Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 4961–4966
Bioorganic & Medicinal Chemistry Letters

Synthesis and SAR of highly selective MMP-13 inhibitors

Jianchang Li,[a,*] Thomas S. Rush, III,[a] Wei Li,[a] Dianne DeVincentis,[a] Xuemei Du,[c] Yonghan Hu,[a] Jennifer R. Thomason,[a] Jason S. Xiang,[a] Jerauld S. Skotnicki,[c] Steve Tam,[a] Kristina M. Cunningham,[a] Priya S. Chockalingam,[b] Elisabeth A. Morris[b] and Jeremy I. Levin[c]

[a]*Department of Chemical and Screening Sciences, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140, USA*
[b]*Department of Women's Health and Bone, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140, USA*
[c]*Department of Chemical and Screening Sciences, Wyeth Research, 401 North Middletown Road, Pearl River, NY 10965, USA*

Received 18 April 2005; revised 3 August 2005; accepted 4 August 2005
Available online 8 September 2005

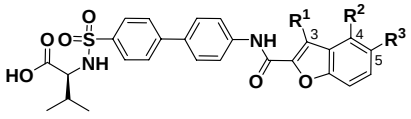
Abstract—The structure-based design and synthesis of a series of novel biphenyl sulfonamide carboxylic acids as potent MMP-13 inhibitors with selectivity over MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-14, Aggrecanase 1, and TACE are described.

MMP-13 (matrix metalloproteinase-13, also known as collagenase-3) belongs to a large family of zinc-containing enzymes that are involved in the degradation and remodeling of extracellular matrix proteins. The expression of MMP-13 by chondrocytes in human osteoarthritic cartilage and its activity against type II collagen, the main structural component of articular cartilage, suggest that this enzyme plays a crucial role in the etiology of osteoarthritis,[1] and that inhibition of MMP-13 may provide an effective treatment paradigm for this disease. The therapeutic potential for potent, orally active, small molecule inhibitors of MMP-13, and other MMPs, to treat a variety of pathologies including arthritis, cancer, and pulmonary disease, has made them prime targets for drug development.[2]

Early preclinical testing of non-selective MMP inhibitors has shown that these inhibitors are able to prevent the destruction of cartilage in some animal models of osteoarthritis.[3] However, clinical trials of broad spectrum MMP inhibitors have also been plagued by dose-limiting toxicity in the form of musculoskeletal side effects.[4] This side effect has been postulated to result from the inhibition of MMP-1, or MMP-14, or sheddases, such as TACE. As a result, interest in more selective MMP-13 inhibitors has increased.[5–9]

We have recently disclosed[10] compound **1** (Fig. 1) ($R^1 = R^2 = R^3 = H$), an early lead compound in our MMP-13 program, which shows excellent selectivity for MMP-13 over MMP-1, MMP-9, MMP-14, Aggrecanase 1 (Agg1), and TACE due to its long, rigid P1′ group. However, compound **1** lacks selectivity against some other MMPs, including MMP-2, MMP-3, MMP-7, and MMP-8.

In an effort to improve the selectivity of **1**, available MMP X-ray data were examined and computer modeling analyses of MMP S1′ subsites were performed. These studies indicated that the loop region of MMP-2 that forms its S1′ pocket is two amino acids shorter than the analogous region in MMP-13. Thus, the S1′ pocket of MMP-2 is constricted, relative to that of MMP-13. Structure-based design indicated that incorporating a substituent at the 4-position (R^2) of the benzofuran would take advantage of this size difference and enhance selectivity. This structural analysis also indicated that if



(**1**)

Figure 1. Benzofuran amide biphenyl sulfonamide carboxylates.

