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Potent and selective 2-naphthylsulfonamide substituted hydroxamic acid inhibitors of matrix metalloproteinase-13

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ABSTRACT

The matrix metalloproteinase enzyme MMP-13 plays a key role in the degradation of type II collagen in cartilage and bone in osteoarthritis (OA). An effective MMP-13 inhibitor would provide a disease modifying therapy for the treatment of arthritis, although this goal still continues to elude the pharmaceutical industry due to issues with safety. Our efforts have resulted in the discovery of a series of hydroxamic acid inhibitors of MMP-13 that do not significantly inhibit MMP-2 (gelatinase-1). MMP-2 has been implicated in the musculoskeletal side effects resulting from pan-MMP inhibition due to findings from spontaneously occurring human MMP-2 deletions. Analysis of the SAR of hundreds of previously prepared hydroxamate based MMP inhibitors lead us to 2-naphthylsulfonamide substituted hydroxamates which exhibited modest selectivity for MMP-13 versus MMP-2. This Letter describes the lead optimization of **1** and identification of inhibitors exhibiting >100-fold selectivity for MMP-13 over MMP-2

The matrix metalloproteinase (MMPs) are unregulated in osteoarthritis (OA) and are largely responsible for the destruction of collagens and proteoglycans in cartilage and bone, leading to loss of joint function in this disease. MMP-13 is the primary enzyme which cleaves type II collagen and thus, inhibition of this enzyme is viewed as one of the most promising approaches to the treatment of cartilage degradation in arthritis. There have been many efforts to target MMPs as therapeutic approaches,[1] predominantly using broad-based hydroxamic acid inhibitors, which have been hampered due primarily to musculoskeletal side effects, the exact nature is still uncertain.[2,3] The cause of these side effects has been significantly debated and one hypothesis that we were concerned with was a possible link to MMP-2 inhibition. MMP-2's role in causing musculoskeletal side effects was implicated by familial genetic studies reported by Martignetti et al.[4]

Given these findings, we set out to identify selective MMP-13 inhibitors with respect to MMP-2. Given the similarity of these enzymes (60% homology; 100% at the active site), as illustrated in Figure 1, we viewed this as a formidable task when we initiated these efforts. Earlier studies towards compounds that spared MMP-1 could exploit the smaller S1′ pocket in this enzyme.[5] However, MMP-2 has a very similar S1′ channel to MMP-13 as do most other MMPs. Thus, the identification of MMP-13 inhibitors sparing these other isoenzymes would require taking advantage of more subtle differences in the active sites. During the course of this work, the feasibility of achieving selectivity between these enzymes has been demonstrated by several groups. Hydroxamic acid derived inhibitors of MMP-13 sparing other family members have been reported by Barta and coworkers.[6–11] Also, several series of specific, non-zinc-binding MMP-13 inhibitors have also been identified.[12,13]

Our efforts were initiated by analyzing the vast SAR established from our previous approaches towards MMP-13 inhibitors.[5,14] Most of the compounds we examined exhibited little or no selectivity for MMP-13 over MMP-2. Figure 2 illustrates the correlation for MMP-13 and MMP-2 activity for the MMP inhibitors from these previous efforts. The activity trend between the two enzymes is easy to see and relatively few compounds exhibited 10-fold selectivity for MMP-13. Through this analysis, we noticed that the 2-naphthyl sulfonamide substituted inhibitor **1**, exhibited modest selectivity (~10-fold).

Interestingly, this modest selectivity was sensitive to the presence of a substituent on the sulfonamide nitrogen as exemplified by comparing **1** and **2** as illustrated in Figure 3. This effect was surprising given that we expected the *N*-alkyl substituents to point into solvent based on our previous experience with CGS027023.[14] This

Abbreviations: MMPs, matrix metalloproteases; OA, osteoarthritis; IA, intra-articular.

