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Pyran-containing sulfonamide hydroxamic acids: potent MMP inhibitors that spare MMP-1

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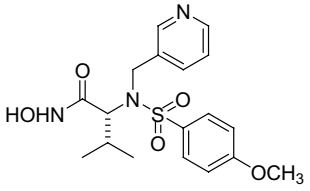
Abstract—The SAR of a series of sterically hindered sulfonamide hydroxamic acids with relatively large P_1' groups is described. The compounds typically spare MMP-1 while being potent inhibitors of MMP-13. The metabolically more stable compounds in the series contain either a monocyclic or bicyclic pyran ring adjacent to the hydroxamate group. Despite the sparing of MMP-1, preclinical and clinical studies revealed that fibrosis in rats and MSS in humans is still produced.

Therapeutically useful inhibitors of the various matrix metalloproteases (MMP's) have been sought for over 30 years. The disclosure of the sulfonamide hydroxamate CGS-27023A in 1994 revolutionized this pursuit.[1] Prior to this time, research efforts focused on peptide-like, hydroxamic acid-containing inhibitors that suffered not only from rapid metabolism of the hydroxamic acid but also from enzymatic cleavage of the two or three amide bonds typically present in this class of inhibitors.[2] The metabolic instability of these peptide-like compounds together with their sub-optimal physical properties—high molecular weight and low aqueous solubility—diminished their prospects for becoming useful therapeutic agents. The sulfonamide hydroxamate series eliminated most of these issues with metabolism of the hydroxamic acid remaining as the key problem. The vast number of publications and patents on related compounds that have appeared since 1994 attest to the impact the disclosure of the sulfonamide hydroxamate series has made on this research area.[3]



CGS-27023A

Concurrent with the disclosure of CGS-27023A were two other reports of critical importance to research in the MMP field.[4] The first of these was the identification of MMP-13,[5,6] a third collagenase, which has been implicated to play a key role in the pathology of osteoarthritis (OA). MMP-13 is present in OA cartilage tissue in humans,[5,7] turns over type II collagen,[5,6] is co-localized with cleaved type II collagen in OA cartilage tissue,[8] and degrades cartilage.[9] The second critical report related to side effects that were observed upon dosing humans with broad spectrum (i.e., nonselective) MMP inhibitors.[10] These side effects, collectively termed musculoskeletal syndrome (MSS), were postulated by us and others[11] to arise from the inhibition of MMP-1 owing to its presumed role in the normal turnover of extracellular matrix in connective tissue.

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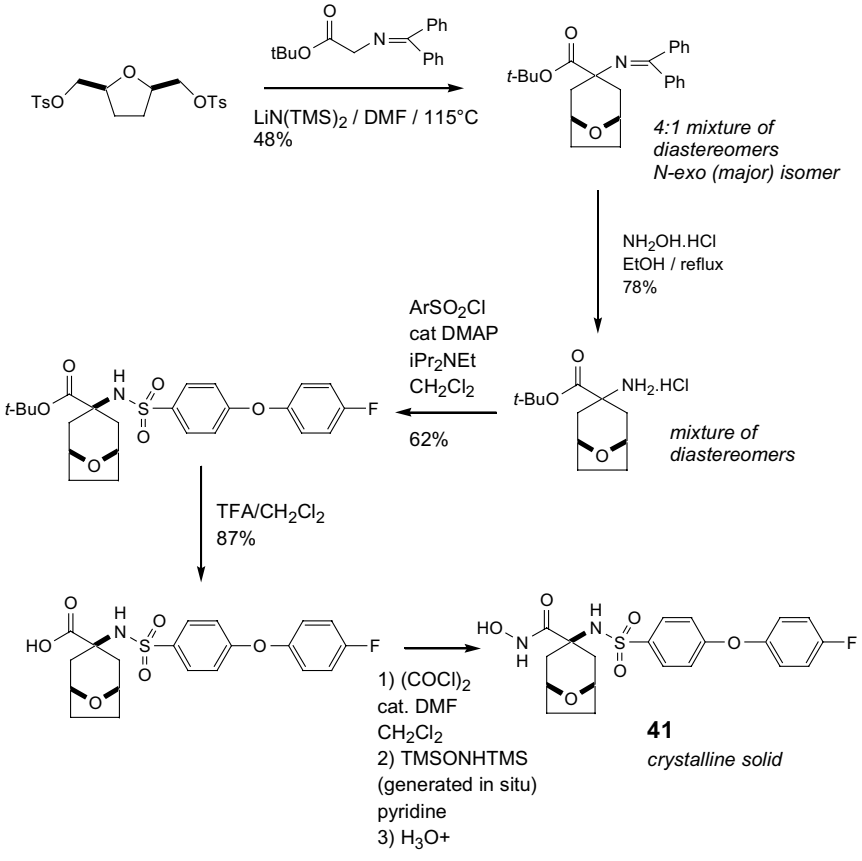
The conjunction of these research findings led us, in our efforts to identify compounds useful for treating OA, to seek an MMP inhibitor from the sulfonamide hydroxamate series that potently inhibited MMP-13, spared MMP-1, and which had metabolic stability consistent with once or twice daily dosing in humans.