* Corresponding author. E-mail: JCLI@wyeth.com

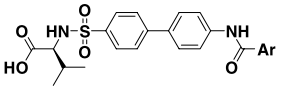
0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.08.001

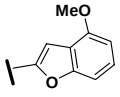
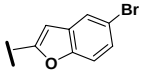
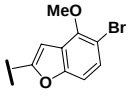
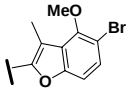
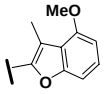
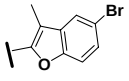
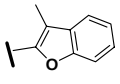
selectivity was optimized for MMP-13 over the closely related MMP-2, we were likely to achieve selectivity over MMP-3, -7, and -8 as well.[11]

In fact, compound **1a** ($R^1 = R^3 = H$, $R^2 = OCH_2(CH_3)$-CO_2H) had been shown to provide 100-fold selectivity for MMP-13 over MMP-2.[10] A smaller methoxy substituent at the 4-position of the benzofuran of compound **1b** ($R^1 = R^3 = H$, $R^2 = OCH_3$) still yields a potent MMP-13 inhibitor, but it is unfortunately only 7-fold selective, since the methoxy group does not probe deeply enough into the S1′ pocket of MMP-2 (Table 1). Similarly, compound **2**, the 5-bromobenzofuran derivative, is non-selective, though extremely potent against MMP-13. This is in accord with the predicted structure of **2** bound to MMP-2 and -13, as the 5-position is not directed at the S1′ loop region of MMP-2 which differs from that of MMP-13.

We now report on our efforts to enhance the selectivity of these inhibitors for MMP-13 over MMP-2 by extending the SAR of this scaffold to compounds bearing multiple substituents on the benzofuran P1′ ring system. The resulting novel biphenyl sulfonamide carboxylic acids of general structure **1**, bearing a 3,4,5-tri-substituted benzofuran 2-carboxamide P1′ moiety, have been found to be potent and highly selective MMP-13 inhibitors.[12]

Table 1. Identification of groups that are responsible for the selectivity



Compound No.	Ar	IC_{50} (nM)[a]		
		MMP-2	MMP-13	MMP-2/MMP-13
1b		16	2.3	7
2		0.91	0.61	1
3		7.1	0.4	18
4		1700	2.3	740
5		1050	9.5	110
6		81	3.0	27
7		259	5.9	44

[a] The assays used to obtain the data for this table were performed as detailed in Ref. 12.

The first disubstituted analog prepared was benzofuran carboxamide **3**, a hybrid of compounds **1b** and **2**, substituted at both the 4- and 5-positions. While this derivative is extremely potent against MMP-13, it still displays only 18-fold selectivity over MMP-2, not a substantial improvement. However, we were delighted to find that when a methyl substituent is appended to the 3-position of 4,5-disubstituted benzofuran **3** to provide the 3,4,5-trisubstituted benzofuran amide **4**, selectivity improves quite drastically. Thus, compound **4** retains potency against MMP-13 ($IC_{50} = 2.3$ nM), but is also now more than 700-fold selective over MMP-2. Furthermore, compound **4** is not only very selective over MMP-2, but also has significantly improved selectivity against MMP-3 ($IC_{50} = 144$ nM), MMP-7 ($IC_{50} = 866$ nM), MMP-8 ($IC_{50} = 73$ nM), and maintains the selectivity over MMP-1 ($IC_{50} = 30$ μM), MMP-9 (66% inhibition at 25 μM), MMP-14 ($IC_{50} = 15$ μM), Aggrecanase 1 ($IC_{50} = 5.6$ μM), and TACE ($IC_{50} = 34$ μM) in accord with our initial assumption. To assess the origin of this excellent selectivity, three additional analogs bearing the 3-methyl substituent, **5**, **6**, and **7**, were prepared. Elimination of the 5-bromo group from analog **4** gave 3-methyl-4-methoxy benzofuran **5** and resulted in a slightly diminished MMP-13 potency and a concomitant diminution of selectivity to 110-fold. Deletion of the 4-methoxy group from **4** provided analog **6**, essentially equipotent to **4** against MMP-13, but with a devastating loss of selectivity to only 27-fold selective over MMP-2. Finally, the 4,5-unsubstituted 3-methyl benzofuran **7** was 44-fold selective. Therefore, the exceptional selectivity of compound **4** for MMP-13 over MMP-2 clearly results from a synergistic effect of all three 3-, 4-, and 5-substituents on the P1′ benzofuran.

