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MMP-13 selective α-sulfone hydroxamates: A survey of P1′ heterocyclic amide isosteres

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ABSTRACT

Seeking compounds preferentially potent and selective for MMP-13, we reported in the preceding Letter on a series of hydroxamic acids with a flexible benzamide tail groups.[1a] Here, we replace the amide moiety with non-hydrolyzable heterocycles in an effort to improve half-life. We identify a hydroxamate tetrazole **4e** that spares MMP-1 and -14, shows >400-fold selectivity versus MMP-8 and >600-fold selectivity versus MMP-2, and has a 4.8 h half-life in rats. X-ray data (1.9 Å) for tetrazole **4c** is presented.

Matrix metalloproteinases (MMPs) are a family of about 27 zinc-dependent enzymes responsible for the turnover of collagen in connective tissue. There are a variety of disease states where degradation of collagen contributes to the pathology, specifically, in osteo- and rheumatoid arthritis; in tumor angiogenesis and metastasis; and in post-MI cardiovascular remodeling. In the previous Letter,[1a] we note that joint-stiffening, 'musculoskeletal syndrome' (MSS), upon prolonged dosing with MMP inhibitors (MMPi's) has prevented approval of an MMPi. Efforts have been made to spare the MMP isozymes that are thought to contribute to MSS, specifically, MMP-1 and -14 (MT1-MMP) (**SD-2590**, Fig. 1),[1b] but a more focused approach toward realizing efficacious MMP inhibitors with reduced side effects should be to focus on optimizing a single MMP isozyme that confers the most therapeutic benefit, reducing the probability of off-target protease binding. MMP-13, upregulated in osteoarthritic joints and in cancer, is an attractive isozyme to target, and structural studies show that -13 differs from other MMP's deep in the S1′ pocket, suggesting that inhibitors that extend further into the S1′ pocket may confer selectivity.

With this in mind, we elaborated a series of rigid piperidinoketones (compound **2**, Fig. 1) with lengthier P1′ subunits and, with optimization, we were able to achieve significant selectivity for MMP-13 versus other MMP isozymes.[2] Conceptually dissecting the piperidine ring in compound **2**, we also wanted to explore acyclic-chain analogs such as amide **3** (Fig. 1).[1,3]

While excellent MMP-13 selectivity (Table 1) was achieved with a number of amides related to compound **3**, the amides displayed short half-life in rats, presumably due to hydrolytic cleavage of the amide bond. In an effort to prepare compounds with suitable selectivity and PK, we incorporated the SAR findings from the acyclic amide series into a small series of compounds where the amide is replaced by isosteric heterocycles. This Letter summarizes that effort.

Among the isosteres we wanted to consider were tetrazoles.Entry into this series began by alkylating the requisite 5-phenyl-1*H*-tetrazoles (e.g., **5**, Scheme 1) using *O*-tetrahydropyranyl-3-chloropropanol. Alkylation afforded predominantly the desired 2-isomers for 5-[4-methoxyphenyl]- and 5-[4-trifluoromethoxyphenyl]-tetrazole, and the products were purified by chromatography. The THP

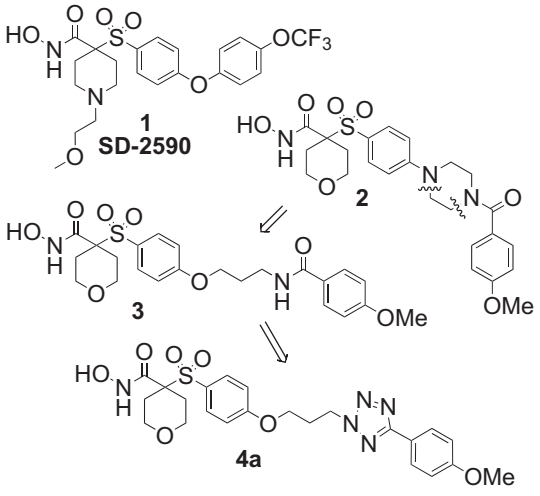

Figure 1. MMP inhibitors. Compound **1** (**SD-2590**) spares MMP-1; compounds **2**, **3**, and **4a** are MMP-13 selective.

