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Orally bioavailable dual MMP-1/MMP-14 sparing, MMP-13 selective α-sulfone hydroxamates

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ABSTRACT

A series of phenyl piperidine α-sulfone hydroxamate derivatives has been prepared utilizing a combination of solution-phase and resin-bound library technologies to afford compounds that are potent and highly selective for MMP-13, are dual-sparing of MMP-1 and MMP-14 (MT1-MMP) and exhibit oral bioavailability in rats.

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The matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes that degrade all components of the extracellular matrix.[1,2] There are at least 24 isozymes in the MMP family, and they are roughly classified on the basis of their substrate specificity: collagenases (MMP-1, -8, -13 and -18), gelatinases (MMP-2, and-9), stromelysins (MMP-3, -10 and -11) and membrane-type MMPs (MMP-14, -15, -16, -17, and -24) and others (MMP-7, -11, -12, -19, -20, -21, -22, and -23). Clinical experience with the pan MMP inhibitor Marimastat has revealed a constellation of adverse effects collectively referred to as musculoskeletal syndrome (MSS).[3] We have hypothesized that this is predominantly a result of inhibiting both MMP-1 and MMP-14, and that MMP inhibitors sparing these two isozymes should be devoid of MSS.[4] Toward obtaining efficacy in mitigating damage suffered in osteoarthritic patients, it has been reported that MMP-13 mRNA levels are increased in osteoarthritic cartilage.[5] Thus, we envisioned the development of a selective inhibitor of MMP-13 sparing both MMP-1 and MMP-14 as a safe means of treating osteoarthritis (OA) which we refer to as the dual-sparing hypothesis.

In the preceding paper,[4] we demonstrated that the N-substituted phenyl isonipecotamide hydroxamic acid template **1** (Fig. 1) yielded potent and selective MMP-13 inhibitors. Figure 2 shows a sequence comparison for a set of MMP family members focused on the S_1' loop. There are differences in both amino acid identity and in length of the loop, as MMP-1, -2 and -9 are two residues shorter than MMP-13, -8 and -14. Interaction of the amide N-substituents of **1** deep in the S_1' pocket was expected to affect isozyme selectivity across the MMP family. In an effort to further investigate SAR in this region, we designed templates **2** and **3**, where the distal phenyl group resides in approximately the same region as the amide N-substituents of **1**. To explore the effect of substituents on the distal aryl rings of **2** and **3**, we undertook a parallel synthetic approach with the goal of optimizing MMP-13 potency and selectivity.

A solid-phase parallel synthesis approach was used to create a small library of *N*-arylpiperazine α-sulfone hydroxamic acid derivatives (**2**) from commercially available *N*-aryl piperazines **5**. Nucleophilic aromatic substitution of the previously reported polymer-bound aryl fluoride **4**[4] with *N*-arylpiperazines was found to require a 10-fold excess of **5** and presence of 2 equiv of cesium carbonate in *N*-methylpyrrolidinone (NMP) at 100 °C over night to achieve good conversions. Acidic deprotection with trifluoroacetic acid afforded α-sulfone hydroxamic acids **2** in good yields (Scheme 1).

Alternatively, a solution phase approach was developed to synthesize analogs with a basic amine in the α-heterocycle (**8**). THP-protected hydroxymate **7** was obtained by reaction of carboxylic acid **6** with THP-protected hydroxylamine using the water-soluble carbodiimide EDC.[6] Subsequent nucleophilic aromatic substitution

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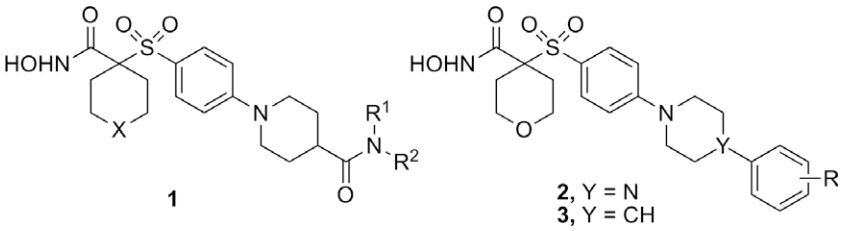


Figure 1. 4-Substituted piperidine/piperazine sulfone hydroxamic acids.