The potency and selectivity of compound **4** can be explained on the basis of modeling studies based on X-ray crystallographic data (Fig. 2). Computational studies of the 3D conformations of **4** suggest that the 3-methyl group causes the conjugated amide-benzofuran system to be displaced from planarity by about 20 degrees, which helps direct the 4-methoxy substituent directly toward THR229 of the MMP-2 S1′ pocket. The bromine atom at position 5, with its large van der Waals radius, additionally helps constrain the mobility of the methoxy group such that, if the molecule were docked like the unsubstituted benzofuran analog, **1**, the methyl group of the methoxy moiety would lie within 1.8 Å of the THR229 Cβ atom. No such steric clash exists for the benzofuran substituents with the S1′ pocket of MMP-13.

The effect of the configuration of the amino acid portion of the biphenyl sulfonamide scaffold on potency and selectivity was investigated. A comparison of the (*S*)- and (*R*)- isomers of three benzofuran P1′ analogs is shown in Table 2. The pair of enantiomers, **1** and **8**, bearing the unsubstituted benzofuran P1′ group has virtually identical potency against both MMP-13 and

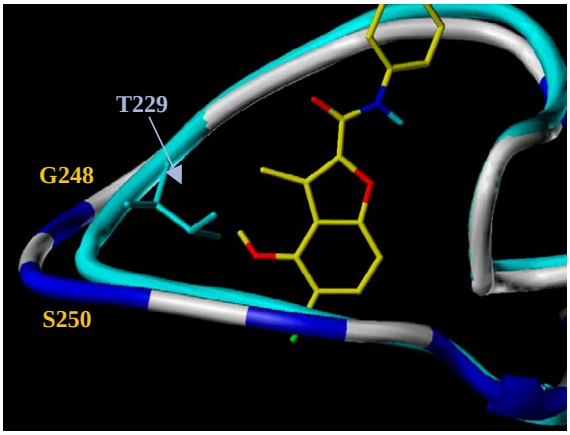
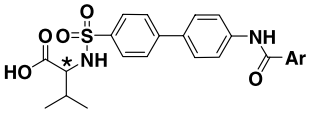
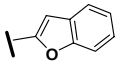
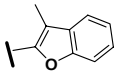
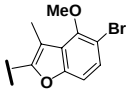


Figure 2. A close-up and schematic view of the predicted binding mode of compound **4** to MMP-13, overlaid with the catalytic domain of MMP-2. The white tube represents MMP-13, while the cyan tube represents MMP-2. The blue coloring in the MMP-13 tube highlights the positions of amino acid differences between the two proteins.

Table 2. Comparison of potency and selectivity of (*R*)- and (*S*)-isomers

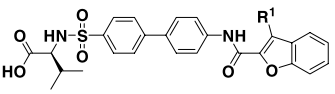


Ar	Compound No.	*	IC_{50} (nm) MMP-2	MMP-13	MMP-2/MMP-13
	**1**	(*S*)-	5	2.4	2
	8	(*R*)-	4.6	2.6	2
	**7**	(*S*)-	259	5.9	44
	9	(*R*)-	164	17	10
	**4**	(*S*)-	1,700	2.3	739
	10	(*R*)-	688	3.4	202

MMP-2. In contrast, for the pair of enantiomers with the 3-methylbenzofuran P1′ terminus, **7** and **9**, the (*S*)-enantiomer is more potent against MMP-13 and more selective over MMP-2 than the corresponding (*R*)-isomer. A similar SAR exists for (*S*)-enantiomer **4** and its epimer, **10**. In this case although the MMP-13 activity is similar for both enantiomers, the (*S*)-analog is more than 2-fold less potent against MMP-2.