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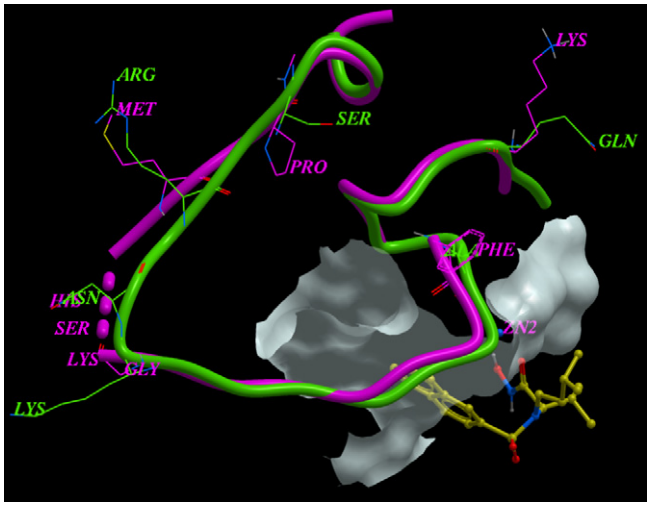


Figure 1. Sequence differences between MMP-13 (magenta) and MMP-2 (green) in the S1′ binding region. The colored ribbons represent the path of the backbone atoms for both proteins. The catalytic Zinc for the MMP-13 structure is shown and labeled 'ZN2'. Where the sequences differ between the proteins, the residue atoms and name is given. The white surface depicts the binding cleft and entry into the S1′ pocket. MMP-13 has three residues that are not resolved in the crystal structure, which are represented with three dashes in the ribbon and the three letter codes for the amino acid residues.

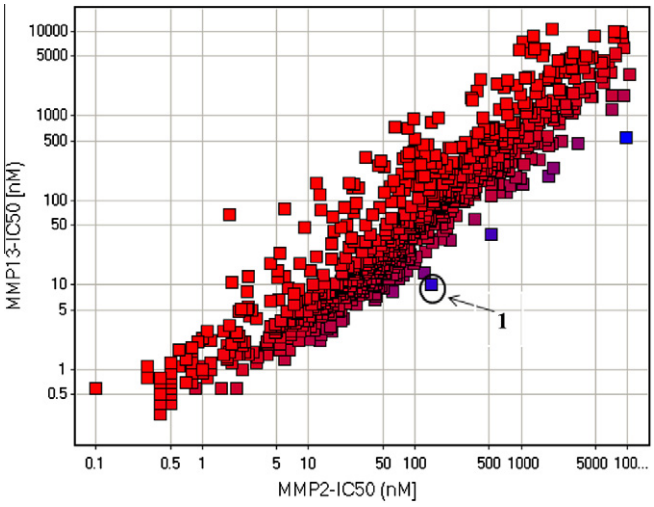


Figure 2. Summary of selectivity for MMP-13 overMMP-2 for our collection of MMP inhibitors.1 is highlighted by the circle as one of the compounds exhibiting modest selectivity.

