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SAR studies of non-zinc-chelating MMP-13 inhibitors: Improving selectivity and metabolic stability

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ABSTRACT

SAR studies to improve the selectivity and metabolic stability of a class of recently discovered MMP-13 inhibitors are reported. Improved selectivity was achieved by modifying interactions with the S1′ pocket. Metabolic stability was improved through reduction of inhibitor lipophilicity. This translated into lower in vivo clearance for the preferred compound.

The matrix metalloproteinases (MMPs), comprised of collagenases, stromelysins, gelatinases, and membrane-type MMPs, are a family of more than 27 zinc- and calcium-containing enzymes that play a critical role in degradation of extracellular matrixes (ECM) and in tissue remodeling.[1] Of the collagenase family (MMP-13, MMP-1 and MMP-8), MMP-13 exhibits the most efficient cleavage of type II collagen.[2] Inhibition of MMP-13 reduces cartilage degradation associated with the progression of rheumatoid arthritis and osteoarthritis in animal models.[3] Consequently, MMP-13 has become an attractive therapeutic target for treatment of these diseases. Clinical data indicates that broad-spectrum MMP inhibitors exhibit a dose-limiting toxicity referred to as musculoskeletal syndrome (MSS) that involves painful joint stiffness and inflammation.[4] It is hypothesized that MSS might be caused by inhibition of normal extracellular matrix turnover due to inhibition of MMPs other than MMP-13.[5] However, this is yet to be proven, and it remains unclear which MMP isoforms may be involved[6] and to what extent they individually contribute to MSS. Therefore, selective MMP-13 inhibitors might avoid MSS while providing therapeutic benefits. Thus, the research in this field has shifted from broad-spectrum MMP inhibitors to highly selective MMP-13 inhibitors.[7–9]

We recently reported[10] a new class of potent and selective MMP-13 inhibitors with a unique binding mode in which the inhibitors bind in the active site but do not interact with the catalytic zinc. That work started with compound **1** (Fig. 1). Potency for MMP-13 and selectivity were improved mainly through modifying the interactions with the MMP S1′ pocket by replacing the chlorine with pyrazole ether (compound **2**). Compound **2** shows good MMP-13 potency (4 nM) and selectivity against most MMPs tested. However, its selectivity against MMP-3 and -10 is modest (46- and 24-fold, respectively). Compound **2** also has poor metabolic stability (HLM: 90% Q_H). Here we report our continued efforts to improve the selectivity against both MMP-3 and -10 and the metabolic stability of this class of MMP-13 inhibitors.

To further improve selectivity over MMP-3 and -10 for this class of inhibitors, we investigated alternative ways of interacting with

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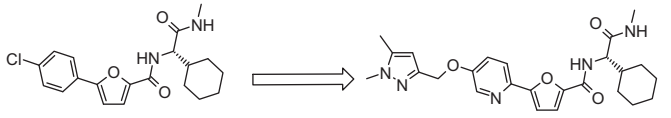
Our previous report:[10]



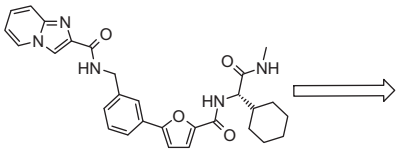
1

MMP-13 IC_{50}: 430 nM

2

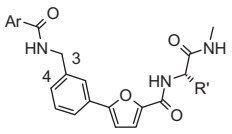
MMP-13 IC_{50}: 4 nM
selectivity: MMP-3: 46-fold; MMP-10: 24-fold

This work:



3

MMP-13 IC_{50}: 100 nM
selectivity: MMP-3: 150-fold; MMP-10: 23-fold



4

best compound: MMP-13 IC_{50}: 5 nM
selectivity: MMP-3: 600-fold; MMP-10: 200-fold

Figure 1. Two approaches to gain potency and selectivity.

the S1′ pocket. The starting point of this optimization was the result of a hybridization of compound **1** with another series of MMP-13 inhibitors[11] based on an overlay of their crystal structures. This resulted in compound **3**. Although compound **3** is less potent than compound **2**, the selectivity profile is equivalent to **2**. We considered compound **3** a reasonable starting point for further exploration. We reasoned that aryl groups appended at the C-3 position of phenyl ring through a methyl amide linkage (as shown in general structure **4**) must occupy the MMP S1′ pockets somewhat differently than the analogous functionality in compound **2**. Presumably this would offer different opportunities to improve the selectivity against MMP-3 and -10. To test this hypothesis, SAR studies started with replacing the imidazopyridyl group of **3** with other aromatic derivatives (Table 1).