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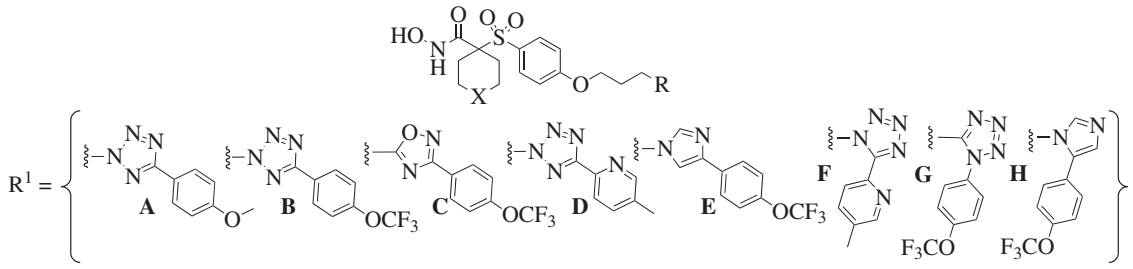
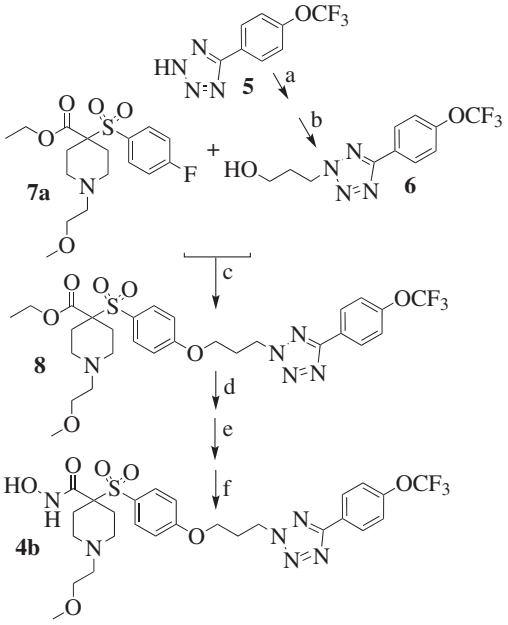
Table 1
Selectivity and PK of heterocyclic MMP-13 selective analogs

