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Bioorganic & Medicinal Chemistry Letters 16 (2006) 3096–3100
Bioorganic & Medicinal Chemistry Letters

Synthesis and SAR of α-sulfonylcarboxylic acids as potent matrix metalloproteinase inhibitors

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Received 16 February 2006; revised 20 March 2006; accepted 21 March 2006

Abstract—A series of novel carboxylic acid-based α-sulfone MMP inhibitors have been synthesized and the in vitro enzyme SAR is discussed. A potential binding mode in the active site of the MMP-9 homology model was highlighted. These compounds are potent MMP-9 inhibitors and are selective over MMP-1.

The wide variety of matrix metalloproteinases (MMPs) normally participate in many different homeostatic tissue remodeling events. The over-expression of MMP activities has been shown to play a negative role in a variety of disease states, such as oncology,[1a] rheumatoid arthritis,[1b] cardiovascular diseases,[1c] and neurological disorders.[1d] Therefore, design and synthesis of potent, small molecule MMP inhibitors (MMPIs) has been an area of intense focus in medicinal chemistry.

To date the hydroxamate-based compounds have attracted the most interest due to their high in vitro potency. With the disclosure of the spiro-β-sulfone hydroxamate **1** as a clinical candidate, reports of a series of hydroxamate-based α-sulfone MMPIs have followed,[2,3] exemplified by structure **2** (Fig. 1).[3] The enzyme profile and ADME properties of the α-sulfone hydroxamates were reported to be superior to the β-sulfone series.[3] Nevertheless, it has been suggested that the poor pharmacokinetic (PK) profiles of the hydroxamate inhibitors may be associated with in vivo toxicity.[4] The carboxylic acids, the precursors of the hydroxamates, have been shown to demonstrate more favorable PK properties.[4] However, the simple replacement of hydroxamate by carboxylic acid as zinc-binding group (ZBG) causes 100- to 2000-fold loss in potency.[5] Moreover, high serum protein binding is typically suffered by carboxylic acid MMPIs.[6] A representative carboxylic acid MMPI is tanomastat (**3**) with moderate MMP activities (Fig. 1).

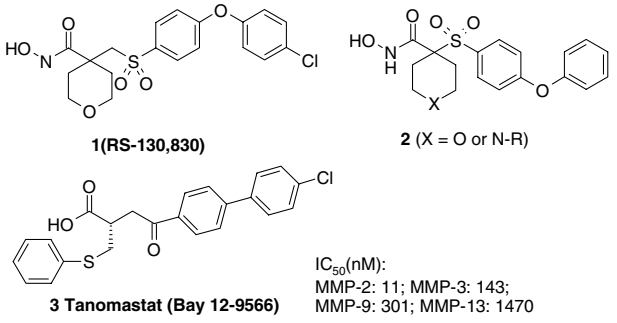
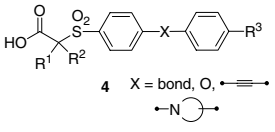


Figure 1. Selected MMPIs.

Our program has focused on the discovery of potent and selective MMPIs. Here, we disclose a novel family of carboxylic acid-based α-sulfone inhibitors **4** with excellent enzyme potency and good selectivity over MMP-1. We will describe the enzyme SAR and highlight a potential binding mode with S_1' interaction in the MMP-9 homology model. The impact of the α-substitution of **4** on the MMP inhibitory activities will also be discussed.