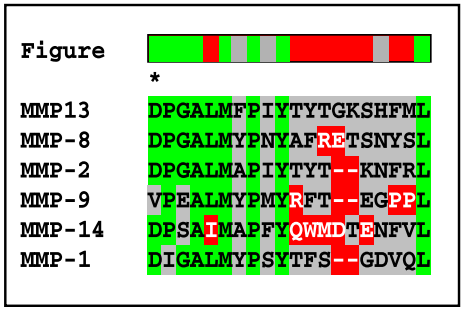


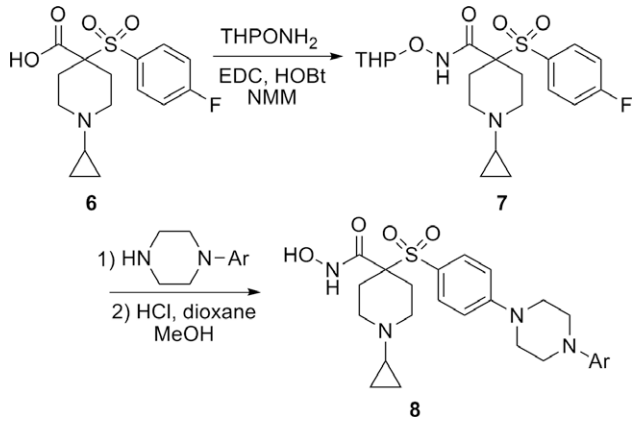
Figure 2. S_1' loop sequence variation across selected MMP family members.

with the requisite *N*-arylpiperazines followed by acidic deprotection afforded α-sulfone hydroxamic acids **6** in high yields.

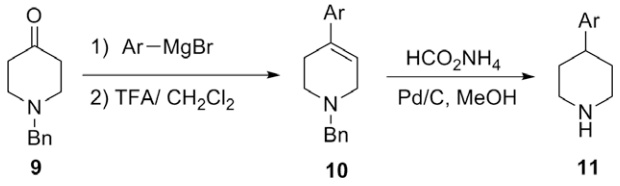
For the synthesis of 4-arylpiperidine phenyl sulfones **3,** the required 4-aryl piperidines **11** were purchased commercially or prepared either via the Grignard route (Scheme 3) or via Suzuki coupling (Scheme 4). For the Grignard route, similar to the method of Burns,[7] the appropriate aryl Grignard was added to *N*-benzyl piperidine-4-one followed by dehydration with TFA in methylene chloride. Reduction then gave 4-arylpiperidines **11.** Alternatively, enol triflate **12** was reacted with the requisite arylboronic acid with a catalytic amount of tetrakistriphenylphosphine palladium to afford *N*-Boc-4-aryl tetrahydropyridine **13**, following the procedure of Wustrow and Wise[8] (Scheme 2). Catalytic hydrogenation of **13** followed by removal of the *N*-Boc protecting group afforded 4-arylpiperidines **11.**

Assembly of the *N*-arylpiperidine sulfone hydroxamic acids **3** was accomplished by a solution phase approach (Scheme 5) similar to that described above. Carboxylic acid **14**[6] was coupled with THP-protected hydroxylamine, then aromatic nucleophilic substitution with **11** followed by acidic deprotection afforded α-sulfone hydroxamic acids **3** in good yields.

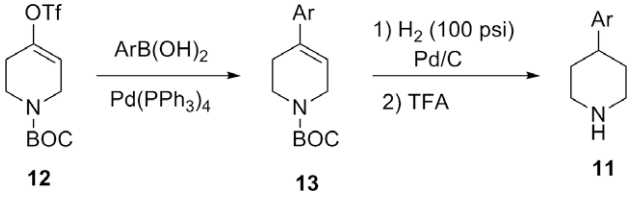
The MMP inhibitory potency values for *N*-aryl piperazine α-sulfone hydroxamic acids (**2** and **8**) are summarized in Table 1. All compounds were determined to have no measurable potency at MMP-1 (IC_{50} >10,000 nM), hence selectivity for MMP-13 over MMP-1 is >1000× in most cases. The *N*-aryl piperazines (**2a–2j** and **8a–8b**) exhibited mostly single-digit nanomolar potency for MMP-13, but most were also potent for MMP-2, resulting in only very modest selectivity for MMP-13 over MMP-2 with a number of compounds which were nearly equipotent. *N*-Phenyl piperazine **2a** was very potent for MMP-13 (IC_{50} = 1.7 nM) with a 14-fold selectivity versus



Scheme 2. Solution phase synthesis of *N*-arylpiperazine sulfone hydroxamic acids **8**.