Sequence analysis and a homology model of MMP-13 constructed from an MMP-1 X-ray crystal structure indicated that MMP-13 belongs to the set of MMPs that have a deep S_1' pocket. X-ray crystal structures of both enzymes subsequently confirmed this.[12] Since MMP-1 has a shallow S_1' pocket, obtaining selectivity over MMP-1 (and other shallow S_1' pocket enzymes) was expected to be possible by increasing the size of the P_1' substituent in the inhibitor. Furthermore, we reasoned that sterically hindering the hydroxamic acid would reduce metabolism of this functionality.

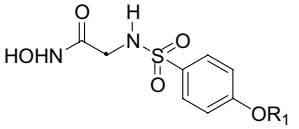
Scheme 1 outlines the synthesis of **41** as an illustration of the methods used to prepare target compounds. Alkylation of the benzophenone imine of *tert*-butyl glycine[13] with the *bis*-tosylate[14] yielded the [3.2.1]oxabicyclic system in good yield. In this case, a mixture of diastereomers was obtained whereas, in the monocyclic cases, only a single isomer would result from this reaction. Subsequent deprotection with hydroxylamine efficiently yielded the amine.[15] The minor *endo* diastereomer was generally not separated after either of these steps since it was later purged during the sulfonylation step in which it is less reactive than the *exo* isomer. Cleavage of the ester with TFA and conversion of the resultant acid to the acid chloride was followed by coupling with *bis*-TMS-hydroxylamine, prepared in situ, to yield, after aqueous acid work-up, the hydroxamic acid.[16] Esters of many of the simple cycloalkyl amino acids were readily available. In some cases, the corresponding methyl or ethyl esters were employed with the appropriate substitution of a saponification step to release the free acid.[17] The synthesis of the symmetrical pyran utilized bis(bromoethyl)ether in the first step.[18] The chiral pyrans and tetrahydrofurans were prepared starting with a protected serine derivative[19] followed by appropriate modification of the substituents to form either five- or six-membered rings.[20] The hydroxamic acids could alternatively be prepared by coupling of the intermediate acids with *O*-benzylhydroxylamine followed by hydrogenolysis.[21]

Our initial investigations showed that a substituent on the sulfonamide nitrogen of CGS-27023A is not necessary for potent inhibition of MMP-13. Thus, **1** (Table 1) displays potent MMP-13 inhibition and is reasonably selective over MMP-1.[22] Increasing the bulk adjacent to the hydroxamic acid to sterically inhibit metabolism of this group diminishes both MMP-13 and MMP-1 activities and reduces selectivity (**2**–**4**). However, these analogs do not take advantage of the deeper S_1' pocket



Scheme 1. Synthesis of **41**.