Keywords: MMP inhibitors; MMP-9; MMP-2; α-sulfonylcarboxylic acids.
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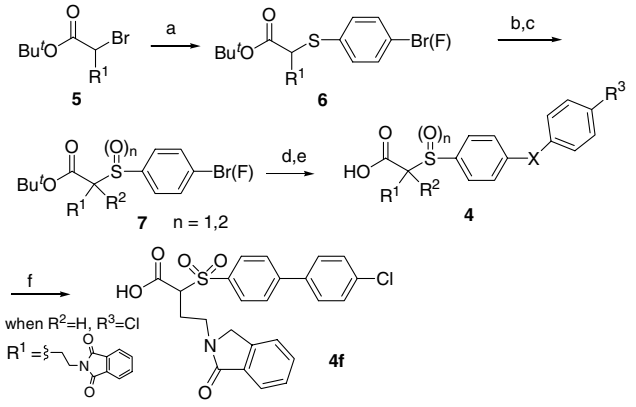
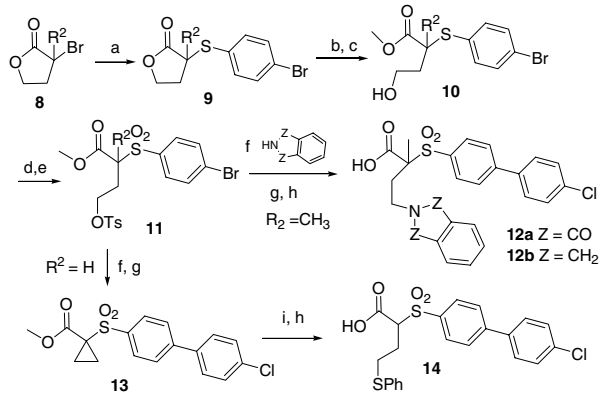
doi:10.1016/j.bmcl.2006.03.065



Scheme 1. Reagents and conditions: (a) HSPh(4-Br or -F), TEA, CH_2Cl_2; (b) OXONE®, MeOH/THF (1:1); (c) R^2Br, K_2CO_3, 18-crown-6(cat.), acetone, reflux; (d) i—when X = bond, (4-R^3)PhB(OH)$_2$, 5 mol% $Pd(PPh_3)_4$, Na_2CO_3 (2 M), toluene, 90 °C; ii—when X = acetylenyl, H–≡–Ph(4-R^3), 5 mol% CuI, 5 mol% $Pd(PPh_3)_2Cl_2$, TEA, 60 °C; iii—when X = O, (4-R^3)PhOH, K_2CO_3, DMA, 90 °C; iv—when X = –NR′R″–, HNR′R″-Ph(4-R^3), K_2CO_3, DMF, 90 °C; (e) TFA/CH_2Cl_2 (1:2); (f) Zn/$HgCl_2$, concd HCl, reflux.



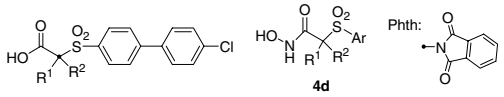
Scheme 2. Reagents and conditions: (a) HSPh(4-Br), TEA, CH_2Cl_2; (b) NaOH (1.0 equiv), DMF/H_2O (4:1); (c) MeI (1.5 equiv), $NaHCO_3$ (1.0 equiv), 18-crown-6 (0.1 equiv); (d) TsCl, TEA, CH_2Cl_2; (e) *m*-CPBA, CH_2Cl_2; (f) K_2CO_3, DMF; (g) (4-Cl)PhB(OH)$_2$, 5 mol% $Pd(PPh_3)_4$, Na_2CO_3 (2 M), toluene, 90 °C; (h) **12a**: 0.5 N HCl/AcOH (1:1), 100 °C; **12b**: aq LiOH, THF/MeOH; i—PhSH, NaOMe, toluene, 90 °C.

The carboxylic acid **4** was synthesized as shown in Scheme 1. Reaction of α-bromo *tert*-butyl ester **5**[7] with thiophenols gave sulfide **6**. Oxidation of **6** with OXONE® followed by alkylation at the acidic α-carbon with halides gave sulfone **7** ($n = 2$). α-Sulfinyl analogs **7** ($n = 1$) may be obtained by controlling the reaction time and equivalents of OXONE® used. Manipulation of aryl bromide or fluoride of **7** via various chemical transformations such as Suzuki coupling, Sonagishiro reaction, and simple displacement of fluorine with phenols or amines, followed by TFA deprotection of Boc, yielded a variety of carboxylic acids **4**. Further reduction of phthalimide **4** according to Hall's procedure[8] gave phthalimidine **4f**.