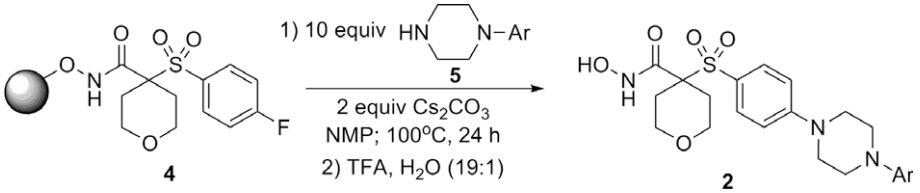


Scheme 3. Syntheses of 4-arylpiperidines via the Grignard route.

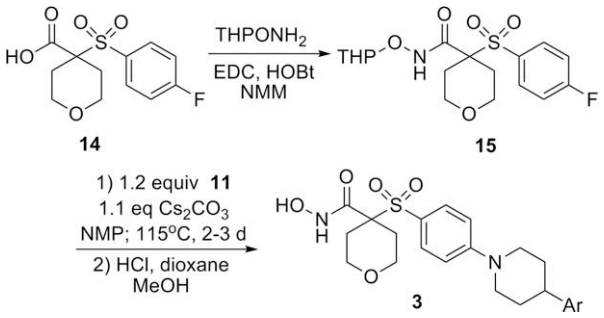


Scheme 4. Syntheses of 4-arylpiperidines via Suzuki coupling.

MMP-2, and nearly 6000-fold selectivity versus MMP-14, whereas the corresponding α-piperidine **8a** was nearly equipotent at MMP-13 and MMP-2 (IC_{50} = 3.3 and 5.4 nM, respectively.) The reduction in selectivity due to the change from X = O to X = *N*-cyclopropyl was unexpected given the continuity between α-tetrahydropyran



Scheme 1. Solid phase synthesis of *N*-arylpiperazine sulfone hydroxamates **2**.



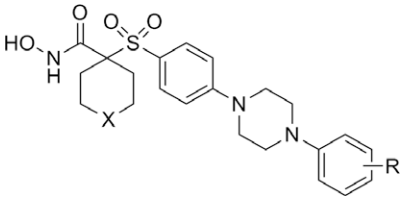
Scheme 5. Solution phase synthesis of 4-arylpiperidine sulfone hydroxamates.

and α-piperidine analogs in our earlier MMP-1 sparing series,[6] although this single pair does not necessarily constitute a trend. The *ortho*-fluorinated derivative **2b** exhibited similar potency to the *N*-phenyl parent **2a**, whereas the bulkier *ortho*-methyl and chloro derivatives **2c**–**2d** dropped five-fold in potency for MMP-13, and the *ortho*-methoxy derivative **2e** dropped 76-fold in potency. The *meta*-derivatives **2f** and **2g** suffered a similar loss in potency for MMP-13. On the other hand, *para*-substituted derivatives maintained high potency and selectivity for MMP-13, in particular *para*-methoxy derivative **2h** with an IC_{50} = 0.5 nM for MMP-13, a 40-fold selectivity versus MMP-2, and the highest selectivity observed versus MMP-14 (>20,000). *para*-Methyl and *para*-trifluoromethyl derivatives **2i** and **8b** exhibited good potency for MMP-13 (1.9 and 2.4 nM, respectively) and selectivity versus MMP-14 (both >4000×), noting that **8b** is an α-piperidine. The more sterically demanding 2,4-dimethylphenylpiperazine **2j** suffered a drop in potency at MMP-13 (IC_{50} = 28.6 nM), although selectivity against MMP-2 was the highest of all *N*-arylpiperazines at approximately 50×.

