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Potent, selective spiropyrrolidine pyrimidinetrione inhibitors of MMP-13

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Abstract—Explorations in the pyrimidinetrione series of MMP-13 inhibitors led to the discovery of a series of spiro-fused compounds that are potent and selective inhibitiors of MMP-13. While other spiro-fused motifs are hydrolytically unstable, presumably due to electronic destabilization of the pyrimidinetrione ring, the spiropyrrolidine series does not share this liability. Greater than 100-fold selectivity versus other MMP family members was achieved by incorporation of an extended aryl–heteroaryl P1′group. When dosed as the sodium salt, these compounds displayed excellent oral absorption and pharmacokinetic properties. Despite the selectivity, a representative of this series produced fibroplasia in a 14 day rat study.

In an effort to identify new compounds that can modulate the progression of osteoarthritis (OA), our group has focused on inhibitors of MMP-13.[1–11] In many respects, MMP-13 appears to be an ideal point of therapeutic intervention in this debilitating disease. Not only is MMP-13 present in human OA cartilage,[12] and co-localized with cleaved type II collagen,[13] but it also degrades both type II collagen and cartilage.[14,15] An agent that could slow or stop this process has been the ultimate goal of many research groups over the last two decades.[16–25]

Although a number of MMP inhibitors have been advanced into clinical trials, the results of these studies have been disappointing. The most consistent clinical finding has been the observation of musculoskeletal syndrome (MSS).[6,26,27] This side effect is observed as significant joint stiffening, which is reversible when dosing is interrupted. It is reasonable to suggest that this effect is due to the inhibition of normal extracellular matrix turnover, possibly due to inhibition of MMPs other than MMP-13. To test this hypothesis, we began a research program that was distinct from our earlier efforts in this disease area,[6] one designed to discover potent MMP-13 inhibitors at least 100× selective against a panel of related MMPs.[1]

Recent publications by several groups, including ours, have described the utility of the pyrimidinetrione as a zinc binding moiety.[1,2,20,21] As described by Reiter et al., extension of a long, lipophilic P1′substituent in conjunction with the proper placement of heteroatoms can produce compounds which meet our selectivity criteria for development candidates. In a parallel effort, a series of related spirocyclic analogs were also investigated (Fig. 1).[28]

Keywords: Pyrimidinetrione; Matrix metalloprotease; MMP-13; Collagenase-3.
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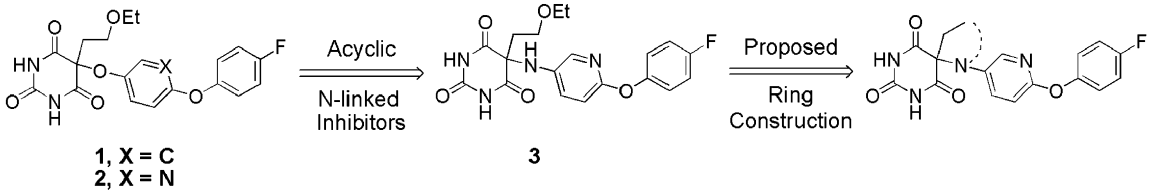


Figure 1. Sequential acyclic nitrogen replacement analogs, and proposed cyclization strategy.

A cyclic design would not be possible with a divalent oxygen atom as a point of attachment, and would require a nitrogen atom link to the pyrimidinetrione. Thus, our first objective was to explore sequential, single atom changes to understand their separate effects on potency and selectivity.

The single change of nitrogen for carbon at position X, **1** versus **2** (Table 1), showed a distinct drop in potency, and reduced MMP-12 selectivity relative to compound **1**.[29] The threefold improvement in potency of diaza analog **3** (over **2**) demonstrated that a nitrogen link was compatible with potent MMP-13 activity and encouraged us to pursue the proposed N-linked spirocyclic derivatives.