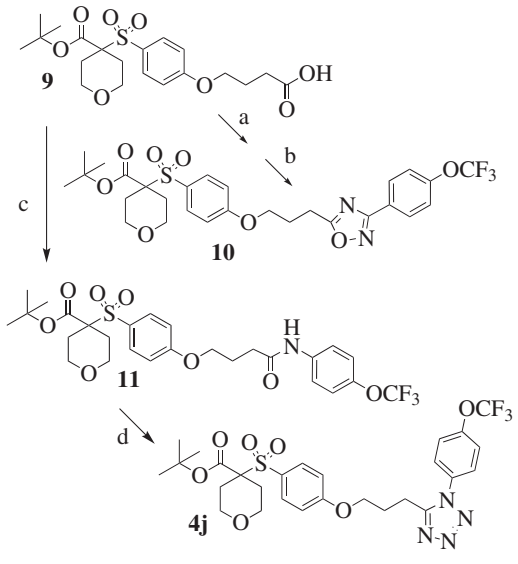


Compd #[b,c]	*R*	hMMP inhibition K_i (nM)[a]						BA	$t_{1/2}$	Rat PK C_{max} (ng/ml) (MPK)	Cl (ml/min/kg)
		−2	−3	−7	−8	−9	−13				
1	N/A	<0.1[c]	29[c]	7000	1.7[c]	0.2[c]	<0.1[c]	68	2.9	21,900 (20)	–
2	N/A	1300[c]	90[c]	>10k[c]	1200[c]	1200[c]	0.70[c]	14	1.2	4200 (20)	–
3	N/A	550	900	–	900	>10k	1.6	1.5	0.59	0.02 (20)	–
4a	A	48[c]	39[c]	–	190[c]	1100[c]	0.20[c]	–	–	–	–
4b	B	410	28	>10k	170	1200	0.66	32	2.4	61 (1.5)	12
4c[b]	B	230	8.7	8600	80	160	0.13	26	1.3	1400 (20)	
4d	D	110	44	3000	240	2400	0.66	1.7	2.0	3500 (50)	46
4e	F	400	3.0	970	250	430	0.60	5.0	4.8	3000 (5)	63
4f	C	410	31	>10k	180	1600	1.5	22	1.4	240 (20)	14
4g[b]	C	410	37	>10k	260	370	2.0	28	2.4	2200 (20)	19
4h	E	530	59	6000	74	1800	1.7	–	–	–	–
4i	H	9200	130	>10k	140	>10k	3.7	–	–	–	–
4j	G	430	9.9	7100	72	1700	1.2	7.3	4.0	3500 (5)	42

[a] MMP-1 and -14 >10k nM except for **1** (MMP-14 = 14 nM), and **4a**, **4d** (MMP-1 = 5600, 3700 nM).
[b] For **4a–k,** X = O except: **4c**, where X = NCH_2CH_2OMe and **4g**, X = NCH_2CH_3
[c] IC_{50} instead of K_i.



Scheme 1. Reagents and Conditions: (a) NaH (2.1 equiv), NMP, rt; then 2-(3-chloropropoxy)tetrahydro-2*H*-pyran (1.1 equiv) rt to 70 °C (45%) (b) AcCl (3.8 equiv), MeOH, rt (94%) (c) **6** (1.05 equiv), NaH (1.1 equiv), NMP, 55 °C, 1 h (70%) (d) NaOH (50% aq, 10 equiv), THF, EtOH, rt to 60 °C, then acidify w/HCl, concn, azeotrope CH_3CN (e) triethylamine (XS), HOBT, $THPONH_2$ (1.5 equiv), EDC (1.5), DMF, 40 h (65%) (f) AcCl (4 equiv), MeOH (74%).



Scheme 2. Reagents and Conditions: (a) DMF, HOBT (1.4 equiv), triethylamine (1.2 equiv), 4-(trifluoromethoxy)-benzamideoxime (1.2 equiv), EDC (1.5 equiv), rt, 2 h (b) toluene, 90 °C, 30 h (c) HOBT (1.3 equiv), 4-(trifluromethoxy)aniline (1.3 equiv), EDC (1.33 equiv), DMF, rt, 4 h (80%); (d) PPh_3 (2.0 equiv), dioxane; then DEAD (2.0 equiv); then TMS–N_3 (2.0 equiv), rt, 16 h (66%).

protecting group could be removed with acid and the product alcohol (e.g., **6**) reacted with the known aryl fluoride **7**.[1] The *t*-butyl ester **8** was cleaved and the resulting carboxylic acid reacted with *O*-tetrahydropyranyl hydroxylamine in the presence of EDC. Removal of the THP gave the desired hydroxamic acids **4b**. In the case of 5-[4-methyl-2-pyridyl]-tetrazole,[4] alkylation gave a 3:2 mixture, still favoring the 2-position. The lack of selectivity in this alkylation step afforded us the opportunity to isolate meaningful quantities of both 2- and 1- isomers and to carry the isomers individually on to final product (**4d** and **4e**, Table 1).