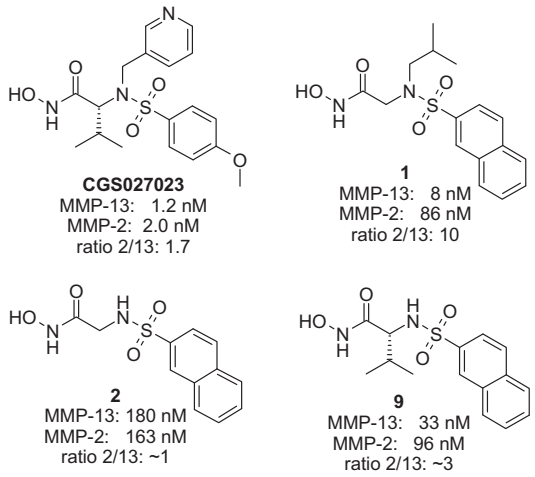
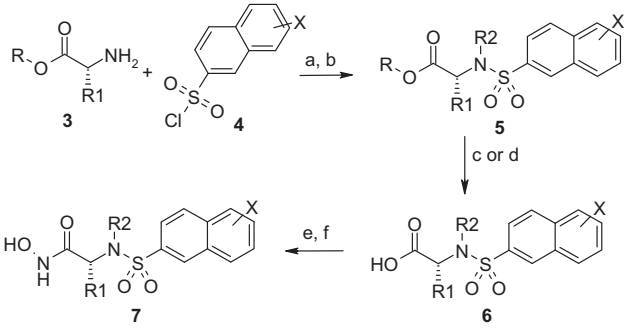
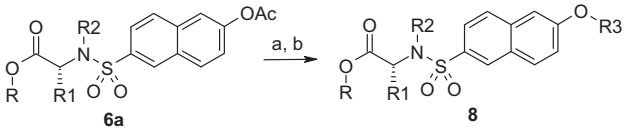


Figure 3. Structure, activity and selectivity of initial naphthyl hydroxamate leads in comparison to CGS027023.



Scheme 1. General route to naphthylsulfonamide substituted hydroxamates. Reagents: (a) Et_3N, CH_2Cl_2; (b) R^2-I, K_2CO_3, DMF; (c) HCl, EtOAc; (d) H_2, 10% Pd/C, EtOAc; (e) *O*-trityl-hydroxylamine, NMM, HOAt, EDCI, CH_2Cl_2; (f) TFA, Et_3SiH, CH_2Cl_2.



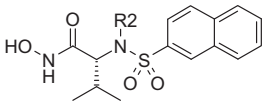
Scheme 2. Routes to 6-substituted naphthylsulfonamide analogs. Reagents: (a) K_2CO_3, EtOH/water; (b) R^3-I, K_2CO_3, DMF.

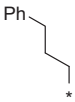
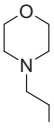
effect is not observed in the absence of the naphthyl sulfonamide as various other hydroxamates (including CGS027023) were in this screening set (data not shown). It appeared to us that both the naphthyl and the N-substituent were required to achieve enzyme selectivity. Thus, we set out to better understand this effect and determine whether improvement was possible. Herein we report the optimization of **1** which has lead to the discovery of potent MMP-13 inhibitors with >100-fold selectivity over MMP-2.

A general route to naphthyl substituted hydroxamates was utilized in analogous fashion to work we have reported previously.[8,14] as illustrated in Scheme 1. Sulfonylation of amino acid ester, **3** (R = ^{t}Bu), followed by N-alkylation yielded the *t*-butyl sulfonamide ester **5** in good yields, however the rate of reaction diminished with increasing steric bulk of the alpha substituent. Removal of the *t*-butyl ester by the action of HCl in EtOAc followed by coupling with tritylhydroxylamine afforded the trityl protected hydroxamates which were deprotected by the action of TFA and triethylsilane in dichloromethane. Alternatively, amino acid benzyl esters (**3**, R = Bn) could be used as starting materials as this also allowed mild ester deprotection. Thus, after similar sulfonylation and alkylation, deprotection of the benzyl esters by hydrogenolysis using 10% Pd/C in EtOAc afforded **6** in excellent yields.

Synthesis of the 6- and 7-alkoxy substituted naphthyl analogs was accomplished via preparation of the acetoxy intermediate **6a** under conditions described above starting from the commercially available acetoxy-naphthyl sulfonyl chlorides. As shown in Scheme 2, the 6-acetoxy group was hydrolyzed in ethanol/water to yield the phenol, which was converted to alkyl ethers, **8**, via alkylation mediated by K_2CO_3 in DMF. Conversion of **8** to the desired hydroxamic acid derivates was accomplished as described above in Scheme 1. Preparation of the desired 7-alkoxy substituted analogs was affected in an analogous manner from the commercially available 7-acetoxy naphthyl sulfonyl chloride.