The first cyclic variant examined was spiro-lactam **4** (Table 2),[30] a compound that is structurally similar to a series of spirocyclic lactams that have since been disclosed by a research group at Bristol-Myers Squibb. The potency of this compound corroborated their earlier reported findings.[20] The fact that **4** and **3** were roughly equipotent and showed similar selectivity confirmed the original hypothesis that changing from an acyclic to a cyclic linker could be a productive strategy. While these compounds had lost 5–6× potency relative to the original ethoxyethyl analog **1**, a larger problem of solution stability with the spirocyclic lactam systems was discovered. Exposing these analogs to PBS (pH 7.2) at 25 °C caused rapid decomposition of the parent analog ($t_{1/2}$ = 3.8 days). We reasoned that the decomposition could be due to lactam ring opening, and thus examined a range of other possible spirocyclic motifs (Table 2).

Unfortunately, most of these systems were less potent than lactam **4**. Changing the lactam to a cyclic sulfonamide produced compound **5**, which was approximately 40-fold weaker than the original lactam. Substitution of the original five membered lactam with *gem*-dimethyl groups gave **6** which was twofold weaker than the unsubstituted lactam. These analogs were also less stable in solution that the original lactam. The addition of a single methylene unit to form the six membered lactam **7** resulted in a threefold drop in potency. Both methylated and unsubstituted cyclic ureas (**8** and **9**) were fivefold less potent.

Table 1. MMP-13 potency and selectivity for acyclic nitrogen replacement analogs

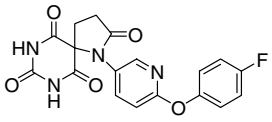
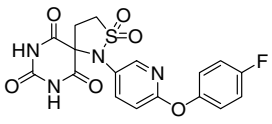
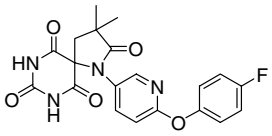
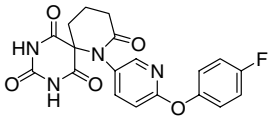
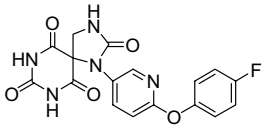
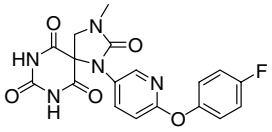
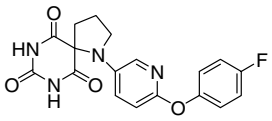
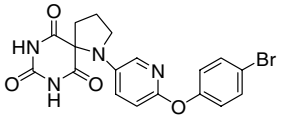
Compound	MMP-13 IC_{50} (nM)	MMP-2 selectivity (X-fold)	MMP-12 selectivity (X-fold)
1	0.6	8.3	46.5
2	8.9	16.6	7.1
3	2.9	14.7	10.7

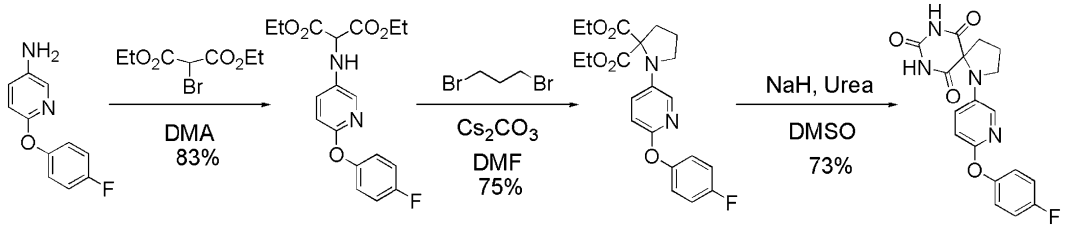
Since compounds **5** and **6** were less stable in solution than the original lactam, we considered the possibility that the solution instability was due to pyrimidinetrione ring opening which would be enhanced by the presence of electron withdrawing groups (e.g., lactam, sulfonamide). To test this idea, spirocyclic pyrrolidines were prepared as shown in Scheme 1. Reaction of aminopyridines with bromodiethylmalonate produced alkylated aniline derivatives. These could be cyclized to pyrrolidines by treatment with 1,3-dibromopropane and cesium carbonate in DMF. The 2,2′-dicarboxyethyl pyrrolidines could then be converted to the corresponding pyrimidinetrione by treatment with urea and sodium ethoxide.

