10-22-2001

Alpha-Alkyl-alpha-amino-beta-sulphone Hydroxamates as Potent MMP Inhibitors that Spare MMP-1

Daniel Becker
Loyola University Chicago, dbecke3@luc.edu

Gary A. DeCrescenzo

John Freskos

Daniel P. Getman

Author Manuscript
This is a pre-publication author manuscript of the final, published article.

Recommended Citation

Becker, Daniel; DeCrescenzo, Gary A.; Freskos, John; and Getman, Daniel P.. Alpha-Alkyl-alpha-amino-beta-sulphone Hydroxamates as Potent MMP Inhibitors that Spare MMP-1. Bioorganic & Medicinal Chemistry Letters, 11, 20: , 2001. Retrieved from Loyola eCommons, Chemistry: Faculty Publications and Other Works, http://dx.doi.org/10.1016/S0960-894X(01)00557-1

α-Alkyl-α-Amino-β-Sulphone Hydroxamates as Potent MMP Inhibitors Which Spare MMP-1

Daniel P. Becker*[a], Gary DeCrescenzo,[b] John Freskos,[b] Daniel P. Getman,[b]
Susan L. Hockerman,[a] Madeleine Li,[a] Pramod Mehta,[b] Grace Munie[b], Craig Swearingen[b]

Departments of Medicinal Chemistry and Inflammation-Oncology
Pharmacia Research & Development
[a]*4901 Searle Parkway, Skokie, IL 60077*
[b]*700 Chesterfield Village Parkway, St. Louis, MO 63198*

Abstract: A series of α-alkyl-α-amino-β-sulphone hydroxamates was prepared and evaluated for potency versus MMP-2 and MMP-13, and for selectivity versus MMP-1. Low nanomolar potency was obtained with selectivity versus MMP-1 ranging from >10 to >1,000. Selected compounds were orally bioavailable.

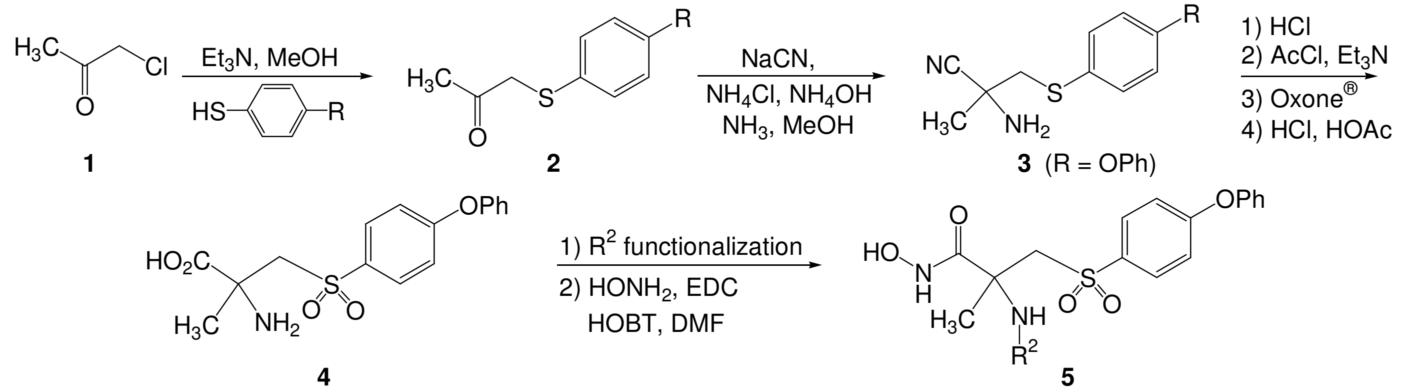
Introduction

In our previous letter we descirbed a series of α-amino-β-sulphone hydroxamates which are potent inhibitors of MMP-13 which spare MMP-1.[1] Overexpressed MMPs play a crucial role in tumor growth and metastasis in cancer, and in the destruction of articular cartilage in osteoarthritis (OA) and rheumatoid arthritis (RA). Hence, the inhibition of the relevant MMP enzymes may prove to be clinically effective in halting the advance of these diseases.[2] The gelatinases A and B (MMP-2 and MMP-9) have been implicated in tumor progression,[3] and MMP-13 has been implicated in the destruction of articular cartilage in arthritis.[4] Herein we report the preparation and preliminary SAR of a series of α-amino-α-alkyl-β-sulphones which are highly selective in sparing MMP-1, based on the hypothesis that the musculoskeletal side effect observed clinically with the broad-spectrum inhibitor marimastat[5] is due to potent inhibition of MMP-1. Alkyl substituents alpha to the hydroxamate were employed to modulate pharmacokinetic properties including absorption and half-life, as well as physicochemical properties, while the P_1' substituent was varied to optimize potency and selectivity.