Table 1
N-Alkyl substituted naphthyl hydroxamates



Compound	R^2	IC_{50} (nM)		Ratio (MMP-2/-13)
		MMP-13	MMP-2	
9	H	33	96	2.9
10	Me	2.9	54	18
11		7	308	44
12		3.0	384	128
13		28	706	25
14		2.0	200	100
15		24	798	33
16		7	200	28
17		15	25	1.7
18		2.2	232	116
19		32	607	19
20		18	144	8

Our initial exploration of the selectivity observed with **2** was centered around understanding the impact of the N-substituent on selectivity. Toward this end, we prepared a variety of analogs with relatively large substituents as well as analogs containing water solublizing groups at this position. The results of these studies are summarized in Table 1 where assays were performed as previously described.[5] Interestingly, the selectivity for MMP-13 versus MMP-2 is very dependent on the nature of the N-substituent and appears driven by effects on both enzymes. Generally, the N-substituent has a beneficial effect on MMP-13 activity as exemplified by the 10-fold improvement in MMP-13 activity for entry **10** in comparison with **9**. In this particular case, MMP-2 activity is only two-fold improved for **10**. As the size of the alkyl substituent increases, however, there is a slight drop in the MMP-2 activity. When combined, these effects can result in a marked improvement in selectivity as illustrated with entries **12** and **14** in Table 1, which achieve greater than 100-fold selectivity for MMP-13 over MMP-2. It is noteworthy that polar substituents, as in entries **19** and **20**, are disfavored by both enzymes. An interesting exception to this however, is the *o*-pyridyl analog **18**, which maintains good selectivity due to its potent MMP-13 activity. It was also observed that the *m*-pyridyl analog **17**, which contains the identical *N*-alkyl modification as CGS27023, was the most potent MMP-2 inhibitor and the least selective analog in this subset of compounds.

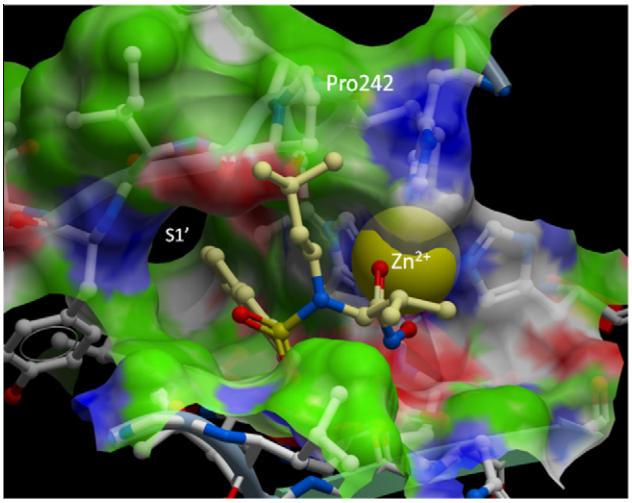
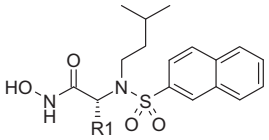


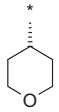
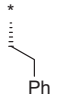
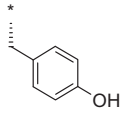
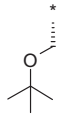
Figure 4. X-ray crystal structure of **12** in MMP-13. The protease domain of MMP-13 was co-crystallized with compound **12** and the x-ray structure was determined to a resolution 1.3 Angstroms. The napthyl group is in the S1′ pocket, the hydroxamate is chelating the catalytic Zn (yellow sphere) and a sulfonamide oxygen is forming a hydrogen with the protein backbone across from the S1′ pocket (behind the valine in the foreground). Coordinates and X-ray data for this structure are available from the Protein Data Bank, deposition code 3zxh.