Table 1. SAR of α,α-disubstituted hydroxamic acids



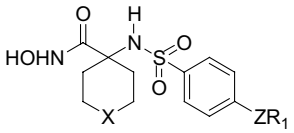
	Substitution	R_1	MMP-13 IC_{50} (nM)	MMP-1 IC_{50} (nM)	Ratio	C log*P*	hLH Er[a]	hLM Er[a]	rLM Er[a]	Hamster % inh @ 30 mg/kg po
	CGS-27023A		18	2.5	7	1.59	—	—	—	—
1		$-CH_3$	1.7	170	100	0.97	—	—	—	—
2		$-CH_3$	17	1100	65	0.35	—	—	—	—
3		$-CH_3$	50	900	18	1.10	—	—	—	—
4		$-CH_3$	49	550	11	1.66	—	—	—	—
5		4-F–Ph–	0.90	1200	1300	2.71	0.55	<0.37	<0.42	56%
6		4-F–Ph–	0.93	500	540	2.35	0.48	<0.34	0.47	56%
7		4-F–Ph–	0.53	280	530	2.91	0.75	<0.39	0.32	51%
8		4-F–Ph–	0.90	65	72	3.47	0.75	0.33	0.40	23%
9		4-F–Ph–	0.97	330	340	4.03	0.70	0.32	0.32	39%
10		4-F–Ph–	0.75	420	560	1.56	<0.30	<0.20	<0.20	68%

[a] hLH: extraction ratio human liver hepatocytes, hLM: human liver microsomes, rLM: rat liver microsomes, see Ref. 27.

of MMP-13. Increasing the size of the P_1' group to 4-fluoro-phenoxy to take advantage of the deeper pocket yielded **5**, **8**, and **9**, which display increased MMP-13 potency ($IC_{50} < 1$ nM) and, in the case of **5** and **9**, high selectivity (>100-fold). Compounds containing the smaller cyclopropyl and cyclobutyl rings, **6** and **7** respectively, also display good potency and selectivity. The pyran analog **10**, which was prepared in an attempt to identify compounds with improved solubility (lower C log*P* than **5**–**9**), was found to be as active and selective as other compounds in the series. While the solubility of this compound is not substantially different from that of the other analogs (all >65 μg/mL), unexpectedly, **10** was found to be significantly more stable when incubated with human liver hepatocytes, having an extraction ratio (Er) of <0.30. Its somewhat improved potency over the cycloalkyl derivatives in our in vivo hamster model[23] (52% inhibition at 15 mg/kg po) is possibly a manifestation of its improved metabolic stability. These findings led us to continue our investigation of the SAR of the series by focusing on pyrans and closely related compounds.

In this exploration of the SAR, we initially examined the effect of changing the substitution pattern on the terminal P_1' phenoxy ring (Table 2). The unsubstituted analog **11**, is somewhat less potent than the 4-fluoro-phenoxy analog and displays a lower potency in our in vivo hamster model. Such a decrease in potency in the hamster model between a 4-substituted phenoxy analog and the corresponding unsubstituted derivative had been observed in other series. We believe this reflects rapid metabolism at C-4 of the phenoxy group. Altering the position of the fluorine atom on the phenoxy group does not make a significant difference to potency (**12** and **13**). Compounds **12** and **13** are stable when incubated with human liver microsomes (data not shown); however, they are notably less stable than **10** in a rat microsome preparation, again emphasizing the metabolic benefit of blocking C-4 of the phenoxy group with a substituent. Chloro substituents at C-2 (**14**) and C-3 (**15**) decrease the potency significantly indicating that although the S_1' pocket may be deep, it is also relatively narrow—able to accommodate *ortho* or *meta* fluoro but not chloro groups. Compounds containing 4-chloro