Table 2 shows MMP inhibitory potencies of 4-aryl piperidine α-sulfone hydroxamates (**3**). 4-Phenylpiperidine **3a** was 3× less potent at MMP-13 than *N*-phenylpiperazine **2a** but its potency for MMP-2 increased to 4.4 nM, making **3a** equipotent for MMP-13 and MMP-2. A substantial boost in MMP-13 selectivity was achieved by the presence of an *ortho*-methoxy substituent (**3b**). Potency of **3b** for MMP-13 dropped threefold from the parent compound (**3a**), while MMP-2 potency dropped 840-fold, generating a selectivity ratio of 211X. On the other hand, *para*-chloro analog **3c** was found to have an increased potency relative to parent compound **3a** at both MMP-13 and -2. The substantial effect of *ortho* substitution on selectivity prompted further evaluation of additional *ortho*-substituted analogs (**3d–i**). Generally, MMP-13 potencies were similar and reduced compared to **3a**, but IC_{50}'s for MMP-2 (and thus the MMP-2/13 selectivity ratio) corresponded approximately to the size of the substituent, with methoxy being optimal: H < Cl, OH < CH_3, CF_3 < OMe, OEt, 4-F–C_6H_4. The effect of an additional substituent was explored in an attempt to increase potency for MMP-13 while maintaining micromolar affinity for MMP-2. The 1-naphthyl derivative **3j** was slightly more potent than the *ortho*-methoxy analog **3b** at MMP-13, but potency at MMP-2 increased 7-fold. Other disubstituted analogs (**3k–n**) showed a similar trend, except for **3n** with a 2-methoxy and a 5-isopropyl substitution where MMP-13 potency dropped fourfold. Presumably the decreased affinity for MMP-13 was due to steric reasons. Comparison of the MMP-2/13 selectivity for *ortho*-methoxy substituted *N*-aryl piperazine **2e** (2.8-fold) with that of the 4-arylpiperidine analog **3b** (211-fold) is noteworthy. Presumably, **3b** adopts a conformation where the aryl group is orthogonal to the piperidine ring, evidenced by the substantial effect of *ortho*-substitution on selectivity. The energetic penalty for an *N*-aryl piperazine to adopt such a conformation would be high, which is likely responsible for the reduced potency of **2e** at MMP-13 and the increased potency at MMP-2 relative to **3b**.

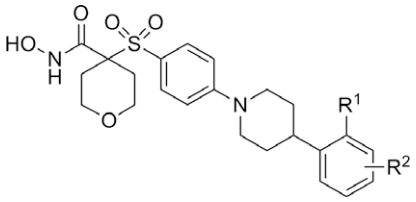
Based on the superior MMP-13 potency and dual MMP-1 and -14 sparing profiles of the *p*-substituted *N*-aryl piperazines, additional analogs were prepared for more thorough enzyme and PK evaluation (Table 3). Potent MMP-13 inhibition was observed for compounds **2l**, **2m** and **8c** with IC_{50}'s of 0.6, 1.0, 0.5 nM, respectively. Selectivity versus other MMP family members was generally ≫100-fold except for MMP-2 (4–20-fold) and MMP-3 (58–500-fold). Rat PK for these three compounds showed low to moderate values for half-life and bioavailability. Aryl piperazine **8c** had an acceptable BA of 20.7%, but a very short $t_{1/2}$ of only 0.24 h. Aryl piperidine **2l** exhibited a modest bioavailability of 16%, but a much improved half-life of 2.59 h, which we attribute to the trifluoromethylphenyl moiety in P_1', which has enhanced the PK of other series as well. 4-Chlorophenyl piperidine **2m** possessed a longer half-life but a disappointing BA of only 7.4%. Included for comparison is broader-spectrum, MMP-1 sparing α-sulfone **SC-276**.[6] Compound SC-276 lacks selectivity among MMPs, only significantly

Table 1
MMP inhibitory potency of *N*-aryl piperazine α-sulfones **2** (X = O) and **8** (X = N-*c*Pr)



