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α-Alkyl-α-amino-β-sulphone Hydroxamates as Potent MMP Inhibitors that Spare MMP-1

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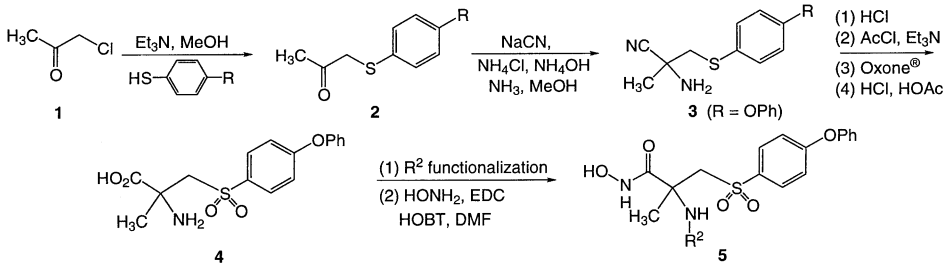
Abstract—A series of α-alkyl-α-amino-β-sulphone hydroxamates was prepared and evaluated for potency versus MMP-2 and MMP-13, and for selectivity versus MMP-1. Low nanomolar potency was obtained with selectivity versus MMP-1 ranging from >10 to >1000. Selected compounds were orally bioavailable.

In our previous letter, we described a series of α-amino-β-sulphone hydroxamates that 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 that 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.

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



Scheme 1.

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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**.

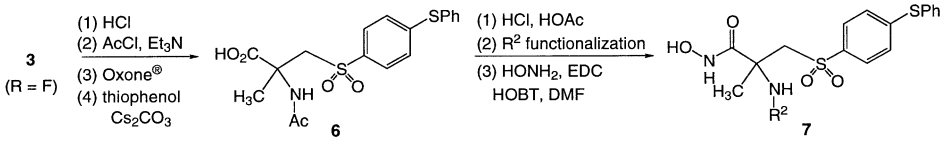
The diaryl thioether **7** was prepared commencing with the reaction of chloroacetone (**1**) with 4-fluorothiophenol (R = F). Strecker synthesis gave nitrile **3** (R = F), which was hydrolyzed and protected as the acetamide (Scheme 2). Oxidation then afforded the corresponding 4-fluorophenylsulphone, 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**.

As illustrated in Scheme 3, α-pyrrolidine-β-sulphones were prepared from racemic *N*-Cbz-proline methyl ester (**8**). Alkylation of **8** with methylene diiodide[7] gave the α-iodomethyl derivative, which was used to alkylate 4-phenoxythiophenol. The resulting aryl sulfide was oxidized to furnish 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).

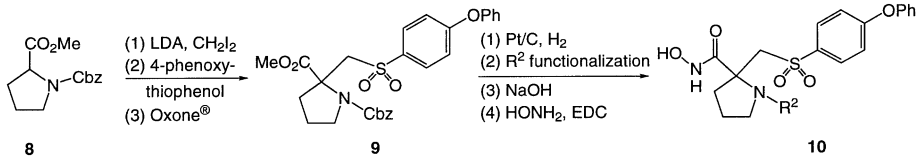
The α-phenyl-α-amino derivative **15** (Scheme 4) was prepared from D,L-phenylglycine (**11**) by benzoylation and treatment with acetic anhydride to give the 2-phenyloxazolone **12**[8] (Scheme 4). Alkylation of this azlactone with methylene diiodide gave iodomethyl azlactone **13**, and displacement of the iodide with 4-phenoxythiophenol and subsequent oxidation with *meta*-chloroperbenzoic 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).

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 occasionally the thioethers were noted to be somewhat more selective in sparing MMP-1 (**5b** vs **7b**). Amides of the α-amino group (**5a**, **5j**, **7a**, and **15a**) were significantly less potent for both MMP-2 and MMP-13, whereas simple alkyl and aralkyl amines were potent for both of these enzymes. 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 1000× 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.