Table 2. SAR of P_1' residues on pyran hydroxamic acids



	X	Z	R_1	MMP-13 IC_{50} (nM)	MMP-1 IC_{50} (nM)	Ratio	C log*P*	Hamster % inh @ 15 mg/kg po	rLM Er[a]
11	O	O	Ph–	1.5	490	330	1.37	19%	
12	O	O	2-F–Ph–	0.64	180	280	1.36		0.57
13	O	O	3-F–Ph–	0.56	1100	1960	1.56		0.61
10	O	O	4-F–Ph–	0.75	420	560	1.56	52%	<0.20
14	O	O	2-Cl–Ph–	9.7	1700	180	1.97		0.53
15	O	O	3-Cl–Ph–	4.6	3900	850	2.13		0.79
16	O	O	4-Cl–Ph	1.2	320	270	2.13	48%	<0.20
17	O	O	4-CH_3O–Ph–	0.87	780	900	1.34		0.43
18	O	O	4-NC–Ph–	1.7	4800	2820	1.01		0.93
19	O	O	1-Naphthyl–	210	4900	23	2.55		0.67
20	O	O	2-Naphthyl–	5.0	3900	780	2.55		
21	O	O	Benzyl–	6.5	5400	830	0.96	11%	
22	O	O	2-F-benzyl–	19	9600	500	1.10		
23	O	O	3-F-benzyl–	24	8800	370	1.10		
24	O	O	4-F-benzyl–	11	6500	590	1.67	0%	
25	O	O	2-Pyridyl–	13	12,000	920	0.57		
26	O	O	3-Pyridyl–	25	550	22	0.22		
27	O	O	4-Pyridyl–	5.7	12,000	2100	0.22	50%	<0.20
28	O	O	5-F-2-Pyridyl–	14	3800	270	0.74		
29	O	O	5-Cl-2-Pyridyl–	1.5	1400	930	0.96		
30	O	S	4-F–Ph	4.6	5900	1280	1.40	31%	
31	O	—	4-F–Ph	4.4	200	45	1.01	26%	
32	S	O	4-F–Ph–	1.5	750	500	2.59	51%	0.45
33	SO_2	O	4-F–Ph–	2.0	550	280	0.33	6%	

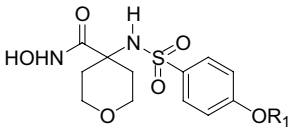
[a] rLM: extraction ratio rat liver microsomes, see Ref. 27.

(**16**), 4-methoxy (**17**), and 4-cyano (**18**) groups are about as potent as **10**. However, despite having C-4 blocked, only the 4-chloro derivative displays appreciable stability in rat microsomes with the C-4 methoxy and cyano groups apparently being subject to another mode of metabolism. Larger groups, such as naphthyl or benzyl diminish activity and substitution on the benzyl groups decrease potency even further (**19**–**24**). Of the two naphthyl derivatives, the more 'linear' 2-naphthyl analog is the more potent, again indicating that the S_1' pocket is deep and narrow. Replacing the phenoxy group with a heterocycle, 2-, 3-, or 4-pyridinyloxy, is also detrimental to activity whether the pyridine is substituted or not (**25**–**29**). The diminished activity of these pyridines presumably reflects the lower compatibility of the relatively hydrophilic pyridyl groups with the hydrophobic S_1' pocket (see C log*P*s in Table 2). Other structural alterations as represented by the thiophenoxy analog **30** or the biphenyl derivative **31** lead to a loss of potency presumably owing to the altered geometry of the P_1' side chain. Replacing the pyran with a thiopyran as in **32** is tolerated but at the cost of a significant increase in the log *P* (2.59) and a decrease in stability in the rat microsome preparation. Nevertheless, the compound shows good activity in the hamster model. The corresponding sulfone **33** is less lipophilic but is also less potent as an MMP-13 inhibitor and shows very weak activity in the hamster model. Owing to the combination of potency, activity in the hamster assay and stability in rat liver microsomes, we continued our work focusing on compounds containing 4-fluoro- and 4-chlorophenoxy P_1' side chains.