The optimization of the benzofuran 3-substituent is shown in Table 3. The potency and selectivity of analogs bearing groups at the 3-position, ranging in size from a simple hydrogen atom to a phenyl group, were examined. Compound **1**, the 3-hydrogen derivative, shows equal activity against MMP-2 and MMP-13. Compound **7**, with a methyl substituent, is a 5.9 nM inhibitor of MMP-13 with 44-fold selectivity for MMP-13 over MMP-2. However, when the size of the 3-substituent

Table 3. SAR of 3-substituted benzofuran 2-carboxamide P1′



Compound No.	R^1	IC_{50} (nm) MMP-2	MMP-13	MMP-2/MMP-13
1	H	5	2.4	2
7	CH_3	259	5.9	44
11	CH_2CH_3	1770	55	32
12	Ph	1200	220	6

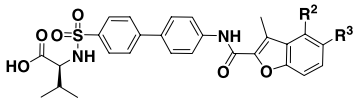
was increased further, selectivity does not increase proportionately. In addition, the potency of the inhibitors decreased rapidly as the size of the 3-substituent was increased from methyl to ethyl to phenyl. Compound **11**, with an IC_{50} of 55 nM, is almost 10-fold less potent than methyl derivative **7**, and the phenyl analog, **12**, is more than 30-fold less potent than **7**. Overall, the methyl group appears to offer the best combination of potency and high selectivity.

With the 3-position of the benzofuran 2-carboxamide fixed, the SAR of a variety of 3,4,5-trisubstituted benzofuran 2-carboxamides was examined. As shown in Table 4, all inhibitors, **13**–**18**, bearing a 4-methoxy group on the benzofuran are potent against MMP-13. Selectivity does not vary significantly with the size of the halogen 5-substituent of compounds **4**, **13**, and **14**, all three analogs providing over 650-fold selectivity. The lowest levels of selectivity in the 4-methoxy series are seen with the 5-hydroxymethyl moiety, **15**, and the small 5-cyano group, **17**, although both of them are still well over 100-fold selective. A significant increase in selectivity, with no loss in MMP-13 potency, is also noted in going from the 5-methyl analog **16** to 5-ethyl derivative **18**.

Compound **19** has the lowest selectivity (20-fold) among the 3,4,5-trisubstituted analogs. We speculate that an intra-molecular hydrogen bond between the 4-hydroxy and 5-acyl group contributes to reduced selectivity, although we do not have any direct structural information. In analog **20**, where such an orientational restriction of the hydroxy is absent, selectivity is even greater (250-fold). Larger 4-substituents are also tolerated in the 3,4,5-trisubstituted analogs. Thus, the isopropyl ethers **22** and **23** maintain reasonable potency and selectivity for MMP-13 over MMP-2. The 4-benzyloxy derivative, **21**, is only moderately potent against MMP-13, which results in diminished selectivity over MMP-2.

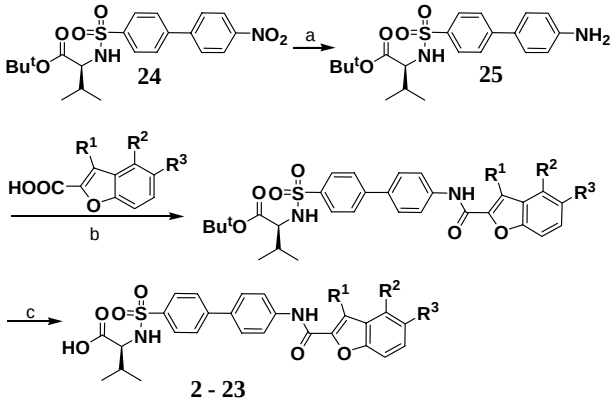
The synthesis[13] of the biphenyl sulfonamide carboxylic acid is shown in Scheme 1. The preparation of nitro-biphenyl sulfonamide **24** has been reported.[14] Reduction of the nitro group afforded aniline **25** in very good yield. After coupling of aniline with the benzofuran carboxylic acid, ester hydrolysis gave the desired products (**2**–**23**). In some cases, the methyl ester of the amino acid was