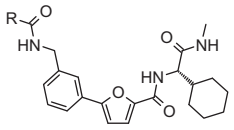
The compounds reported herein (Table 1 and 2) were synthesized in a straightforward manner as shown in Scheme 1.

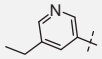
The imidazopyridyl group of **3** is clearly important since replacing it with a methyl group significantly lowers both potency and selectivity (compound **5**). Simple methyl-substituted imidazopyridines (**6** and **7**) showed no impact on either potency or selectivity. Due to the relatively high molecular weight (513 dalton) of **3**, we concentrated primarily on replacing the imidazopyridyl group with smaller aromatic rings. We were pleased to find that a number of five- and six - membered aromatic groups not only improved the potency to the same level of compound **2**, but also improved the selectivity over MMP-3 and -10 significantly. Among the fivemembered aromatics we examined, the most potent compounds (**9**, **13**, and **16**) appear to have structural features combining an H-bond acceptor at 2-position (next to the carbon with the carboxamide group, see structures in Table 1) and a methyl group at 3-position (next to the H-bond acceptors). However, their selectivity compared to compound **3** remained the same or became worse. Among the six - membered aromatics (pyridines and pyrimidines), an H-bond acceptor (N) at the 2-position also appeared to be beneficial for the MMP-13 potency (**19** vs **20**; **25** vs **26**). Substitutions (Me, Cl or CF_3 groups) at the 3-position for compounds with an H-bond acceptor at 2- position do not affect MMP-13 potency (**21** and **22** vs **17**; **26** and **27** vs **20**). However, the bulkier trifluoromethyl group at 3-position (compounds **22** and **27**) significantly improves selectivity over MMP-3 and -10 to almost 400-fold. Small substitutions (mostly methyl group) at other positions of either five- or six - membered aromatics are not beneficial for MMP-13 potency (**10** vs **8**; **14** vs **13**; **23** and **24** vs **17**). Appending the same arylcarboxamide groups to the C-4 position, rather than the C-3 position of the phenyl template resulted in much weaker inhibitors (data not shown).

Investigating different aryl groups that presumably bind in the S1′ pocket resulted in compounds with good overall MMP selectivity and good MMP-13 potency. However, the best compounds (**22** and **27**) were metabolized rapidly in vitro (HLM: 81% and 66% Q_H for **22** and **27**, respectively) (Table 2). We postulated that the high lipophilicity of these compounds contributed to the high rate of metabolism. The calculated log *P* (*c* log *P*) value is 4.98 for **22** and 4.13 for **27**. One way we investigated the impact of reducing lipophilicity on rates of metabolism concentrated on modifying the cyclohexyl group. Since the cyclohexyl group binds in the S2′ pocket and is partially solvent-exposed as shown by the co-crystal structure of MMP-13 and compound **1**,[10] we thought it would be possible to modify this group without affecting potency and selectivity by reducing the size and/or adding an oxygen. These modifications lowered the *c* log *P* by up to 2.4 units. For the compounds **28**–**31** with 6-trifluoromethylpyridyl group, these modifications did not have much effect on the metabolic stability. For the pyrimidine analogs **32**–**35**, the smaller groups (isopropyl or cyclopropyl) had no effect on the metabolic stability (**32** and **33** vs **27**). However, the more polar groups improved the metabolic stability to less than 25% Q_H (**34** and **35** vs **27**). These structural changes have no, or minor effects on MMP-13 potency: ~3 fold better for the 4-tetrahydropyranyl group (**30** vs **22**; **34** vs **27**), and three to five fold less potent for cyclopropyl group (**29** vs **22**; **33** vs **27**). In general the changes decreased the MMP-2, -3 and -10 selectivities to some extent. However, the best compound (**35**) from these modifications has a good balance of potency, selectivity and metabolic stability. It also has good aqueous solubility (>50 μg/mL) at both pH 4.5 and 7.4.

To establish whether the in vitro improvement of metabolic stability of **35** translated into in vivo clearance, the intravenous pharmacokinetics of compounds **35** and **33** were evaluated in male SD rats at a 1 mg/kg dose (Table 3).[14] The in vivo clearance of the two compounds is comparable to their in vitro clearance, with compound **35** having the lower clearance.