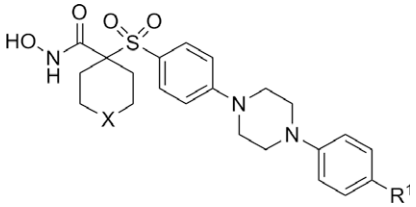
Compd	X	R	IC_{50} (nM) at MMP-X				Ratio MMP 2/13
			2	**9**	**13**	**14**	
2a	O	H	23.5	450	1.7	>10,000	13.8
2b	O	2-F	21.1	356	2.7	>10,000	7.8
2c	O	2-Me	88.0	2860	7.7	>10,000	11.4
2d	O	2-Cl	40	2090	9.0	>10,000	4.4
2e	O	2-MeO	370	—	130	—	2.8
2f	O	3-MeO	48.5	163	8.0	2860	6.1
2g	O	3-CF_3	330	—	20	—	16.5
2h	O	4-MeO	18.4	722	0.63	>10,000	29
2i	O	4-Me	35.0	682	1.9	8220	18.4
2j	O	2,4-diMe	1400	—	28.6	—	49.0
8a	N-*c*Pr	H	5.4	—	3.3	—	1.6
8b	N-*c*Pr	4-CF_3	32.6	>10,000	2.4	>10,000	13.6

Table 2
MMP inhibitory potency of *N*-aryl piperidine α-sulfones (**3**)



Compd	R^1	R^2	IC_{50} (nM) at MMP-X				Ratio MMP 2/13
			2	**9**	**13**	**14**	
3a	H	H	4.4	265	6.0	>10,000	0.7
3b	MeO	H	3700	6700	17.5	>10,000	211
3c	H	4-Cl	2.0	350	0.7	>10,000	2.9
3d	Cl	H	82	—	42.5	—	1.9
3e	Me	H	700	—	32.7	—	21.4
3f	CF_3	H	900	—	28.8	—	31.3
3g	EtO	H	3100	—	35.0	—	88.6
3h	OH	H	70	>10,000	11.3	>10,000	6.2
3i	4-F–C_6H_4	H	5400	—	33.7	—	160
3j	2,3-(CH=CH) (naphthyl)		500	2501	11.4	>10,000	43.9
3k	Me	4-MeO	505	>10,000	7	>10,000	72.1
3l	MeO	4-diMeO	1750	>10,000	11	>10,000	159
3m	MeO	5-diMeO	800	—	11.4	—	70.2
3n	MeO	5-*i*Pr	>10,000	—	70	—	143

Table 3
MMP inhibitory potency of *N*-aryl piperazine α-tetrahydropyranyl sulfone hydroxamates **8c** and **2** compared with **SC-276**



Compd	X	R^1	IC_{50} at MMP-X (nM)								*c*Log *P*	C_{max}	C_{6h}	$t_{1/2}$ (h)	BA (%)
			1	2	3	7	8	9	13	14					
2l	O	CF_3	>10000	12.1	300	>10000	670	5000	0.6	>10000	1.76	4210	10	2.59	16.3
2m	O	Cl	>10000	3.7	130	—	1000	270	1.0	5000	1.46	49	36	1.91	7.4
8c	*c*Pr-N	OCH_3	>10000	5.3	24.5	—	59.2	729	0.42	>10000	1.32	751	19	0.24	20.7
SC-276[a]			8660	0.33	13.0	>10000	1.8	1.5	0.40	19	2.04	13630	281	1.1	28

[a] Data for **SC-276** from Ref. 6, except for MMP-7 and MMP-14 were not previously reported.

sparing MMP-1, yet this compound has the very high exposure in the rat that is compelling for development, consistent with its potent and efficacious antitumor activity.[6]

In summary, the related series of compounds described herein have demonstrated single-digit to sub-nanomolar potency for MMP-13 combined with exceptional selectivity versus MMP-1 and MMP-14 of typically >100× up to 20,000×. Selectivities versus other MMPs when tested varied for MMP-3 (40–500×), MMP-8 (140–2500×) and for MMP-9 (20 to >4000×). Selectivity for MMP-13 over MMP-2 ranged from equipotency to 200×, thus selectivities were somewhat lower relative to the related isonipecotate α-sulfone hydroxamate series.[4] Rat PK for selected members of these series demonstrated bioavailabilities of up to 20.7% (**8c**) and a half lives of up to 2.6 h (**2l**) yet individual compounds lacked a compelling complete package to initiate development. Undoubtedly the high molecular weights of these analogs (551 a.u. for **2m**) plays a role given the recommendations of Lipinski although the limited number of rotatable bonds[9] favors the limited bioavailability that was observed. We therefore turned our attention to lower molecular weight species, while applying our learnings about P_1' manipulations toward optimizing MMP-13 selectivity.

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