Table 4. Selectivity of 3,4,5-trisubstituted benzofuran derivatives[a]



Comp. No.	R^2	R^3	IC_{50} (nm), or % inhibition at 25 μM										
			MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-14	Agg1	TACE	MMP-13	MMP-2/MMP-13
4	OMe	Br	30,000	1,700	144	866	73	66%	15,000	5,600	34,000	2.3	740
13	OMe	I	60,000	1,370	1,060	3,010	404	51%	30,000	15,000	38%	2.1	650
14	OMe	Cl	34,000	1,490	—	—	—	—	12,400	—	—	1.9	785
15	OMe	CH_2OH	—	1,410	—	—	—	—	—	—	—	7.8	180
16	OMe	Me	37,100	1,610	442	534	52	76%	15,000	8,600	39%	4.9	330
17	OMe	CN	—	522	—	—	—	—	—	—	—	3	175
18	OMe	Et	28,000	2,500	561	1,260	101	64%	30,000	>15,000	43%	3.8	660
19	OH	COMe	—	63	—	—	—	—	—	—	—	3.2	20
20	OH	Et	23,400	1,760	492	458	94	55%	15,800	4,400	42%	7.1	250
21	OCH_2Ph	Et	—	4,340	—	—	—	—	—	—	—	67	65
22	O(*i*-Pr)	Et	—	7,000	—	—	—	—	—	—	—	27	260
23	O(*i*-Pr)	Cl	37,100	3,010	1,090	1,640	110	51%	50,000	14,300	98%	11	275

[a] Lines indicate that biological activity data for that MMP are not available.

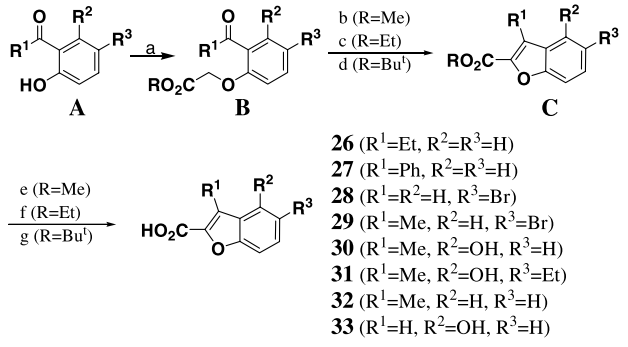


Scheme 1. Reagents and conditions: Preparation of benzofuran biphenyl sulfonamide carboxylates. (a) H_2, Pd/C, 50 psi, rt, 5 h, (90%); (b) BOP, DIEA, DMF, rt, overnight, (40–80%); (c) TFA/CH_2Cl_2 (1:1), rt, 3 h, (70–100%).

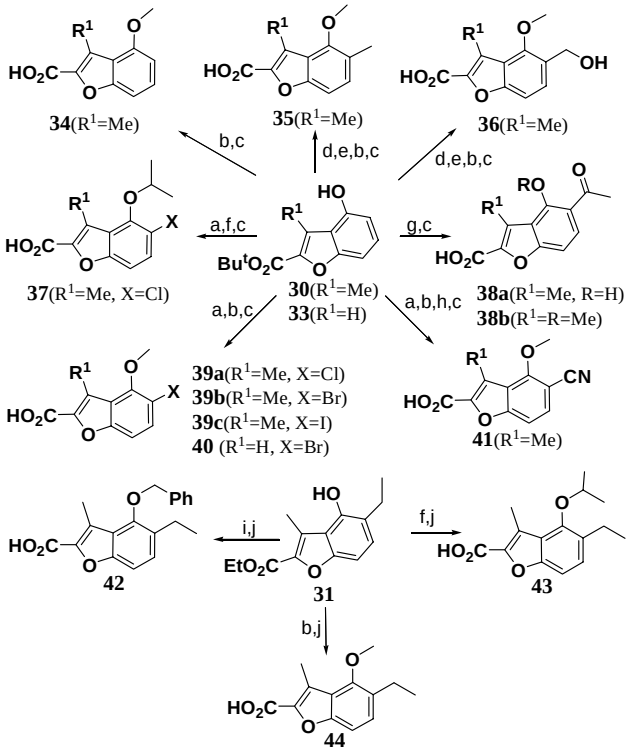
used and a basic (LiOH/MeOH/H_2O) hydrolysis was carried out.