To rapidly explore the SAR of α-substitutions of **4**, an alternative synthesis from α-bromo lactone **8** was pursued which is outlined in Scheme 2. Displacement of the bromide **8** with 4-bromothiophenol gave **9**. The attempts of trans-esterification of lactone **9** into methyl ester **10** failed under various conditions. Finally, hydrolysis and alkylation with methyl iodide in one-pot reaction furnished **10**. Tosylation of **10** and subsequent oxidation gave **11**. The reaction of **11** with various nucleophiles, followed by Suzuki coupling and hydrolysis, yielded **12** (exemplified by **12a** and **12b**). α-Spiro sulfone **13** was obtained from **11** by base-promoted intramolecular cyclization. Further manipulation of electron-deficient cyclopropane **13** via Michael-type addition followed by hydrolysis gave the ring-opened product **14**.

Initially, as we fixed the P_1' moiety as a linear 4-chloro biaryl group, a series of α-sulfonylcarboxylic acids with diverse α-side chains were synthesized and their inhibitory activities were examined against MMP-2 and MMP-9 (Table 1). All compounds in Table 1 demonstrated moderate to potent activity against MMP-2. However, an amide or phthalimide side chain seems critical for MMP-9 inhibitory activity. Simple hydrophobic side chains (**4a** and **14**) gave no MMP-9 activity. Compounds **12a** and **12b** were compared, the absence of a carbonyl

Table 1. In vitro IC_{50} and SAR of α-substitution of compounds **4**



Compound	R^1	R^2	MMP-2[a]	MMP-9[a]
4a	–$(CH_2)_2CH_3$	H	792	10,005
14	–$(CH_2)_2$SPh	H	295	>10,000
4b	–CH_2Phth	H	556	1049
4c	–$(CH_2)_2$Phth	H	1.8	14
4d (HOHNOC–)	–$(CH_2)_2$Phth	H	0.62	1.4
4e	–$(CH_2)_3$Phth	H	145	2124
4f	See Scheme 1	H	8.6	96.5
12a	–$(CH_2)_2$Phth	–CH_3	52	114
12b	See Scheme 2	–CH_3	3060	>10,000

[a] IC_{50} (nM) the average value of at least two experiments.

functionality on **12b** resulted in no inhibition of MMP-9. Phthalimidine **4f** gave an IC_{50} of 8.6 nM on MMP-2 and about 7-fold loss of MMP-9 inhibition compared to **4c**. This observation was consistent with the reported work on β-sulfone hydroxamate inhibitors.[9] The length of the side chain was also important. The optimal ethyl phthalimido derivative **4c** was over 150-fold more potent than the propyl homolog **4e** and 75-fold more than methyl analog **4b**. Fully α-substituted **12a** gave 8-fold less potency against MMP-9 and about 30-fold less against MMP-2 than **4c**. This is in contrast to SAR observed on the reported α-sulfone hydroxamate MMPI.[2] Interestingly, different from previously reported α- and β-sulfone hydroxamate series,[2,3,9,10] there was only a 10-fold potency loss on MMP-9 and a 3-fold loss on MMP-2 by replacing the hydroxamate ZBG (**4d**) with the carboxylic acid (**4c**). This suggested that the novel α-sulfonylcarboxylic acid scafold provides optimal interactions with enzyme subsites and therefore compensates for the loss of potent bidentate bindings with zinc cation and hydrogen bond interactions with the enzyme backbones offered by hydroxamates.

Since an ethyl phthalimido group proved to be the most favorable P_1/P_2 substituent and thus was chosen as the benchmark, we turned our attention to SAR of the P_1' substituent. A series of P_1' modifications were performed and the results of in vitro MMP-2/-9 inhibitions are shown in Table 2. It appeared that at least one oxygen on the sulfur of **4** is required for better interaction with the enzyme backbone. The IC_{50} on MMP-9 for **4r′** (diastereomer mixture) was improved to 1.4 nM, 22-fold more potent than **4r″**, however, an additional oxygen of **4r** gave only slight improvement. The linear, rigid