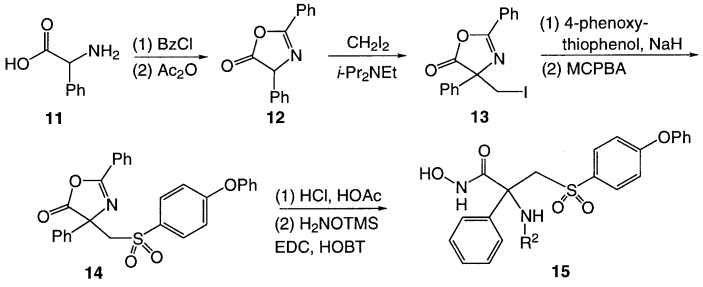
Table 2 shows the enzyme potency of proline-derived analogue **10**. Since the racemate **10** was found to be quite potent, the material was resolved into its enantiomers via chiral chromatography.[9] The first eluter, hydroxamate **10a**, was found to be the more potent enantiomer (eutomer) by at least two orders of



Scheme 2.

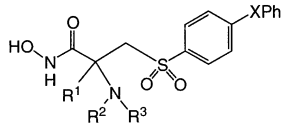


Scheme 3.



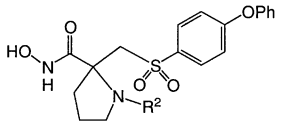
Scheme 4.

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



Compd	R^1	R^2	R^3	X	MMP-13	MMP-2	MMP-1	MMP-1/13
5a	CH_3	Ac	H	O	41.5	40.0	>10,000	>240
5b	CH_3	H	H	O	0.2	0.6	170	850
5c	CH_3	CH_3	CH_3	O	24.0	5.0	>10,000	>416
5d	CH_3	CH_2CH_3	H	O	1.6	1.3	1600	1000
5e	CH_3	CH_2Ph	H	O	0.3	0.2	1200	4000
5f	CH_3	CH_2CH_2Ph	H	O	2.4	1.3	2400	1000
5g	CH_3	3,4-Methylenedioxybenzyl	H	O	1.1	0.5	2350	2136
5h	CH_3	2-Naphthylmethyl	H	O	1.4	0.4	>10,000	7143
5i	CH_3	Propargyl	H	O	0.6	0.2	700	1167
5j	CH_3	Pyrrolidineacetyl	H	O	160	80	>10,000	>62
7a	CH_3	Ac	H	S	580	540	>10,000	>17
7b	CH_3	H	H	S	2.4	3.2	4400	1833
15a	Ph	Benzoyl	H	O	161	184	>10,000	>62
15b	Ph	H	H	O	0.4	0.2	130	325
CGS 27023A					5.1	4.6	34.3	6.7
Marimastat					2.0	0.75	2.9	1.4

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



Compd	R^2	MMP-13	MMP-2	MMP-1	MMP-1/13
10 (racemic)	Propargyl	1.3	0.2	400	308
10a (eutomer)	Propargyl	<0.1	<0.1	300	>3000
10b (distomer)	Propargyl	60.0	19.3	>10,000	>167

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 (3000×).

Selected analogues were dosed orally in rats at 20 mpk to assess absorption by measuring C_{max}, and the concentration remaining at 6 h was used as an initial rough indicator of the half-life. The α-methyl-α-amino analogue **5b** showed a high C_{max} of 6.43 μg/mL, somewhat greater than the corresponding thioether **7b** (C_{max} = 1.54 μg/mL). *N*-Ethyl and *N*-benzyl analogues **5d** and **5e** were moderately well absorbed (C_{max} = 0.561 and 0.216 μg/mL, respectively), and *N*-propargyl amine **5i** exhibited a C_{max} of 1.37 μg/mL. The propargyl substituent was selected for inclusion with the expectation of increasing the oral exposure, based on in-house experience. However, all of the compounds tested were less than 15 ng/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 that are potent inhibitors of both MMP-2 and MMP-13, and that spare MMP-1. Several analogues 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

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9. The resolution of **30** was accomplished using a Chiralpak AD column (4.6 mm×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 Knight, C. G. et al. *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.