attain by synthesizing analogues with water-solubilizing groups built into the structure. Additionally, we felt we might be able to extend the half-life of compounds by increasing steric hindrance around the potentially metabolizable hydroxamate moiety. X-ray crystallography (of **4n** in MMP-8)[7] revealed that substituents on the W, X, and Y positions are solvent exposed rather than pointing towards the enzyme backbone. Thus, replacing the hydrogens in these positions should not deleteriously impact enzyme potency. The W position looked particularly attractive as a substitution point that could improve $t_{1/2}$ because of its proximity to the hydroxamate (Table 1).



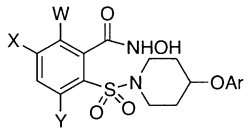
4a W,X,Y = H; Ar = p-CF_3-Ph

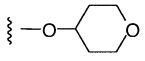
Figure 2. Aryl-backbone MMPIs.

*Corresponding author. Tel.: +1-847-982-4639; fax: +1-847-982-4714; e-mail: barta@netmug.org

0960-894X/01/$ - see front matter
PII: S0960-894X(01)00487-5

Table 1. SAR of aryl-linked compounds



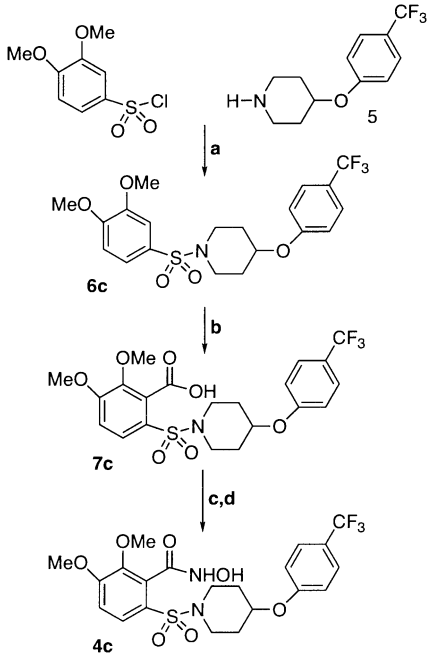
Compd	W	X	Y	Ar	MMP-1 (nM)[a]	MMP-2 (nM)[a]	MMP-13 (nM)[a]	C_{max}[b] (μg/mL)	$t_{1/2}$[c] (h)	%BA
1					23.5	0.3	0.5	2.06	1.6	28
2					2.9	0.75	2.0	2.40	0.9	9
3					800	0.4	0.6	1.37	1.5	22
4a	H	H	H	*p*-CF_3-Ph	$>10^4$	1.2	27	1.23	0.8	23
4b	H	H	H	*p*-OCF_3-Ph	$>10^4$	2.2	33	0.67	—	39
4c	MeO–	MeO–	H	*p*-CF_3-Ph	$>10^4$	2.4	2.7	22.5	1.9	32
4d	MeO–	MeO–	H	*p*-OCF_3-Ph	$>10^4$	0.8	3.7	5.16	1.5	31
4e	MeO–	MeO–	H	*o*-OMe-Ph	$>10^4$	330	2500	—[d]	—	—
4f	MeO–	MeO–	H	*m*-OMe-Ph	$>10^4$	12	250	—	—	—
4g	MeO–	MeO–	H	*p*-OMe-Ph	$>10^4$	1.8	14	—	—	—
4h	MeO–	MeO–	H	Ph	$>10^4$	1.1	6.7	—	—	—
4i	MeO–	MeO–	H	*p*-Cl-Ph	$>10^4$	0.3	1.5	—	—	—
4j	MeO–	MeO–	H	Piperonyl	$>10^4$	1.0	13	9.20	—	—
4k	–O-CH_2-O–		H	*p*-CF_3-Ph	$>10^4$	3.0	18	3.06	—	—
4l	–O-CH_2-O–		H	Piperonyl	$>10^4$	1.1	19	—	—	—
4m	–O-CH_2CH_2-O–		H	*p*-CF_3-Ph	$>10^4$	1.4	7.7	3.20	—	—
4n	F–	H	H	*p*-CF_3-Ph	$>10^4$	3.3	12	—	—	—
4o	Cl–	H	H	*p*-CF_3-Ph	$>10^4$	1.9	14.8	1.31	—	—
4p	CH_3-O-$(CH_2)_2$-O–	H	H	*p*-CF_3-Ph	$>10^4$	1.0	4.3	2.67	—	—
4q		H	H	*p*-CF_3-Ph	$>10^4$	1.1	2.2	—	—	—
4r	MeO–	H	MeO–	*p*-CF_3-Ph	$>10^4$	21	110	—	—	—

[a]See ref 12 for assay conditions.
[b]Oral dose of 20 mpk, in rats. See ref 13 for assay conditions.
[c]iv dose of 20 mpk, in rats. See ref 13 for assay conditions.
[d]Not performed.