The spiropyrrolidine series was found to be stable in solution ($t_{1/2}$ > 1000 days, for **10b** tested as a surrogate for **10a**), which supported our hypothesis that electronic destabilization of the pyrimidinetrione caused solution instability. While slightly less potent than acyclic analog **1**, **10a** was more potent than any other nitrogen-linked analog (cyclic or acyclic) containing a simple terminal fluorine atom. In the overall comparison of **1** and **10a**, the slight drop in potency (2×) was reasonably balanced by a slight drop in lipophilicity (clog *P* drops by ~0.25 U), providing opportunity for further optimization. While the pyrrolidine did not display an inherent improvement in selectivity, we felt that optimization to improve selectivity by extension of the P1′group, and the proper placement of heteroatoms within that extended tail was possible.

To this end, the fluorine atom at the terminal phenyl ring was replaced by more elaborate aryl–heteroaryl systems which had already provided potent and selective inhibitors of MMP-13 in related, acyclic phenyl oxazole[1,31] and benzimidazole systems.[32] In these compounds, the spirocyclic pyrrolidine modification gave modest (5–10×) increases in potency, relative to the acyclic, oxygen-linked analogs (Table 3). In general, high levels of selectivity observed in the acyclic analogs for MMP-12 and MMP-8 translated to comparably high levels in the spirocyclic pyrrolidine system.[33,34] This was not surprising, since the extended P1′group in this system should be positioned to contact the same variable loop at the base of the S1′pocket which is likely responsible for the observation of selectivity in the acyclic system.[1] Unfortunately, the same was not true for MMP-2 selectivity. MMP-2 selectivity was somewhat compromised in the spirocyclic analogs. In several cases (see compounds **14**, **16**, and **20**) the selectivity ratio

Table 2. Various spirocyclic linkers

Compound	Structure	MMP-13 IC_{50} (nM)	MMP-2 selectivity (X-fold)	MMP-12 selectivity (X-fold)	$t_{1/2}$ solution stability (days)
4		3.49	16.4	23.2	3.8
5		138	7.39	2.09	1.1
6		7.33	13.6	17.6	2.8
7		11.7	9.40	86.5	ND
8		15.1	16.1	21.5	ND
9		12.0	13.8	14.2	ND
10a		1.57	8.92	33.6	ND
10b		0.6	5.83	22.0	>1000

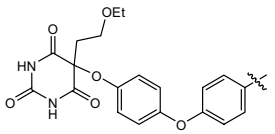


Scheme 1. Synthesis of spiropyrrolidine **10a**.

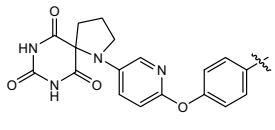
dropped below the desired 100× threshold for progression through our screening cascade. Within the 4-phenyl-oxazole series, SAR suggested that MMP-2 selectivity at the desired 100-fold level was only attainable with substituents in the *para*-position.