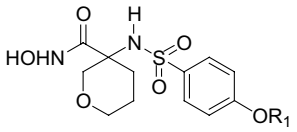
Two approaches were taken toward further improving the characteristics of the series. One was to move the heteroatom of the pyran ring closer to the hydroxamic acid. Since introduction of a heteroatom into the original cycloalkyl series led to the metabolically improved pyran series, we postulated that placing the heteroatom even closer to the site of metabolism could lead to further reduction in turnover. The second approach was to place additional steric hindrance around the hydroxamic acid by incorporating a bicyclic system.

In the first of these, both pyrans and tetrahydrofurans were prepared. These chiral analogs of **10** and **16** display enantiospecific differences in that the *S* isomers, **36**, **38**, and **40** are all somewhat more potent than the corresponding *R* isomers **35**, **37**, and **39** (Table 3). Modeling suggested that this may be due to differences in the interactions of the pyran or furan oxygen atom with the water network in the P_1 region of the protease. Although some attributes of these compounds are improved over those of **10** and **16**, on balance none of the compounds is clearly superior. For example, the in vivo characteristics of **35** are quite promising with the half-lives in rats and dogs being improved over those of the

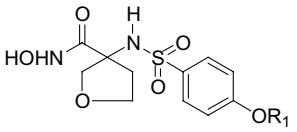
Table 3. SAR of chiral pyran, chiral tetrahydrofuran, and bicyclic analogs



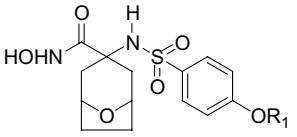
Achiral 6-membered ring series



Chiral 6-membered ring series



Chiral 5-membered ring series



6-5 Bicyclic ring series

	Ring size/ stereochem/X R_1 = 4-X–Ph	MMP-13 IC_{50} (nM)	MMP-1 IC_{50} (nM)	Ratio	hLH Er[a]	hLM Er[a]	rLH Er[a]	rLM Er[a]	Hamster % inh (@ 15 mg/kg)	Rat PK[b]				Dog PK[b]			
										Cl*p*	V_{ss}	$t_{1/2}$	*F*	Cl*p*	V_{ss}	$t_{1/2}$	*F*
10	6/—/F	0.75	420	560	<0.30	<0.20	0.33	<0.20	52%	52.6	1.9	0.9	29	10.3	1.6	6.5	52
16	6/—/Cl	1.2	320	270		0.41	0.08	<0.20	48%	12.7	2.1	3.6	72	8.0	1.8	6.0	62
34	6/*R*/F	0.56	290	520	0.90	<0.28	0.23	<0.27		21.8	3.2	3.9	—	19.2	3.6	5.8	—
35	6/*R*/Cl	1.0	350	350	0.60	<0.33	0.43	<0.34	50%	7.9	1.6	4.9	31	10.2	3.1	11.0	—
36	6/*S*/Cl	0.35	59	170			0.36	0.37									
37	5/*R*/F	1.3	1200	920		<0.22											
38	5/*S*/F	0.77	740	960		0.36				205	5.8	0.8	—				
39	5/*R*/Cl	0.93	870	930		0.34				142	—	0.6	—				
40	5/*S*/Cl	0.37	260	700		<0.42				39.4	1.5	1.5	—				
41	6–5/*exo*[c]/F	0.50	150	300	<0.29	<0.30	<0.48	<0.30	54%	27.7	1.5	1.1	90	7.8	1.5	6.5	86
42	6–5/*exo*[c]/Cl	0.65	180	280					71%	8.9	2.8	7.4	39				
43	6–5/*endo*[c]/F	3.3	1500	450													

[a] hLH: extraction ratio human liver hepatocytes, hLM:—human liver microsomes, rLH: rat liver hepatocytes, rLM: rat liver microsomes, see Ref. 27.