In order to better understand the observed selectivity, the co-crystal structure of **12** in MMP-13 was solved (Fig. 4). As predicted from other structures, the N-substituents are solvent exposed and not in proximity to residues that differ in MMP-13 and MMP-2. We consider it most likely that the intrinsic flexibility of these S1′ pockets differ. The S1′ pockets in MMP-13 and MMP-2 are more accurately described as tunnels. The 'bottom' of the pocket is fully solvent exposed and able to accommodate very large, extended molecules. The top of these pockets, as illustrated in Figure 1, are formed by an extended loop. A deletion in the amino acid sequence of MMP-2 relative to MMP-13 near the bottom of the S1′ pocket may contribute to changes in flexibility. The hydroxamate's interactions with the catalytic Zn, and the sulfonamide's interactions with the backbone of the protein rigidify or 'lock-in' the positioning of the core scaffold and contribute greatly to the binding energy. Increasing the rigidity of the scaffold favors MMP-13 which appears to be better able to adapt to the naphthyl substituent. This trend has been observed in other studies[15] based on different scaffolds.

Beyond the selectivity gain from having an N-substituent, there are clearly additional effects from the nature of substituent. We observe favorable hydrophobic interactions between aliphatic substituent of compound **12** and Pro242 in MMP-13; however, in the absence of high-resolution co-crystal structures of MMP-2, it is difficult to fully understand which interactions with MMP-2 may influence the selectivity of the compounds. Nonetheless, a few interesting features stand out including the sensitivity of the pyridyl N position in selectivity. The 4-pyridyl analog **16** increases potency for both MMP-2 and -13 to a similar degree with nearly identical selectivity as **13**. Replacement with 3-pyridyl (**14**), the

Table 2
Amino acid variations

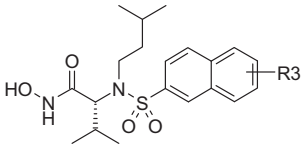


Compound	R^1	IC_{50} (nM)		Ratio (MMP-2/-13)
		MMP-13	MMP-2	
12		3.0	384	128
21		0.6	128	213
22		1.3	83	66
23		12	81	7
24		26	458	18
25		28	706	25
26		2.2	200	100
27		34	3670	108
28		3.2	111	37

same *N*-alkyl substituent as CGS27023, results in a compound with equal selectivity as the latter compound, and with similar potency as **13**. The 2-pyridyl analog **18** was essentially unchanged from **12** in terms of potency and selectivity, but with a $\Delta c \log P$ of −1.8.

Given our results with analogs depicted in Table 1, we chose the N-isoamyl analog (**12**) as a benchmark for further study. We then focused our attention on the amino acid substituent. As illustrated in Table 2 both MMP-2 and MMP-13 are rather tolerant of a variety of *alpha* substituents on the amino acid moiety. The switch from valine to leucine (compound **21**) improved potency against both MMP-13 and -2, with a slight improvement in selectivity. It was known from previous efforts, however, that hydroxamic acids become more susceptible to enzymatic hydrolysis in vivo when β-substitution was decreased so the overall benefit of **21** is assumed less than the in vitro data might suggest. We were somewhat surprised by the 10-fold loss of MMP-13 activity of entries **24** and **25**. Inspection of the crystal structure of MMP-13 does not shed light on the reason for this loss of activity. We found the *t*-leucine analog, **27**, to be particularly interesting given the MMP-2 activity was driven into the micromolar range for the first time. Unfortunately, a similar 10-fold loss in MMP-13 activity resulted with this analog. The *N*-alkyl and amino acid variants are in proximity to each-other when bound to the protein. The uniform loss of activity with the *t*-leucine analog in both enzymes suggests it sterically hinders the ligand from adopting its bound conformation. While modification of the amino acid could play a role in optimizing ADME properties of the molecule, we did not find analogs that stood out as being superior to the valine derived analog **12**.