In the benzimidazole series (compounds **22**, **24**, and **26**) the spirocyclic linker still provided a 5–10× potency increase. In this subseries, however, the selectivity trends were different. It was no longer difficult to achieve high levels of MMP-2 selectivity, and MMP-8 selectivity was

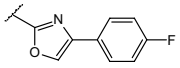
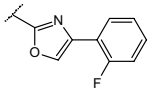
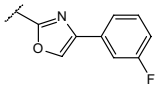
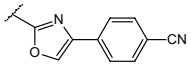
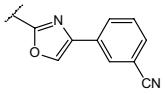
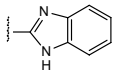
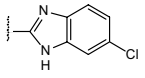
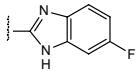
Table 3. Spirocyclic pyrrolidines versus oxygen-linked ethoxyethyl analogs



Series A



Series B

Compound	R	Series	MMP-13 (nM)	MMP-2 (X)	MMP-12 (X)	MMP-8 (X)
1		A	0.59	9	48	ND
10		B	1.6	6	34	ND
11		A	0.68	400	568	237
12		B	0.12	127	1198	312
13		A	0.93	537	849	269
14		B	0.16	67	ND	ND
15		A	0.35	273	906	128
16		B	0.09	32	ND	ND
17		A	0.43	444	394	247
18		B	0.05	137	931	303
19		A	0.52	31	133	156
20		B	0.11	15	ND	ND
21		A	0.49	280	99	643
22		B	0.11	252	107	273
23		A	0.96	150	39	438
24		B	0.1	552	85	349
25		A	0.4	353	147	648
26		B	0.08	238	167	ND

also attainable. Now, MMP-12 selectivity became more challenging (similar to the acyclic analogs **21**, **23**, and **25**). While the use of the spirocyclic linker did provide modest increases in selectivity, these were not always enough to meet our goal of 100-fold for progression through our entire screening cascade.

Given the selectivity and potency in this series, a number of compounds were progressed to rat pharmacokinetic studies. Among these, **12** was found to have an excellent PK profile (Clp 3.9 mL/min/kg, V_{dss} 1.3 L/kg, $t_{1/2}$ 4.5 h). When compared to the corresponding analog in the acyclic series, these spirocyclic analogs generally gave both increased volume and clearance, the net effect of which resulted in a very similar $t_{1/2}$ value. As with the oxygen-linked analogs, high oral absorption is obtained when these compounds are dosed as the sodium salt. Compound **12** is very effective at preventing the MMP-13 induced in vitro degradation of bovine nasal cartilage (as measured by hydroxyproline release) with an IC_{50} of 12 nM.[35] Compound **12** also performed very well in our in vivo hamster model of direct intraarticular injection of MMP-13 into the knee joint (>80% inhibition at 10 mg/kg po).[36]

Owing to its positive attributes, **12** was chosen to test the hypothesis that a selective inhibitor of MMP-13 from this spirocyclic series could avoid the MSS side effect. Thus, **12** was advanced to a 14-day rat fibroplasia study, a surrogate for the production of MSS in humans.[37] No acute toxicity was observed at doses of 30, 100, 300, and 800 mg/kg bid. At the highest two doses (300 and 800 mg/kg bid) comparable C_{max} were obtained (63 and 52 μg/mL, respectively). Histological examination revealed one instance of fibroplasia in each of these groups. Whether this fibroplasia resulted from the high C_{max} causing inhibition of MMP-2 or -9 (each of which compound **12** was ~100× selective for), a combination of both, or another unidentified MMP has not been determined.

In conclusion, we have described the discovery of a novel series of spirocyclic pyrimidinetrione inhibitors of MMP-13. Close-in modifications of the electron withdrawing ability of the spirocyclic linker provided dramatic variations in solution stability. Attachment of extended P1′groups gave compounds that were potent, selective, and had excellent pharmacokinetic properties. These compounds provided in vitro and in vivo protection to cartilage, and showed no acute toxicity despite very high doses for 14 days. However, in the same study, pre-clinical signs of MSS were observed. These findings were sufficient to cause the termination of the pre-clinical work on these analogs.