[b] Cl*p*: mL/min/kg; V_{ss}: L/kg, $t_{1/2}$: h, *F*: %.

[c] *exo*: sulfonamide and ring oxygen are *syn*, *endo*: *anti*.

achiral analogs; however, the human liver hepatocyte extraction ratio is significantly higher.

In the second approach, both diastereomers of the bicyclic system were prepared with the *exo* isomer displaying the better potency (**41** vs **43**). The potency, selectivity, stability in in vitro metabolism assays and the in vivo attributes of the 4-fluorophenoxy analog **41** are very similar to those of **10**, plus **41** has the advantage of having better bioavailability in rats and dogs.

Compounds **10** and **41** fulfilled our goal of identifying a sulfonamide hydroxamate that is a potent MMP-13 inhibitor (IC_{50}s 0.75 and 0.50 nM, respectively), spares MMP-1 (560-fold and 300-fold, respectively) and is projected to have once or twice daily dosing in humans ($t_{1/2}$ projected by allometric scaling: 8–13 and 5–10 h, respectively). As a result, both **10** and **41** were advanced into development. Compound **10** was first examined in a two-week rat toxicology study in order to determine its capacity for producing fibroplasia, with this assay acting as a surrogate for the likelihood of a compound producing MSS in humans.[24] It did not display fibroplasia in this two-week study and was therefore advanced into clinical trials. Two-week safety trials in normal volunteers revealed no side effects related to MSS. However, after dosing for four to six weeks in OA patients, exposure related MSS was observed.[25] Concurrent 90-day safety studies in rats revealed that with this long exposure, **10** does produce fibroplasia. Likewise, concurrent two-week toxicology studies with **41** in rats showed that this compound also produces fibroplasia. These results led us to terminate the study of this series of compounds and to conclude that inhibition of MMP-1 alone is not responsible for the MSS side effect that has been seen in humans with a variety of MMP inhibitors. Furthermore, the development of fibroplasia, like MSS, appears to be exposure related with **10** producing this effect only after many weeks while **41**, which has significantly higher bioavailability in rats, produces the effect within two weeks. Since both **10** and **41** are fairly nonselective inhibitors of MMPs other than MMP-1 (see Table 4), just which of these is responsible for the development of side effects in humans and pathology in rats remains unclear. Although MSS was observed with our MMP-1 sparing MMP-13 inhibitor, the reduced production of the neo-epitope formed by the cleavage of type II collagen by MMP-13 in OA patients treated with **10**[26] encourages us to seek MMP-13 inhibitors that possess higher degrees of selectivity over other MMPs.

Table 4. MMP activities of **10** and **41** IC_{50}s (nM)