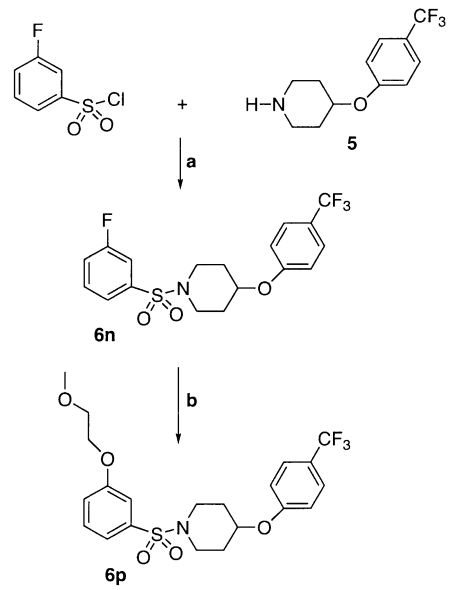
With these goals in mind, we selected 3,4-dimethoxybenzenesulfonyl chloride as one of our starting materials (Scheme 1). The chloride was reacted with piperidine **5**, whose synthesis we described previously.[7] We hoped that ring deprotonation of the resulting sulfonamide would occur preferentially in the 2 position, since that position is doubly activated both by an oxygen from the sulfonamide and by the 3-methoxy. This is, in fact, what we observed. Metalation was typically clean and facile;[10] on quenching with carbon dioxide, good yields of acids were obtained.

When we attempted to perform EDC coupling on the carboxylic acid **7c**, as we had done in our earlier work,[7] we knew immediately that we had achieved our goal of increasing hindrance at the carbonyl. The HOBT ester formed in the coupling reaction proved resistant to displacement by $THPONH_2$ under the reaction conditions. The ester had to be isolated and heated in the presence of excess $THPONH_2$ in order to obtain the THP hydroxamate, and the conversion proceeded in low yield. Fortunately, coupling could be easily achieved by converting the acids into the corresponding, more reactive acid chlorides. The *O*-tetrahydropyranyl hydroxamates thus obtained were deprotected to the corresponding hydroxamic acids in good yield using HCl.

Analogues with more elaborate aryl substituents, such as **4p** and **4q**, could be made by similar methods, except



Scheme 1. (a) TEA, CH_3CN, DMAP, 82%; (b) *t*-BuLi (2 equiv), 0 °C; then CO_2; then HCl (aq), 57%; (c) oxalyl chloride, CH_2Cl_2; $THPONH_2$, pyridine, CH_2Cl_2; (d) AcCl, MeOH, 51% from acid.



Scheme 2. (a) TEA, CH_3CN, DMAP, 84%; (b) $MeO(CH_2)_2OH$, NMP, 115 °C, 20 h, 71%.

that we had to first construct the metalation substrates by performing a fluoride displacement on the intermediate **6n**, as depicted in Scheme 2.

In addition to exploring modifications on the left-hand aryl group of the molecule, one of our goals was to further investigate the right-hand aryl ether moieties which fit into the P1′ pocket in the enzyme. A variety of aryl groups we studied had good enzyme potency, as we see from examination of the data for **4g**, **4h**, **4j**, and **4l**. Aryls with *ortho* or *meta* substitution, such as **4e** and **4f**, were less potent, probably because of steric constraints in the tight P1′ pocket.

Introduction of hindering groups on the 'backbone' aryl ring bearing the hydroxamate (**4a** and **4b** vs **4c** and **4d**, respectively) resulted in an unexpected increase in the MMP-13 potency, which we cannot easily explain from our understanding of the binding of our solved crystal structure, **4n**, in MMP-8.