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28. Concurrent with our work, a group at Bristol-Myers Squibb was also exploring spirocyclic pyrimidinetrione lactam analogs, their work was reported in 2005. See Ref. 20 for details.
29. Synthesis details for compounds **1**–**3**. Compound **1**: see Ref. 2. Compound **2**: 2-chloro-5-nitropyridine and 4-fluorophenol are reacted in the presence of sodium hydroxide to form 2-(4-fluorophenoxy)-5-nitropyridine. The nitro group is then hydrogenated to form 6-(4-fluorophenoxy)pyridin-3-amine. The resulting aniline is subjected to diazotization, displacement by acetate, and hydrolysis to produce 6-(4-fluorophenoxy)pyridin-3-ol. This phenol is coupled directly to 5-bromo-5-(2-ethoxyethyl)pyrimidine-2,4,6-trione according to procedures found in Ref. 2 to form compound **2**. Compound **3**: 6-(4-fluorophenoxy)pyridin-3-amine is reacted with 5-bromo-5-(2-ethoxyethyl)pyrimidine-2,4,6-trione, as in Ref. 2 to form compound **3**.
30. Synthesis details for compounds **4**–**9**: compounds **4**–**9** were prepared according to schemes described in: Bronk, B. S.; Noe, M. C.; Wythes, M. J.; Preparation of 1-aryl-1,7,9-triazaspiro[4.5] decanetetraones and analogs as metallo-

proteinase inhibitors. PCT Int. Appl. WO 02/034753 A2, May 2, 2002.
31. Synthesis details for compounds **11**, **13**, **15**, **17**, and **19**: all of the above compounds were prepared according to procedures found in Ref. 1.
32. Synthesis details for compounds **21**, **23**, and **25**: substituted benzimidazoles (4-(4-(1H-benzimidazol-2-yl)phenoxy) phenols) were prepared by reaction of 4-(4-hydroxyphenoxy)benzaldehyde (see Ref. 38) with appropriately substituted bis-anilines in the presence of $FeCl_3$ and O_2 (see Ref. 39). The resulting extended phenols were each reacted according to procedures found in Ref. 2 to produce compounds **21**, **23**, and **25**.
33. Synthesis details for compounds **12**, **14**, **16**, **18**, **20**: (**12**) 4-(4-fluorophenyl)oxazole is reacted with *n*-BuLi, transmetalated with zinc, and then subjected to a palladium-mediated (Negishi) coupling with diethyl 1-(6-(4-iodophenoxy)pyridin-3-yl)pyrrolidine-2,2-dicarboxylate (prepared by analogy to the corresponding 4-fluorophenoxy derivative shown in Scheme 1). The resulting diester is treated with urea and sodium hydride in DMSO to produce **12**. For (**14**), the same steps are performed using 4-(2-fluorophenyl)oxazole as a starting material. For (**16**), the same steps are performed using 4-(3-fluorophenyl)oxazole as a starting material. For (**18**), the same steps are performed using 4-(oxazol-4-yl)benzonitrile as a starting material. For (**20**), the same steps are performed using 3-(oxazol-4-yl)benzonitrile as a starting material.
34. Synthesis details for compound **22**, **24**, and **26**: for **22**, diethyl 1-(6-(4-iodophenoxy)pyridin-3-yl)pyrrolidine-2,2-dicarboxylate is reacted in a Stille coupling with vinyltributyltin, and the resulting olefin is cleaved with osmiumtetroxide and sodium periodate to provide diethyl 1-(6-(4-formylphenoxy)pyridin-3-yl)pyrrolidine-2,2-dicarboxylate. This aldehyde is reacted with 1,2-diaminobenzene using similar procedures as given for the synthesis of compounds **21**, **23**, and **25** to form diethyl 1-(6-(4-(1H-benzimidazol-2-yl)phenoxy)pyridin-3-yl)pyrrolidine-2,2-dicarboxylate. Treatment of this diester with urea and sodium ethoxide produced **22**. For (**24**), the same steps are performed, but using 1,2-diamino-4-chlorobenzene. For (**26**), the same steps are performed, but using 1,2-diamino-4-fluorobenzene.
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