	10	41
MMP-13	0.75	0.50
MMP-1	420	150
MMP-8	1.4	0.40
MMP-2	1.6	0.26
MMP-9	12	1.4
MMP-3	16	4.2
MMP-12	0.24	—
MMP-14	7.4	—

References and notes

1. MacPherson, L. J., Parker, D. T. European Patent 0 606 046, July 13, 1994; O'Byrne, E. M.; Parker, D. T.; Roberts, E. D.; Goldberg, R. L.; MacPherson, L. J.; Blancuzzi, V.; Wilson, D.; Singh, H. N.; Ludewig, R.; Ganu, V. S. *Inflamm. Res.* **1995**, *44*(Supl 44), S117–S118; MacPherson, L. J.; Bayburt, E. K.; Capparelli, M. P.; Carroll, B. J.; Goldstein, R.; Justice, M. R.; Zhu, L.; Hu, S.-i.; Melton, R. A.; Fryer, L.; Goldberg, R. L.; Doughty, J. R.; Spirito, S.; Blancuzzi, V.; Wilson, D.; O'Byrne, E. M.; Ganu, V.; Parker, D. T. *J. Med. Chem.* **1997**, *40*, 2525.
2. Zask, A.; Levin, J. I.; Killar, L. M.; Skotnicki, J. S. *Curr. Pharm. Des.* **1996**, *2*, 624; Henderson, B.; Docherty, A. J. P.; Beeley, N. R. A. *Drugs Future* **1990**, *15*, 495; Johnson, W. H.; Roberts, N. A.; Borkakoti, N. *J. Enzyme Inh.* **1987**, *2*, 1.
3. Supuran, C. T.; Casini, A.; Scozzafava, A. *Med. Res. Rev.* **2003**, *23*, 535; Skiles, J. W.; Gonnella, N. C.; Jeng, A. Y. *Curr. Med. Chem.* **2001**, *8*, 425; Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735.
4. Clark, I. M.; Parker, A. E. *Expert Opin. Ther. Targets* **2003**, *7*, 19; Henrotin, Y.; Sanchez, C.; Reginster, J.-Y. *Expert Opin. Ther. Patents* **2002**, *12*, 29.
5. Mitchell, P. G.; Magna, H. A.; Reeves, L. M.; Lopresti-Morrow, L. L.; Yocum, S. A.; Rosner, P. J.; Geoghegan, K. F.; Hambor, J. E. *J. Clin. Invest.* **1996**, *97*, 761.
6. Knauper, V.; Lopez-Otin, C.; Smith, B.; Knight, G.; Murphy, G. *J. Biol. Chem.* **1996**, *271*, 1544.
7. Yocum, S. A.; Lopresti-Morrow, L. L.; Reeves, L. M.; Mitchell, P. G. *Ann. NY Acad. Sci.* **1999**, *878*, 583; Borden, P.; Solymar, D.; Sucharczuk, A.; Lindman, B.; Cannon, P.; Heller, R. A. *J. Biol. Chem.* **1996**, *271*, 23577.
8. Freemont, A. J.; Byers, R. J.; Taiwo, Y. O.; Hoyland, J. A. *Ann. Rheum. Dis.* **1999**, *58*, 357.
9. Billinghurst, R. C.; Dahlberg, L.; Ionescu, M.; Reiner, A.; Bourne, R.; Rorabeck, C.; Mitchell, P.; Hambor, J.; Diekmann, O.; Tschesche, H.; Chen, J.; Van Wart, H.; Poole, A. R. *J. Clin. Invest.* **1997**, *99*, 1534; Billinghurst, R. C.; Wu, W.; Ionescu, M.; Reiner, A.; Dahlberg, L.; Chen, J.; Van Wart, H.; Poole, A. R. *Arthritis Rheum.* **2000**, *43*, 664.
10. Hutchinson, J. W.; Tierney, G. M.; Parsons, S. L.; Davis, T. R. C. *J. Bone Joint Surg. (Br.)* **1998**, *80-B*, 907; Wojtowicz-Praga, S.; Torri, J.; Johnson, M.; Steen, V.; Marshall, J.; Ness, E.; Dickson, R.; Sale, M.; Rasmussen, H. S.; Chiodo, T. A.; Hawkins, M. J. *J. Clin. Oncol.* **1998**, *16*, 2150; Griffioen, A. W. *IDrugs* **2000**, *3*, 336; Levitt, N. C.; Eskens, F. A. L. M.; O'Byrne, K. J.; Propper, D. J.; Denis, L. J.; Owen, S. J.; Choi, L.; Foekens, J. A.; Wilner, S.; Wood, J. M.; Nakajima, M.; Talbot, D. C.; Steward, W. P.; Harris, A. L.; Verweij, J. *Clin. Cancer Res.* **2001**, *7*, 1912.
11. Freskos, J. N.; McDonald, J. J.; Mischke, B. V.; Mullins, P. B.; Shieh, H.-S.; Stegeman, R. A.; Stevens, A. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1757; Barta, T. E.; Becker, D. P.; Bedell, L. J.; De Crescenzo, G. A.; McDonald, J. J.; Munie, G. E.; Rao, S.; Shieh, H.-S.; Stegeman, R.; Stevens, A. M.; Villamil, C. I. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2815; Chollet, A.-M.; Le Diguarher, T.; Murray, L.; Bertrand, M.; Tucker, G. C.; Sabatini, M.; Pierré, A.; Atassi, G.; Bonnet, J.; Casara, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 295; Becker, D. P.; Barta, T. E.; Bedell, L. J.; De Crescenzo, G. A.; Freskos, J.; Getman, D. P.; Hockerman, S. L.; Li, M.; Mehta, P.; Mischke, B.; Munie, G. E.; Swearingen, C.; Villamil, C. I. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2719.