Chemistry

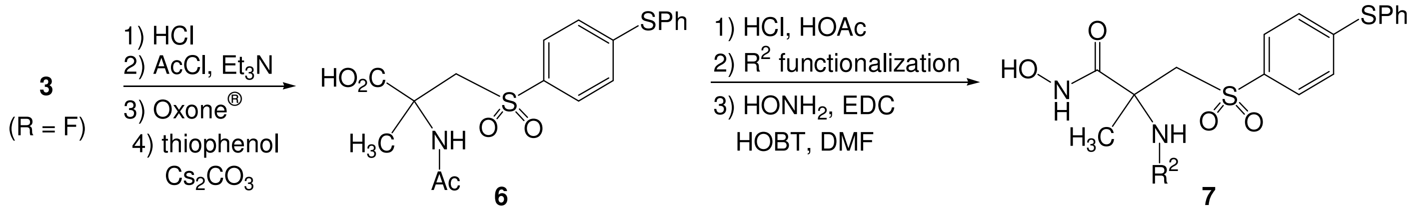
The targeted α-methyl-α-amino diphenyl ether hydroxamates of type **5** were prepared starting with a halide displacement of chloroacetone (**1**) with 4-phenoxythiophenol[6] to afford **2** (**Scheme 1**). Strecker synthesis then gave the nitrile **3** which was hydrolyzed to the carboxylic acid. Oxidation of the sulfide after protection of the amino group as the acetamide, and subsequent deprotection then gave the amino acid **4**. Functionalization of the amino group was accomplished by alkylation, acylation or reductive amination as required, and standard EDC coupling with hydroxylamine afforded the diphenyl ether sulphone hydroxamates **5**.

Scheme 1



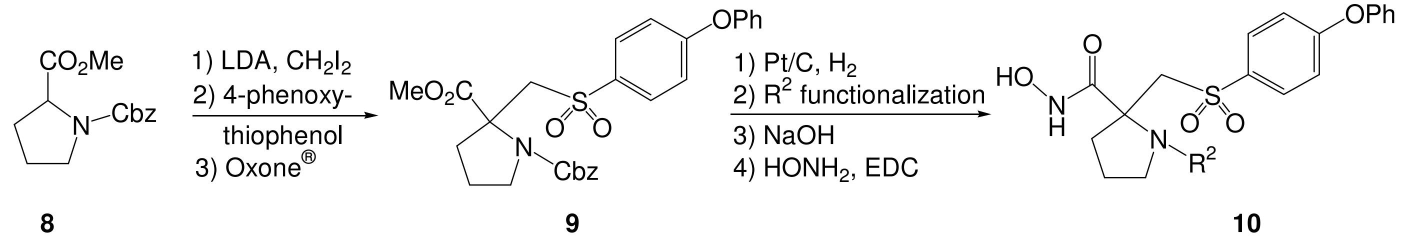
The diaryl thioether **7** was prepared by reacting chloroacetone (**1**) with 4-fluorothiophenol (R = F). Strecker synthesis gave nitrile **3** (R = F) which was hydrolyzed and protected as the acetamide (**Scheme 2**). Oxidation then afforded the corresponding 4-fluorophenylsulphone, and nucleophilic aromatic substitution with thiophenol gave carboxylic acid **6**. Acetamide hydrolysis preceded amino functionalization with the appropriate R^2 reagent, and EDC coupling afforded the hydroxamates **7**.

Scheme 2



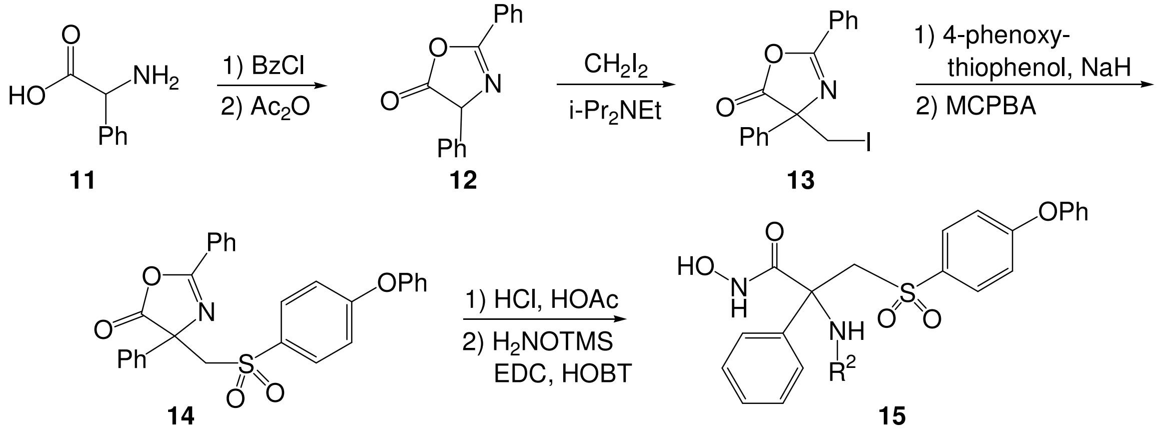
As illustrated in **Scheme 3**, α-pyrrolidine-β-sulphones were prepared from racemic methyl N-Cbz-proline (**8**). Alkylation[7] with methylene diiodide gave the α-iodomethyl derivative which was used to alkylate 4-phenoxythiophenol, and oxidation gave the sulphone **9**. The Cbz protecting group was removed by hydrogenolysis, exposing the amine which was functionalized by alkylation with propargyl bromide. Saponification of the methyl ester and coupling with hydroxylamine then afforded the hydroxamate **10** (R^2 = propargyl).