Most of the substituted benzofuran carboxylic acids we required were not commercially available and were synthesized in one of the two approaches, as shown in Schemes 2 and 3. The first approach was to construct the benzofuran ring with desired substitution (Scheme 2). Salicylaldehydes and ketones **A**, bearing a variety of substituents R^1, R^2, and R^3, are alkylated with α-bromoacetic acid esters to give **B**, which is next cyclized in the presence of an alkoxide base in alcohol or potassium carbonate in DMF to afford the substituted benzofurans **C**. Esters **C** are hydrolyzed with aqueous hydroxide or TFA (for R = *t*-butyl) to give the carboxylic acids **26**–**33**, which, in turn, can be coupled with aniline **25** to make the desired final product. Some of these acids in Schemes 2 and 3 or their esters have been reported in the literature including **26**,[15] **27**,[16] **28**,[17] **30**,[18] **32**,[19] **33**,[20] and **34**.[21]

The second approach to the substituted benzofuran derivatives is shown in Scheme 3. The synthesis of selected 3,4,5-trisubstituted benzofurans through functionalization (**34**–**39c**, **41**) and derivatization (**42**–**44**) is presented. Hydroxybenzofuran **30** can be converted to **34** through methylation with methyl iodide in the presence of potassium carbonate in a polar aprotic solvent, such as DMF or THF. The reaction of **30** with magnesium methoxide, followed by paraformaldehyde, produces the ortho-formyl phenol, which can be reduced to the 5-methyl benzofuran or 5-hydroxymethyl benzofuran. Subsequent methylations of these benzofuran afford **35** and **36**. Phenol **30** and its *O*-alkylated derivative **34** undergo ortho-acylation with acetyl chloride and titanium tetrachloride to give acetophenones **38**. Compounds of structure **30** are readily halogenated with *N*-halogen succinimides to provide 5-halogenated phenol, which, in turn, may be alkylated to give ethers **37** and**39**. Compound **40** was obtained in the same manner starting from **33**. Palladium catalyzed reaction of **39c** with zinc cyanide, followed by hydrolysis, gives nitrile **41**. O-Alkylation of 4-hydroxy-5-ethylbenzofuran **31**



Scheme 2. Reagents and conditions: Constructing the benzofuran ring with desired substitution. (a) $BrCH_2CO_2R$ (R=Me, Et or Bu^t), K_2CO_3, rt, (70–90%); (b) MeONa, MeOH, 60 °C (40–90%); (c) NaOEt, EtOH, 70 °C, (70–90%); (d) K_2CO_3, 130 °C, 1 h (60–90%); (e) LiOH, MeOH, THF, rt. (70–90%); (f) NaOH, H_2O, EtOH, (80–90%); (g) TFA/CH_2Cl_2(1:1), rt, 4 h, (70–90%).