Table 3
6- and 7-alkoxy substituted naphthyl sulfonamides



Compound	R^3	IC_{50} (nM)		Ratio (MMP-2/-13)
		MMP-13	MMP-2	
12	H	3	384	128
29	6-OH	1	178	178
30	7-OH	242	3286	13.6
31	6-OMe	1.3	180	138
32	7-OMe	480	4370	9.1
33	6-OEt	3.6	307	85
34	7-OEt	603	9200	15
35	6-O-*n*Pr	10	197	20
36	6-O-*i*Bu	13	102	7.8
37	6-O-*i*Amyl	176	931	5.3
38	6-OBn	165	1610	9.8
39	6-Et	0.3	45	150

Further optimization centered around deeper exploration into the S1′ site via naphthyl substitutions. As depicted in Table 3, our focus was still on **12** as a benchmark for this comparison and we set out to evaluate the effect of 6- and 7-substitution on the naphthyl group. Based on the crystal structure of **12** in MMP-13, we deemphasized substitution at the other naphthyl positions given that there is no space in the S1′ channel to accept these substitutions. Small substituents were in fact explored, but these analogs exhibited significantly less activity (data not shown). The SAR established with the 6- and 7-alkoxy substituted analogs clearly indicates a preference for the 6-substituted analogs. Thus, further optimization focused solely on substitution at the 6-position. Surprisingly, given the size of the S1′ pocket, large substituents at the 6-naphthyl position lead to loss of MMP-13 activity as exemplified by entries **35**–**38**. While small alkyloxy groups are well tolerated, *n*-propyl and *i*-butyl substitution results in analogs with 10 nM or greater IC_{50}. Moreover, the effect of these changes on MMP-2 appears less significant (e.g., entry **31** vs **35** indicates no effect on MMP-2 while a 10-fold loss on MMP-13). Further increases in size (isoamyl or benzyl, entries **37** and **38**, respectively) reduced potency against MMP-13. A methoxy to ethyl isosteric replacement (**39**) results in increased potency of approximately four-fold with no change in selectivity. It is evident from these examples, that there is a relatively narrow margin to work with in this system to achieve acceptable potency for MMP-13 while maintaining suitable (>100-fold) selectivity versus MMP-2.

We sought to improve the properties of compound **12** including the moderately high lipophilicity ($c \log P = 4.4$) and low solubility (<5 μM at pH 6.8) by seeking a heterocycle isostere of the naphthyl ring. Several quinoline and isoquinoline derivatives (**40–42**) were made and demonstrate a high degree of sensitivity in the S1′ pocket. Absolute potency increased from napthyl to benzothiophene (**43**), dihydrobenzofuran (**44**) and dihydrobenzo[1,4]dioxane (**45**), however all modifications resulted in diminished selectivity relative to **12**. The need for a fused ring system is highlighted in the poor activity of **46**.

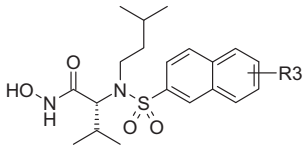
Based on these findings, several analogs were selected for further profiling which included rat pharmacokinetics, evaluation in

cartilage chip assays, as well as efficacy in a rat intra-articular injection model. We first examined the rat pharmacokinetic profile via cassette dosing of selected compounds (Table 5) at 5 mg/kg po and 1 mg/kg iv. In rats, compound **12** had moderate in vivo clearance (2.4 L/h/kg), $t_{1/2}$ of 5.7 h, and marginal oral bioavailability (F = 23.8%) with oral exposure of 1.5 μM h. Hydroxamates typically suffer from enzymatic hydrolysis in vivo and we sought to find modifications that could decrease clearance, improve oral exposure relative to MMP-13 potency while retaining selectivity against MMP-2.[16] To better evaluate compounds, we looked at oral exposure as a function of MMP-13 activity and later analyzed the data to determine if a composite parameter analysis (e.g., lipophilic efficiency or LipE) would help us simplify the complex number of variables involved in achieving this goal.