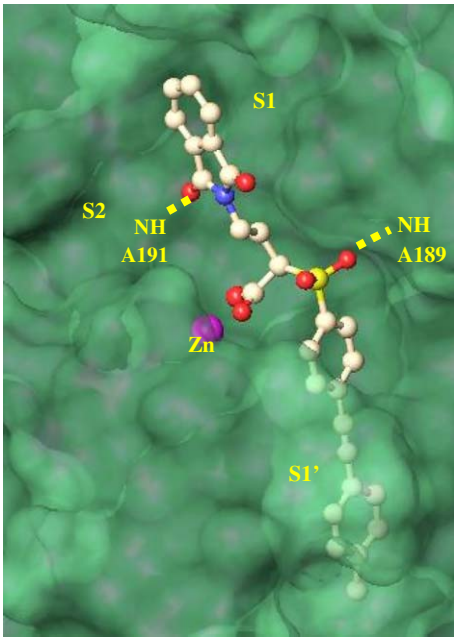
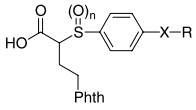
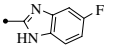


Figure 2. Compound **4r** docked in homology model of MMP-9.

Table 2. MMP IC_{50} and SAR of P_1' group of compounds **4**



Compound[a]	X	R	MMP-2[b]	MMP-9[b]
4c		(4-Cl)Ph–	1.8	14.0
4g		(4-OMe)Ph–	0.84	4.4
4h		(4-CN)Ph–	3.0	15
4i		(4-Me)Ph–	1.2	4.9
4j		(4-SMe)Ph–	0.74	0.96
4k		(4-^{i}Pr)Ph–	0.98	1.6
4l		(4-F)Ph–	6.5	53
4m		(4-CF_3)Ph–	4.4	20
4n[11]			0.7	1.8
4o	O	(4-OCF_3)Ph–	19	23
4p		(4-Cl)Ph–	12	258
4q		(4-CN)Ph–	6.8	120
4r		(4-Me)Ph–	0.7	0.5
4r′ ($n = 1$)		(4-Me)Ph–	1.5	1.4
4r″ ($n = 0$)		(4-Me)Ph–	33	31
4s		(4-Et)Ph–	1.3	0.8
4t		(4-^{n}Pr)Ph–	1.1	9.7
4u		(4-^{n}Bu)Ph–	2.3	22
4v		(4-^{i}Pr)Ph–	1.7	5.1
4w		(4-OCF_3)Ph–	1.3	0.6
4x		(4-Cl)Ph–	1.9	1.2
4y		(3-OMe)Ph–	4.0	25
4z[12]		(4-OMe)Ph–	54	101

[a] $n = 2$ for all compounds except indicated otherwise. **4r′** is a diastereomer mixture.
[b] IC_{50} (nM) the average value of at least two determinations.

Table 3. IC_{50}[a] values against selected MMPs of **4n** and **4r**

Compound	MMP-1	MMP-2	MMP-3	MMP-9	MMP-13
4n	>1000	0.7	34	1.8	0.8
4r	>1000	0.7	28	0.5	1.4

[a] IC_{50} (nM) value of single determination.

Table 4. Pharmacokinetic parameters[a] of **4c** and **4d** in rats and in vitro metabolism

Compound	C_0[b] (μM)	$T_{1/2}$[b] (h)	AUC[b] (μg-h/mL)	V_{ss}[b] (L/kg)	CL[b] (mL/min/kg)	HLM[c] $T_{1/2}$ (min)
4c	41.4	1.4	18.23	0.4	0.6	230
4d	13.9	0.98	2.94	0.1	2.9	12

[a] Mean value of four animals (rat) at 0.5 mg/kg iv dose.
[b] C_0: concentration at $T = 0$; $T_{1/2}$, apparent elimination half-life; AUC, area under the concentration-time curve; V_{ss}, volume of distribution at steady state; CL, systemic clearance.
[c] Human liver microsome.