Scheme 3



The α-phenyl-α-amino derivative **15** (**Scheme 4**) was prepared from D,L-phenylglycine (**11**) by benzoylation and treatment with acetic anhydride to give the 2-phenyloxazolone **12**[8] (**Scheme 4**). Alkylation of this azlactone with methylene diiodide gave iodomethyl azlactone **13**, and displacement of the iodide with 4-phenoxythiophenol and subsequent oxidation with metachloroperbenzoic acid gave the sulphone **14**. The oxazolone was then hydrolyzed and the resulting carboxylic acid coupled with TMS-protected hydroxylamine to afford **15** (R^2 = H). Alternatively, the oxazolone ring was opened directly with hydroxylamine to afford the benzamide hydroxamate (R^2 = Bz).

Scheme 4

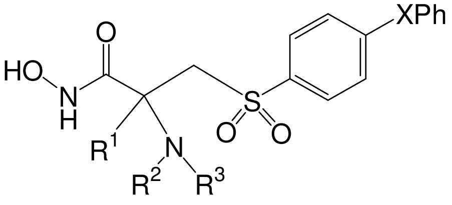


Results and Discussion

Table 1 summarizes the potency versus MMP-2, MMP-13 and MMP-1 for compounds of generic structures **5**, **7** and **15**. The diaryl ethers (X = O) were an order of magnitude more potent than the corresponding thioethers (X = S), although the thioethers were noted to be somewhat more selective in sparing MMP-1 (**5a** and **5b** versus **7a** and **7b**). Amides of the α-amino group (compounds **5a**, **5j**, **7a** and **15a**) were not well tolerated, whereas simple alkyl and aralkyl amines were potent for both MMP-2 and MMP-13. Disubstitution on the amine led to a loss of potency (**5c**). The α-phenyl amine **15b** was potent for MMP-13 and MMP-2, but was also somewhat more potent for MMP-1. Almost all compounds exhibited excellent selectivity versus MMP-1, in several cases exceeding 1000X for the ratio of IC_{50} values (MMP-1/MMP-2 and MMP-1/MMP-13), in contrast to the broad-spectrum inhibitors CGS 27023A and marimastat.

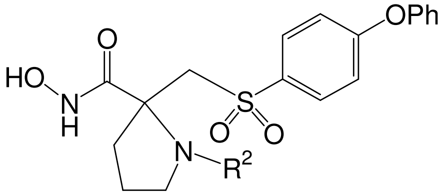
Table 2 shows the enzyme potency of proline-derived analog **10**. Since the racemate **10** was found to be quite potent, the material was resolved into its enantiomers via chiral chromatography.[9] The first eluter, hydroxamate **10a**, was found to be the more potent enantiomer (eutomer) by at least two orders of magnitude against both MMP-13 and MMP-2 as compared to the less potent enantiomer (distomer) **10b**. Compound **10a** was also highly selective in sparing MMP-1 (3000X).

Table 1: IC_{50} (nM)[10] values for α-alkyl-α-amino-β-sulphone hydroxamates



Compound	R^1	R^2	R^3	X	MMP-13	MMP-2	MMP-1
5a	CH_3	Ac	H	O	41.5	40.0	>10,000
5b	CH_3	H	H	O	0.2	0.6	170
5c	CH_3	CH_3	CH_3	O	24.0	5.0	>10,000
5d	CH_3	CH_2CH_3	H	O	1.6	1.3	1600
5e	CH_3	CH_2Ph	H	O	0.3	0.2	1200
5f	CH_3	CH_2CH_2Ph	H	O	2.4	1.3	2400
5g	CH_3	3,4-methylenedioxybenzyl	H	O	1.1	0.5	2350
5h	CH_3	2-naphthylmethyl	H	O	1.4	0.4	>10,000
5i	CH_3	propargyl	H	O	0.6	0.2	700
5j	CH_3	pyrrolidineacetyl	H	O	160	80	>10,000
7a	CH_3	Ac	H	S	580	540	>10,000
7b	CH_3	H	H	S	2.4	3.2	4400
15a	Ph	benzoyl	H	O	161	184	>10,000
15b	Ph	H	H	O	0.4	0.2	130
CGS 27023A					5.1	4.6	34.3
marimastat					2.0	0.75	2.9