As a group, the *N*-alkyl derivatives were wholly devoid of any improvement to clearance or oral exposure. Compounds **14**, **16**, **17** and **19** all had higher clearance and lower oral exposure, likely due to first pass metabolism, relative to **12**. We hypothesize that N-dealkylation may contribute to clearance in vivo and the isoamyl modification appears to have the best balance of potency, selectivity and metabolic stability.

Modification of the amino acid moiety had a more dramatic effect on oral exposure as compounds **22**, **27** and **28** all had similar or greater oral exposure relative to **12** that does not appear attributable to reduced clearance. It is interesting to note that the hydroxy modifications essentially have no effect on MMP-13 potency, but have greater lipophilic efficiency than the corresponding alkyl derivatives (e.g., **28** vs **12**). The serine and threonine based compounds have the highest LipE and the highest oral exposure relative to MMP-13 potency. Unfortunately, their LipE is even greater for MMP-2 as manifest by lower selectivity.

Table 4
Heterocyclic sulfonamide and naphthyl sulfonamide isosteres



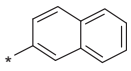
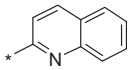
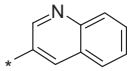
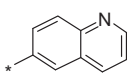
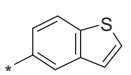
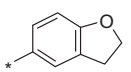
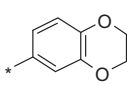
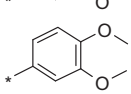
Compound	R^4	IC_{50} (nM)		Ratio (MMP-2/-13)
		MMP-13	MMP-13	
12		3	384	128
40		100	2050	21
41		361	6913	19
42		12	306	26
43		1.8	16	9
44		0.6	10	17
45		0.05	3	60
46		3,892	30,083	8

Table 5
Rat PK (cassette dosing) of selected compounds

Compound	MMP-13		CL (L/h/kg)	AUCpo (μM h)	AUCpo/MMP-13 IC_{50} (h)
	IC_{50} (nM)	LipE			
12	3	4.1	2.4	1.5	406
14	2	4.4	3.3	0.45	224
16	6.8	5.6	7.3	0.32	46
17	15	5.2	6.4	0.55	42
19	32	4.6	14	0.27	8
22	1.3	6.4	2.7	2.4	1993
27	34	2.9	1.6	7.2	209
28	3.2	5.8	3.3	3.1	1001
40	100	3.7	5.5	0.13	1.3
42	12	5.0	1.1	4.6	380
43	1.8	4.5	7.1	1.5	844

Rat cassette PK following oral (5 mg/kg) and intravenous (1 mg/kg) dosing in 20%

Replacement of the naphthyl moiety by various heterocycles was intended to reduce oxidative metabolism (Table 4), however only the quinoline derivative **42** appeared to achieve this goal. The reduced in vivo clearance and higher oral exposure was unfortunately offset by a similar decrease in MMP-13 potency and selectivity against MMP-2.

Most of the analogs we explored failed to significantly exhibit cartilage protection in the bovine articular cartilage chip assay. In the rat injection model, we were also unable to demonstrate cartilage protection (data not shown for both experiments). Presumably, the loss of activity in the tissue and in vivo assays are due to poor physical properties in the series stemming from incorporation of the naphthyl group. Unfortunately, polar N-substitution which was successful in the optimization of CGS027023 was not successful in this case due to loss of potency on MMP-13 as well as selectivity versus MMP-2. The PK results from various modifications helped reprioritize areas for modification and helped determine some of the inherent limitations of this scaffold and advanced our understanding of how to design selective MMP-13 inhibitors. Due to these challenges, optimization of this series was terminated and efforts were focused on cyclic amino acid analogs as well as smaller naphthyl replacements. The results of those studies will be reported in due course.

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