Scheme 3. Reagents and conditions: Functionalization and derivatization of the benzofuran ring. (a) NXS(NCS for **39a**, NBS for **39b** and **40**, NIS for **39c**), CCl_4, 0 °C, 6 h, (50–85%); (b) MeI, K_2CO_3, DMF, rt, overnight, (80–100%); (c) TFA/CH_2Cl_2(1:1), rt, 4 h, (70–90%); (d) (i) $(MgOMe)_2$/MeOH, toluene, reflux, 1 h. (ii) $(CH_2O)_n$, reflux, 30 min, (50%); (e) $NaBH_3CN$, THF, 60 °C, (30–40%); (f) *i*-PrBr, K_2CO_3, DMF, rt, overnight, (80–100%); (g) AcCl, $TiCl_4$, PhCl, 95 °C, pressure tube, (40–60%); (h) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 85 °C, 2 h, (70%); (i) BnBr, K_2CO_3, DMF, rt, overnight, (80%); (j) NaOH, H_2O, EtOH, (80–90%).

gives ethers, which are next hydrolyzed in alkoxide base in alcohol to afford **42**, **43**, and **44.**

In summary, we have described a promising series of biphenyl sulfonamide carboxylic acids that are potent inhibitors of MMP-13 that spare MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-14, Agg1, and TACE. By varying the substituents on the benzofuran portion of the molecules, we were able to modulate the potency and selectivity of this series of inhibitors. Further development and the in vivo efficacy of this series of compounds will be reported in due course.

Acknowledgments

We thank Dr. Nelson Huang, Dr. Yin Ge, and Dr. Walter Massefski for LC-MS, HRMS, and NMR measurements; Ms. Elizabeth Collins for her contribution to the selectivity assays and Dr. Kathy Lee for editing the manuscript.

References and notes

1. 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.
2. Skiles, J. W.; Gonnella, N. C.; Jeng, A. Y. *Curr. Med. Chem.* **2004**, *11*, 2911.
3. (a) 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. *Inflamm. Res.* **1995**, *44*, 5177; (b) Prata, M. A. *Inflamm. Res.* **1995**, *44*, 458.
4. Wojtowicz-Praga, S.; Torri, J.; Johnson, M.; Steen, V.; Marshall, J.; Ness, E.; Dickson, R.; Sale, M.; Rasmussen, H. S.; Chido, T. A.; Hawkins, M. J. *J. Clin. Oncol.* **1998**, *16*, 2150.
5. Skotnicki, J. S.; DiGrandi, M. J.; Levin, J. I. *Curr. Opin. Drug Discov. Devel.* **2003**, *6*, 742.
6. Cherney, R. J.; Mo, R.; Meyer, D. T.; Hardman, K. D.; Liu, R.; Covington, M. B.; Qian, M.; Wasserman, Z. R.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **2004**, *47*, 2981.
7. Noe, K. C.; Snow, S. L.; Wolf-Gouveia, L. A.; Mitchell, P. G.; Lopresti-Morrow, L.; Reeves, L. M.; Yocum, S. A.; Liras, J. L.; Vaughn, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4727.
8. Reiter, L. A.; Robinson, R. P.; McClure, K. F.; Jones, C. S.; Reese, M. R.; Mitchell, P. G.; Otterness, I. G.; Bliven, M. L.; Liras, J.; Cortina, S. R.; Donahue, K. M.; Eskra, J. D.; Griffiths, R. J.; Lame, M. E.; Lopez-Anaya, A.; Martinelli, G. J.; McGahee, S. M.; Yocum, S. A.; Lopresti-Morrow, L. L.; Tobiassen, L. M.; Vaughn-Bowser, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3389.
9. (a) Tullis, J. S.; Laufersweiler, M. J.; VanRens, J. C.; Natchus, M. G.; Bookland, R. G.; Almstead, N. G.; Pikul, S.; De, B.; Hsieh, L. C.; Janusz, M. J.; Branch, T. M.; Peng, S. X.; Jin, Y. Y.; Hudlicky, T.; Oppong, K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1975; (b) Pikul, S.; Ohler, N. E.; Ciszewski, G.; Laufersweiler, M. C.; Almstead, N. G.; De, B.; Natchus, M. G.; Hsieh, L. C.; Janusz, M. J.; Peng, S. X.; Branch, T. M.; King, S. L.; Taiwo, Y. O.; Mieling, G. E. *J. Med. Chem.* **2001**, *44*, 2499; (c) Natchus, M. G.; Bookland, R. G.; Laufersweiler, M. J.; Pikul, S.; Almstead, N. G.; De, B.; Janusz, M. J.; Hsieh, L. C.; Gu, F.; Pokross, M. E.; Patel, V. S.; Garver, S. M.; Peng, S. X.; Branch, T. M.; King, S. L.; Baker, T. R.; Foltz, D. J.; Mieling, G. E. *J. Med. Chem.* **2001**, *44*, 1060.
10. (a) Wu, J.; Hotchandani, R.; Hu, F.; Levin, J. I.; Li, J.; Li, W.; Lovering, F.; Morris, E.; Rush, T.; Wang, Q.; Xu, Z.; Yang, X. X.; "*Design and Development of Potent and Selective MMP-13 Inhibitors*" at the meeting of "Inhibition of Matrix Metallopreoteinases: Expanding the Horizons", New York, October 23, 2004; (b) Wu, J.; Rush, T. S.; Hotchandani, R.; Du, X.; Geck, M.; Collins, E.; Xu, Z.; Skotnicki, J.; Levin, J. I.; Lovering, F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4105.
11. (a) Rush, T. S., III; Powers, R. *Cur. Top. Med. Chem.* **2004**, *4*, 1311; (b) Rao, B. G. *Curr. Pharm. Design* **2005**, *11*, 295; (c) Maskos, K. *Biochimie* **2005**, *87*, 249; (d) Cuniasse, P.; Devel, L.; Makaritis, A.; Beau, F.; Georgiadis, D.; Matziari, M.; Yiotakis, A.; Dive, V. *Biochimie* **2005**, *87*, 393, A manuscript describing the modeling analyses of MMP S1′ pockets is in preparation.
12. (a) The inhibitory ability of small molecules was tested in a continuous fluorescent assay designed for each enzyme in which the substrate is a synthetic peptide containing a fluorescent group (7-methoxycoumarin or 2-aminobenzoyl) that is quenched by energy transfer to 2,4-dinitrophenyl. Enzymes were either prepared at Wyeth Research (MMP-1, -12, -13, Agg-1, TACE) or purchased from Calbiochem (San Diego, CA) (MMP-3, -7, -9), R&D Systems (Minneapolis, MN) (MMP-2), Chemicon International (Temecula, CA) (MMP-14), or Biomol (Plymouth Meeting, PA) (MMP-8). MMP-2 and MMP-14 were

