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Design and Synthesis of 2-Oxo-imidazolidine-4-carboxylic Acid Hydroxyamides as Potent Matrix Metalloproteinase-13 Inhibitors

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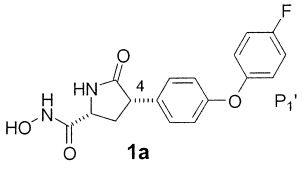
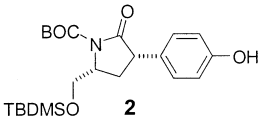
Abstract—A novel series of imidazolidinone-based matrix metalloproteinase (MMP) inhibitors was discovered by structural modification of pyrrolidinone **1a**. Potent inhibition of MMP-13 was exhibited by the analogues having 4-(4-fluorophenoxy)phenyl (**4a**, $IC_{50} = 3$ nM) and 4-(naphth-2-yloxy)phenyl (**4h**, $IC_{50} = 4$ nM) as P1′ groups.

Inhibitors of matrix metalloproteinases (MMPs) have great potential for the treatment of a variety of diseases including arthritis and cancer.[1] We recently described the structure-based design and synthesis of **1a** (Table 1), a potent and novel MMP-13 inhibitor.[2] This compound utilizes a pyrrolidinone ring as a scaffold for correct orientation of groups that bind to the enzyme: a hydroxamic acid for chelation of the active site zinc atom, a 4-(4-fluorophenoxy)phenyl P1′ group for interaction with the hydrophobic S1′ pocket and a *cis* amide group to establish hydrogen bonds with main chain atoms flanking the active site. Here, we describe the discovery of a new series of MMP inhibitors based on **1a** that incorporates an imidazolidinone ring as an alternative scaffold.



1a



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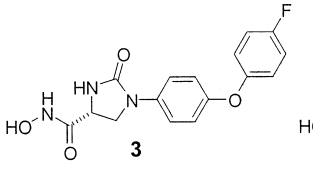

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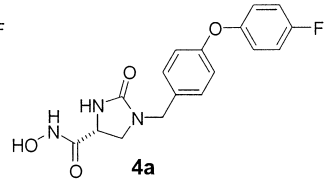

4a

Although **1a** is stable in neutral or mildly basic media, epimerization of the relatively acidic C4 position under moderately basic conditions (e.g., alkoxide) limits the scope of chemistry that can be employed for the synthesis of analogues. For example, formation of appreciable amounts of the *trans* diastereomer[3] occurs during alkylation of the OH group of intermediate **2** using a variety of bases. An intriguing possibility for avoiding epimerization at C4 was to replace this center with a nitrogen atom giving the corresponding imidazolidinone (e.g., **3**). However, based on modeling studies using a homology model of MMP-13,[2] it was clear that P1′ groups would no longer be oriented correctly for occupancy of the S_1' pocket due to the planar geometry of the cyclic urea function. We therefore considered compounds such as **4a** in which a methylene spacer was introduced to allow greater flexibility of the P1′ side chain. Indeed, modeling of **4a** in the active site of MMP-13 showed that this molecule could attain a low

Table 1.[a]

Compound	MMP IC_{50} (nM)				
	1	2	3	9	13
1a	1560 (120)	39 (17)	700 (170)	82 (16)	7 (1)
4a	5450[b]	28 (9)	1380 (330)	62 (13)	3 (1)
4h	12,700[b]	59 (37)	940 (310)	56 (24)	4 (2)[c]

[a]Values are ±SD of 3 determinations unless otherwise noted.
[b]$n = 2$.
[c]$n = 4$.

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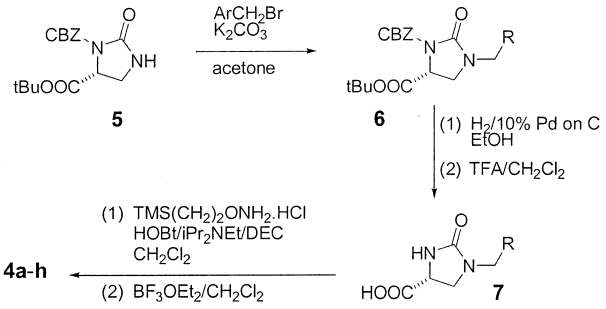
energy conformation positioning the 4-fluorophenoxyphenyl group deep within the S1′ pocket while maintaining important contacts made by the hydroxamic acid and *cis* amide functions.

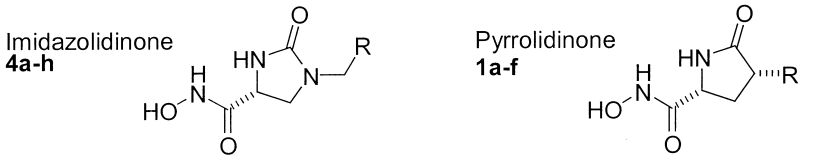
The synthesis of **4a** and analogues (**4b**–**h**, Table 2) was carried out in five steps from the readily available 2-oxo-imidazolidine-4-carboxylic acid derivative **5**[4] (Scheme 1). Alkylation of **5** with benzyl bromide derivatives[5] took place smoothly, albeit slowly, to provide **6** (~75 %). Sequential removal of the CBZ and *tert*-butyl ester protecting groups afforded acid **7** (~60% for the two steps). Finally, formation of the (2-trimethylsilylethoxy)amide and deprotection using $BF_3{\cdot}OEt_2$ introduced the hydroxamic acid function to provide **4a** and analogues (~25% for the two steps). In terms of synthesis, the imidazolidinones have clear advantages over the pyrrolidinone series: easily obtained starting materials, fewer steps and reduced potential for loss of stereochemical integrity. As a result, the synthesis offered the possibility for rapidly exploring a range of different P1′ groups to optimize activity against MMP-13 and related metalloenzymes (e.g., MMP-2 and MMP-9).