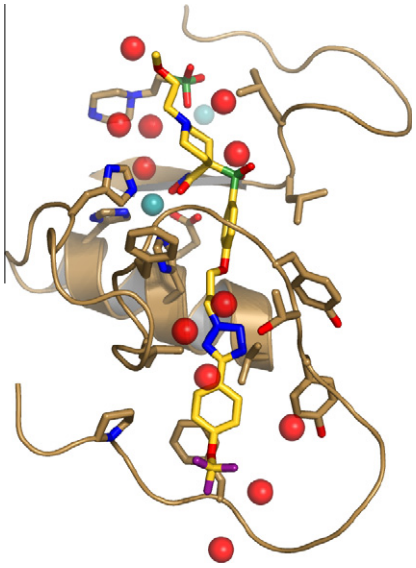


Figure 2. Structure of MMp-13 with compound **4c** bound at the catalytic site. The inhibitor binds deeply within the S1′ pocket of the active site and causes a conformational change opening the loop to accommodate the compound. A HEPES buffer molecule bound adjacent to the inhibitor in two of the four protein molecules in the crystals and an array of solvent atoms (red spheres) form an auxiliary van der Waals surface between the inhibitor and the protein.[6]

Oxadiazoles (e.g., **4f**, Table 1) were prepared by combining the known acid **9**[1] and 4-(trifluoromethoxy)benzamidoxime in the presence of EDC, then heating the coupled product to close the ring. After condensation of the oxadiazole, the *t*-butyl ester (**10**, Scheme 2) was carried on to the hydroxamic acid employing the same transformations used for the tetrazoles. Imidazoles **4h** and **4i** were made by unselective alkylation of the required 4- and 5- phenyl imidazoles.

From the data presented in Table 1, we see that the amide in the MMP-13 selective lead compound **3** (Table 1) could be replaced with various aryl heterocycle combinations: aryl-tetrazoles (**4a–d**); -oxadiazoles (**4f,g**); and -imidazoles (**4h**) affording hydrolytically stable analogs with impressive selectivity for MMP-13 versus MMP-1, -2, -7, -8, -9, and -14. Unexpectedly, we found that the 1,5-isomer of the pyridyl analog (**4e**) has a selectivity profile very similar to its 2,5-substituted isomer (**4d**). These results inspired us to make a similarly disposed imidazole (**4i**) and an isomeric 1,5-substituted tetrazole (**4j**), where the tetrazole carbon connects to the acyclic chain instead of the tetrazole nitrogen[5] (Scheme 2). Both compounds were highly selective.

In the course of our research, we solved a 1.9 Å resolution crystal structure of tetrazole **4c** (Fig. 2).[6] The structure illustrates the depth of the MMP-13 S1′ pocket, which is distinct from other MMP family members such as MMP-1 and MMP-2, which have shallower pockets. The hydroxamate chelates zinc at two positions and makes a hydrogen bond to Glu223. One of the sulfone oxygens interacts with the protein backbone. The tetrazole group forms a single direct hydrogen bond to the peptide at Thr245 (3.0 Å); the remainder of the side chain interactions with the protein are van der Waals contacts. The S1′ pocket of MMP-13 is presumably able to flex to accommodate inhibitors of various sizes and shapes, such as the isomeric aryl heterocycles **4e**, **4i**, and **4j**. This crystal structure adds to the body of structural knowledge within this important class of proteinases.

We achieved the primary goal of this project, to improve on the 0.59 h half-life we measured for the lead amide compound **3**. We see in Table 1 heterocyclic compounds with half-lives ranging from 1.4 to 4.8 h; compounds having good BA (e.g., tetrazole **4c**, 26%; and oxadiazole **4f**, 28%); and analogs with encouraging C_{max} values. Based on our data, we believe selected heterocyclic analogs in this Letter will be promising drug candidates for the treatment of arthritis, cancer, and post-MI left ventricular hypertrophy (CHF), as we will report in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.03.099.

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6. Coordinates have been deposited in the protein data bank (accession code 3O2X). Crystallographic conditions are detailed in the Supplementary data.