12. Lovejoy, B.; Welch, A. R.; Carr, S.; Luong, C.; Broka, C.; Hendricks, R. T.; Campbell, J. A.; Walker, K. A. M.; Martin, R.; Van Wart, H.; Browner, M. F. *Nature Struct. Biol.* **1999**, *6*, 217.
13. O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, *19*, 2641; Kotha, S.; Kuki, A. *Tetrahedron Lett.* **1992**, *33*, 1565.
14. Schiavo, V.; Descotes, G.; Mentech, J. *Bull. Soc. Chim. Fr.* **1991**, 704.
15. O'Donnell, M. J.; Chen, N.; Zhou, C.; Murray, A.; Kubiak, C. P.; Yang, F.; Stanley, G. C. *J. Org. Chem.* **1997**, *62*, 3962.
16. Robinson, R. P. U.S. Patent 6,110,964, 2000; *Chem. Abstr.* **1999**, *131*, 286406.
17. Robinson, R. P.; McClure, K. F. U.S. Patent 6,303,636, 2001; *Chem. Abstr.* **1998**, *129*, 148828.
18. Reiter, L. A. U.S. Patent 6,087,392, 2000; *Chem. Abstr.* **1999**, *131*, 286405.
19. Seebach, D.; aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194.
20. Reiter, L. A. U.S. Patent 6,197,810, 2001; *Chem. Abstr.* **2000**, *134*, 29311; Reiter, L. A. U.S. Patent 6,342,521, 2002; *Chem. Abstr.* **2000**, *134*, 29299.
21. Nikam, S. S.; Komberg, B. E.; Johnson, D. R.; Doherty, A. M. *Tetrahedron Lett.* **1995**, *36*, 197.
22. MMP measurements were made using methods noted in our earlier work: Reiter, L. A.; Mitchell, P. G.; Martinelli, G. J.; Lopresti-Morrow, L. L.; Yocum, S. A.; Eskra, J. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2331.
23. Otterness, I. G.; Bliven, M. L.; Eskra, J. D.; te Koppele, J. M.; Stukenbrok, H. A.; Milici, A. J. *Osteoarthritis Cartilage* **2000**, *8*, 366.
24. Renkiewicz, R.; Qiu, L.; Lesch, C.; Sun, X.; Devalaraja, R.; Cody, T.; Kaldjian, E.; Welgus, H.; Baragi, V. *Arthritis Rheum.* **2003**, *48*, 1742.
25. Vazquez-Abad, M.-D., in preparation.
26. Hellio Le Graverand-Gastineau, M.-P., in preparation.
27. In vitro extraction ratios were calculated from predicted blood clearances (CLb) according to the following equation $Er = Clb/Q$ where 70 and 20 mL/min/kg were assumed hepatic blood flow (Q) for rat and human, respectively. Predicted clearances were obtained from the disappearance of drug in cryopreserved rat and human hepatocytes or microsomes according to the half-life method: Carlile, D. J.; Stevens, A. J.; Ashford, E. I.; Wagela, D.; Houston, J. B. *Drug Metab. Dispos.* **1998**, *26*, 216.