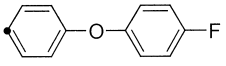
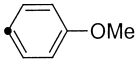
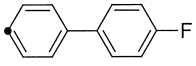
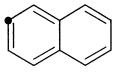
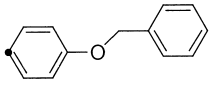
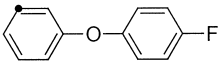
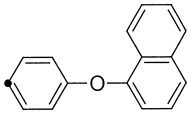
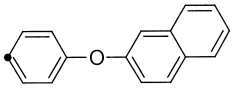
Upon testing, we were pleased that **4a** exhibited potent activity against MMP-13 ($IC_{50} = 3$ nM, Table 1). The compound also displayed moderate potency against MMP-2 and MMP-9 but was significantly less active against MMP-1 and MMP-3. Overall, the activity profile of **4a** against the various MMPs closely resembled that of **1a**. As in the pyrrolidinone series, the weak activity against MMP-1 was considered advantageous in light of side effects attributed to MMP-1 inhibition in vivo.[6]



Scheme 1.

Table 2.[a]



Compound	R	MMP-1 IC_{50} (nM)		MMP-13 IC_{50} (nM)	
		Imidazolidinone[b]	*Pyrrolidinone*	*Imidazolidinone*	*Pyrrolidinone*
a		5450	1560 (120)	3 (1)	7 (1)
b		388	8040 (2410)[c]	281 (60)	1480 (570)[d]
c		25,900	6430 (2340)	331 (65)	182 (20)
d		> 30,000	> 30,000	1590 (380)	3450 (210)
e		> 30,000	> 30,000	123 (41)	946 (340)
f		> 30,000	> 30,000	214 (15)	4760 (580)
g		8020		825 (64)	
h		12,700		4 (2)[c]	

[a]Values are ±SD of 3 determinations unless otherwise noted.
[b]$n = 2$.
[c]$n = 4$.
[d]$n = 5$.

Analogues **4b**–**h** were prepared to probe the MMP-1 and MMP-13 SAR around P1′. In the case of **4a**–**f**, comparison to the P1′ SAR in the pyrrolidinone series (**1a**–**f**) could be made and, with the exception of **4c**, all exhibited modestly increased MMP-13 inhibition relative to the corresponding pyrrolidinones. Most striking is the 3-(4-fluorophenoxy)phenyl analogue **4f** which is over 20-fold more potent against MMP-13 than **1f**. We believe the overall improved MMP-13 potency of the series is a consequence of the greater flexibility permitted by the methylene spacer linking the imidazolidinone scaffold and the P1′ group. This flexibility allows productive binding conformations to be more easily attained. Like the pyrrolidinones, the imidazolidinones are selective for MMP-13 over MMP-1 although in the case of **4b**, the selectivity is very slight ($\sim$1.4). This results from relatively potent inhibition of MMP-1 and is consistent with the general preference of MMP-1 for small hydrophobic P1′ groups.

Despite the overall improved MMP-13 potency of the imidazolidione series relative to the pyrrolidinones, **4b**–**g** are nonetheless relatively weak inhibitors of MMP-13 in comparison to **4a** and **1a**. In sharp contrast to **4b**–**g**, the 4-(naphth-2-yloxy)phenyl analogue **4h** displays potent MMP-13 inhibition ($IC_{50} = 4$ nM). This compound was tested against MMP-2, MMP-3, and MMP-9 giving an inhibition profile against the various MMPs similar to that of **4a** (Table 1). Modeling of **4h** in the active site of MMP-13 shows a high degree of complementarity between the 4-(naphth-2-yloxy)phenyl group and the S1′ pocket.

In summary, we have discovered a novel series of imidazolidinone-based MMP inhibitors by structural modification of pyrrolidinone **1a**, a potent inhibitor of MMP-13. The imidazolidinone scaffold was explored as a strategy for avoiding the epimerization at C4 observed during the synthesis of analogues of **1a**. As in the pyrrolidinone series, the most potent inhibition of MMP-13 was exhibited by the analogue having a 4-(4-fluorophenoxy)-phenyl P1′ group (i.e., **4a**). Potent MMP-13 inhibition was also shown by the P1′ 4-(naphth-2-yloxy)phenyl analogue **4h**. The lack of a relatively acidic chiral center susceptible to epimerization and the comparative ease of synthesis establish the imidazolidones as an attractive new series for the continued pursuit of MMP inhibitors as drugs.

Acknowledgements

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References and Notes

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3. The *trans* diastereomer of **1a** was much less active than **1a** as an inhibitor of MMP-13.[2]
4. The *S*-enantiomer of **5** is known: Shiba, T.; Koda, A.; Kusumoto, S.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2748.
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