P_1' groups such as biaryl or biaryl acetylenyl groups were preferred. More flexible linkers between two phenyl groups of P_1' resulted in loss of activity against MMP-9 (**4o**, **4p**, **4q**, and **4z**). The *para*-substitution on the terminal phenyl was preferred over substitution at the *meta*-position, 3′-OMe compound **4y** gave an IC_{50} value of 25 nM for MMP-9. Generally, hydrophobic, electron-donating substitutions on the terminal phenyl increased MMP potencies, for example, 4′-SMe on **4j** gave an IC_{50} value of 0.96 nM for MMP-9 and 0.74 nM for MMP-2. Polar, electron-withdrawing groups (EWG) such as –CN (**4h**), –F (**4l**), and $-CF_3$ (**4m**) shifted IC_{50} values to double-digit nanomolar range. However, compound **4n**, even with an EWG, fluorine, still gave excellent potency, illustrating benzoimidazole as an effective P_1' group. Longer biaryl acetylenyl groups as P_1' moiety were shown to be superior to biaryl groups for MMP-9 inhibition, although MMP-2 inhibitory activity was unchanged. Further variations on the terminal acetylenyl phenyl substitution were focused on hydrophobic, electron-rich groups based on the SAR of the biaryl P_1' series. The MMP-2 inhibitory activities of compounds **4r**–**4x** were insensitive to the length of the *para*-substituents. However, the methyl (**4r**) or ethyl (**4s**) derivatives have reached the maximal activities against MMP-9. The further elongation of the *para*-substitution leads to significant increase of the IC_{50} values of MMP-9. These results agreed with the same SAR trend of P_1' as the previously reported sulfonamide MMP inhibitors[13] and suggest a rigid, hydrophobic S_1' subsite with a floorboard at the bottom for MMP-9 and a tunnel-like S_1' subsite with an open bottom for MMP-2.

The binding mode of compound **4r** was proposed based on docking the molecule into a homology model of MMP-9 (Fig. 2). The modeling indicates that a linear biaryl acetylenyl group well fits into the S_1' pocket and the α-sulfonyl function forms a hydrogen bond interaction with Ala 189. The phthalimido side chain is located between the S_1 and S_2 pockets, and one of the carbonyls may form a hydrogen bond interaction with Ala 191. This may rationalize that an amide or imide side chain is critical for the maintenance of the activity. To our surprise, the modeling of **12b** (not shown here) indicated that the α-sulfonyl group no longer had any interactions with Ala 189 and the biaryl group does not fit well into the S_1' pocket. This may contribute to the loss in activity against MMP-9 for **12b**.

The selectivity across several MMPs of the representative compounds is summarized in Table 3. As expected, **4n** and **4r** showed high selectivity over MMP-1, which has a shallow S_1' subsite, and moderate selectivity for MMP-9 vs. MMP-3 (20- to 50-fold). The compounds **4n** and **4r** are also potent MMP-13 inhibitors.

The pharmacokinetics of carboxylic acid **4c** and its hydroxamate analog **4d** in rats are evaluated in Table 4. Human liver microsomes (HLM) were also used to predict metabolic stability. Both the AUC and C_0 were improved for carboxylic acid **4c**.

In summary, we have prepared a series of α-sulfone carboxylic acid inhibitors that are potent against MMP-2/-9 and selective over MMP-1. The SAR of both P_1' and P_1/P_2 has shown that a straight, hydrophobic P_1' group with the optimal length is preferred and an amido- or imido-type group is critical for MMP-9 inhibitory activity. The carboxylic acid series exhibits enhanced PK properties in rats compared to its hydroxamate analog. However, the protein binding data with highly lipophilic compounds such as **4r**, **4s**, and **4x** are greater than 99%, indicating that these carboxylic acids are highly protein bound in the blood and therefore faced a hurdle for further development. We are continuing to optimize P_1/P_2 group of the carboxylate inhibitors to minimize the high protein binding issue and hope to report the results in due course.

Acknowledgment

The authors thank the Chem/Bio Support group for ADME tests.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.03.065.

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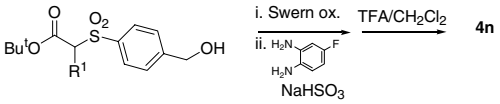
11. For the synthesis of **4n**:



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