Table 2: IC_{50} (nM)[10] values for α-pyrrolidine-β-sulphone hydroxamates



Compound	R^2	MMP-13	MMP-2	MMP-1
10 (racemic)	propargyl	1.3	0.2	400
10a (eutomer)	propargyl	<0.1	<0.1	300
10b (distomer)	propargyl	60.0	19.3	>10,000

Selected analogs were dosed orally in rats at 20 mpk to assess absorption by measuring C_{max}, and the concentration remaining at 6 hours was used as an initial rough indicator of the half-life. The α-methyl-α-amino analog **5b** showed a high C_{max} of 6.43 ug/ml, somewhat greater than the corresponding thioether **7b** (C_{max} = 1.54 ug/ml). N-ethyl and N-benzyl analogs **5d** and **5e** were moderately well absorbed (C_{max} = 0.561 and 0.216 ug/ml, respectively), and N-propargyl amine **5i** exhibited a Cmax of 1.37 ug/ml. However, all of the compounds tested were less than 15 ug/ml in plasma at the 6 h time point.

In summary, we have described a promising series of α-alkyl-α-amino-β-sulphone hydroxamates which are potent inhibitors of both MMP-2 and MMP-13, and which spare MMP-1. Several analogs showed good absorption when administered orally in the rat. The efficacy of these compounds in animal models of cancer and arthritis will be disclosed in due course.

References and Notes

1. Becker, D. P.; Barta, T. E.; Bedell, L.; DeCrescenzo, G.; Freskos, J.; Getman, D. P.; Hockerman, S. L.; Li, M.; Mehta, P.; Mischke, B.; Munie, G.; Swearingen, C.; Villamil, C. I. *Bioorg. Med. Chem. Lett.* **2001**, *##,* ###.
2. Cawston, T. E. *Pharmacol. Ther*. **1996**, *70*, 163.
3. Nelson, A. R.; Gingleton, B.; Rothenberg, M. L.; Matrisian, L. M. *J. Clinical Oncology*, **2000**, *18*, 1135.
4. Freemont, A. J.; Byers, R. J.; Taiwo, Y. O.; Hoyland, J. A. *Ann. Rheum. Dis.* **1999**, *58*, 357.
5. Wojtowicz-Praga, S.; Torri, J.; Johnson, M.; Steen, V.; Marshall, J.; Ness, E.; Dickson, R.; Sale, M.; Rasmussen, H. S.; Chiodo, R. A.; Hawkins, M. *J. Clin. Oncol.* **1998**, *16*, 2150.
6. Freskos, J. N.; Mischke, B. V.; DeCrescenzo, G. A.; Heintz, R.; Getman, D. P.; Howard, S. C.; Kishore, N. N.; McDonald, J. J.; Munie, G. E.; Rangwala, S.; Swearingen, C. A.; Voliva, C.; Welsch, D. J. *Bioorg. & Med. Chem. Lett.* **1999**, *9*, 943.
7. Chan, C. O.; Cooksey, C. J.; Crich, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, *7*, 777.
8. Obrecht, D.; Spiegler, C.; Schoenholzer, P.; Mueller, K.; Heimgartner, H.; Stierli, F. *Helv. Chim. Acta* **1992**, *75*, 1666.
9. The resolution of **30** was accomplished using a Chiralpak AD column (4.6 mm X 25 cm) at a flow rate of 1.0 ml/min eluting with a mobile phase of 35/65 ethanol/heptane with 0.2% trifluoroacetic acid. Tony Yan is gratefully acknowledged for performing the chiral separation.
10. Inhibitors were assayed against purified hMMP-13, hMMP-1 and hMMP-2 using an enzyme assay based on cleavage of the fluorogenic peptide MCA-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2. This is similar to conditions described by C. G. Knight et. al. in *FEBS Lett.* **1992**, *296*, 263, except that 0.02% final concentration of 2-mercaptoethanol was used in the MMP-13 and MMP-1 assays. All basic compounds were tested as their hydrochloride salts except for **10a** and **10b**, which were tested as the trifluoroacetate salts.