Table 1
SAR to improve potency and selectivity[13]



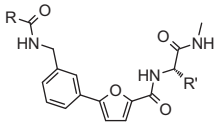
R	Compound	MMP-13 IC_{50} [nM]	MMP-2	MMP-3	MMP-8	MMP-10
			Fold selectivity for MMP-13			
	**3**	100	>190	150	>190	23
	**5**	3300	5	3	>7	0.5
	**6**	110	>45	>45	>45	29
	**7**	140	>37	>37	>37	32
	**8**	75	>270	15	>270	6
	**9**	11	490	34	>1900	16
	**10**	180	>110	>110	>110	17
	**11**	330	>61	9	>61	8
	**12**	310	>64	>64	>64	9
	**13**	24	>430	33	>820	14
	**14**	72	>280	51	>280	19
	**15**	140	>150	20	>150	13
	**16**	8	310	Not tested	1800	7
	**17**	8	>2400	200	>2400	65
	**18**	42	>480	Not tested	48	7
	**19**	31	310	Not tested	>660	4
	**20**	10	290	Not tested	>2000	9
	**21**	4	>4900	240	>4900	87
	**22**	9	>2300	>2300	>2300	>2300
	**23**	100	>200	85	>200	31
	**24**	29	>170	>170	>170	45
	**25**	27	370	Not tested	>740	10
	**26**	3	590	Not tested	>7100	27

(*continued on next page*)

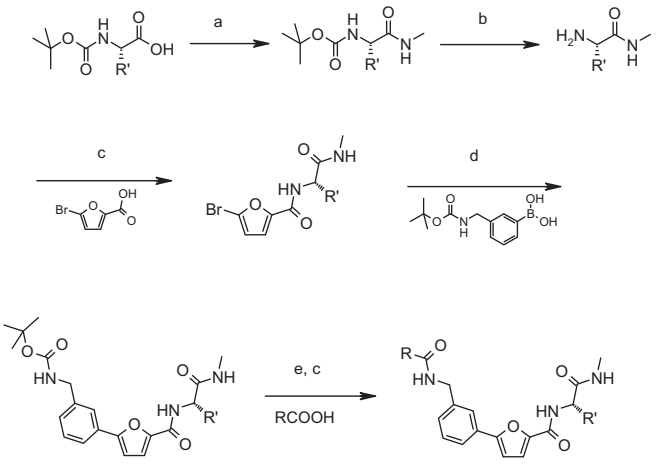
Table 1 (*continued*)

R	Compound	MMP-13 IC_{50} [nM]	MMP-2	MMP-3	MMP-8	MMP-10
			Fold selectivity for MMP-13			
	**27**	7	>2800	>2800	>2800	370

Table 2
SAR to improve metabolic stability[13]



R	Compound	R′	MMP-13 IC_{50} [nM]	MMP-2	MMP-3	MMP-8	MMP-10	HLM [%Q_H]	*c* log *P*
				Fold selectivity for MMP-13					
	22		9	>2300	>2300	>2300	>2300	81	4.98
	28		6	>3600	1000	>3600	260	88	3.79
	**29**		28	>700	>700	>700	400	60	3.31
	30		2	1500	330	7100	130	83	2.58
	31		25	>770	>400	>810	440	62	2.60
	27		7	>2800	>2800	>2800	370	66	4.13
	32		9	850	200	>2100	50	70	2.94
	**33**		36	580	540	>560	170	69	2.45
	34		2	640	250	>11000	100	24	1.73
	35		5	1100	600	>3900	200	14	1.74



Scheme 1. Reagents and conditions: (a) $MeNH_2$·HCl, TBTU, DIEA, DMF, rt; (b) TFA, DCM; (c) HATU, DIEA, DMF; (d) $PdCl_2\{P^tBu_2(p\text{-}NMe_2\text{-}Ph)\}_2$,[12], Na_2CO_3 (2 M), DMF, microwave 100 °C; (e) 4 N HCl in dioxane, MeOH.

In summary, we have described improving the potency and selectivity of a previously reported class of MMP-13 inhibitors possessing a unique binding mode. The improvements in potency and selectivity, especially for MMP-3 and -10, were achieved through the modification of interactions with the S1′ pocket by appending aryl groups with methyl amide linkage from C-3 position of phenyl template. Further optimization of metabolic stability was achieved by reducing lipophilicity to provide **35**. Overall, compound **35** exhibits good potency, selectivity, metabolic stability and aqueous solubility. The improved in vitro metabolic stability of compound **35** also translated into low clearance in vivo.

Table 3
Pharmacokinetic data (iv) of **33** and **35**[a]

Compound	HLM (%Q_H)	CL (%Q_H)	V_{ss} (L/kg)	$T_{1/2}$ (h)
33	69	47	1.2	0.7
35	14	26	0.9	0.95

[a] The compounds were dosed in 70% PEG400 aqueous solution.

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13. Compounds were also tested in MMP-1, -7, -9, -12, -14 assays, and their IC_{50}s are greater than the top concentration (20 μM). For detailed assay conditions, see Ref. 10.
14. For comparison, compound **27** was also selected for an intravenous pharmacokinectics study. But the study failed due to its poor solubility (0.1 μg/mL).