As hoped, the alkoxy substituents on the left-hand aryl ring served to enhance the PK characteristics of the aryl series.[11] The C_{max} values were substantially improved with respect to the unsubstituted analogues. In particular, **4c** and **4d** are seen to have markedly improved C_{max} and half-life values.

In summary, we have prepared a series of aryl-linked[8] hydroxamate inhibitors that are potent for MMP-2 and MMP-13 and which spare MMP-1. Analogue **4c** exhibits enhanced PK properties in rat and was selected for testing in efficacy models. Further details will be reported in due course.

References and Notes

1. Greenwald, R. A.; Zucker, S.; Golub, L. M., Eds. *Inhibition of Matrix Metalloproteinases: Therapeutic Applications*; New York Academy of Sciences: New York, 1999.
2. Lauer-Fields, J. L.; Fields, G. B. *Exp. Opin. Ther. Patents* **2000**, *10*, 1873.
3. Shaw, T.; Nixon, J. S.; Bottomley, K. M. *Exp. Opin. Invest. Drugs* **2000**, *9*, 1469.
4. Spinale, F. G.; Coker, M. L.; Heung, L. J.; Bond, B. R.; Gunasinghe, R.; Etoh, T.; Goldberg, A. T.; Zellner, J. L.; Crumbley, A. J. *Circulation* **2000**, *102*, 1944.
5. Heath, E. I.; Grochow, L. B. *Drugs* **2000**, *59*, 1043.
6. The hypothesis that sparing MMP-1 is necessary and sufficient to prevent the musculoskeletal stiffening has been called into question in view of recent clinical results, where it is observed that certain inhibitors that inhibit MMP-1 nevertheless do not appear to show the side effect. See ref 2.
7. Barta, T. E.; Becker, D. P.; Bedell, L. J.; De Crescenzo, G. A.; McDonald, J. J.; Munie, G. E.; Rao, S.; Shieh, H.; Stegeman, R.; Stevens, A. M.; Villamil, C. I. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2815.
8. Barta, T. E.; Becker, D. P.; Bedell, L. J.; Freskos, J. N.; McDonald, J. J.; Mischke, B. V.; Rao, S. N. WO 9838859, 1998; *Chem. Abstr.* **1998**, *129*, 260344.
9. Recently Wyeth-Ayerst reported a series of very different aryl-backboned MMPIs based on an anthranilate linker. See: Levin, J. I.; Du, M. T.; DiJoseph, J. F.; Killar, L. M.; Sung, A.; Walter, T.; Sharr, M. A.; Roth, C. E.; Moy, F. J.; Powers, R.; Jin, G.; Cowling, R.; Skotnicki, J. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 235.
10. For the halogen examples, **6n** and **6o**, the metalation was conducted at −40 °C to minimize the potential for competing benzyne formation.
11. We were asked by the referees whether the alkoxy groups we introduced in fact increased aqueous solubility (e.g., **4a** and **4b** vs **4c** and **4d**, respectively). We have no data on this, since we do not routinely measure this physical parameter, but we did obtain calculated log P values **4a** and **4c** using several methods and found the results to be within 0.5 log units. This leads us to believe that our improved PK may be more the result of enhanced half-life than enhanced solubility.
12. Assays were conducted at six dilutions with an *n* at least equal to 2. Inhibitors were tested against purified hMMP-13, hMMP-1 and hMMP-2 using an enzyme assay based on cleavage of the fluorogenic peptide substrate MCA-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2. This is similar to conditions described by Knight, C. G.; Willenbrock, F.; Murphy, G. *FEBS Lett.* **1992**, *296*, 263, except that 0.02% final concentration of 2-mercaptoethanol was used in the MMP-13 and MMP-1 assays.
13. One group of four rats receives compound via the oral route at a dosing volume of 2 mL/kg (10 mg/mL, dissolved in 0.5% methylcellulose, 0.1% Tween 20), while another group of 4 rats receives compound via intravenous cannula at a dosing volume of 2 mL/kg (10 mg/mL, dissolved in 10% EtOH, 50% PEG 400, 40% saline). The blood samples are collected from the arterial cannula at 3 (iv only), 15, 30, 60, 120, 240, and 360 min. After each sample, the cannulae are flushed with PBS containing 10 U/mL heparin. Plasma samples are extracted with acetonitrile, evaporated under nitrogen, reconstituted in DMSO, and then analyzed for inhibitor using MMP-13 enzyme and thiopeptolide as a substrate.