activated with AMPA. Enzymatic assay conditions for MMP-1, -2, -7, -9, -13, -14, Agg-1, and TACE have been previously described[12b] and identical assay conditions were used for MMP-3 and -12, except for MMP-3 which used the substrate Mca-PKPLAL-Dpa-AR-NH2 (Bachem, King of Prussia, PA). Measurements were performed in fluorimeter plate readers at the excitation and emission wavelengths of the fluorophore. Note that while IC_{50} values were reported, the assays were established in such a way as to keep the IC_{50} and K_i within 2-fold of each other by manipulating the relationship between a given MMP substrate concentration and its K_m, as dictated by the Cheng-Prusoff equation (see Ref. 12b); (b) Cheng, Y-C.; Prusoff, W. *Biochem. Pharmacol.* **1973**, *22*, 3099; (c) Zhang, Y.; Xu, J.; Levin, J.; Hegen, M.; Li, G.; Robertshaw, H.; Brennan, F.; Cummons, T.; Clarke, D.; Vansell, N.; Nickerson-Nutter, C.; Barone, D.; Mohler, K.; Black, R.; Skotnicki, J.; Gibbons, J.; Feldmann, M.; Frost, P.; Larson, G.; Lin, L.-L. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 348.

13. All new compounds gave satisfactory ^1H NMR, MS in accord with their assigned structure.
14. Fei, X.; Zheng, Q-H.; Liu, X.; Wang, J.-Q.; Sun, H. B.; Mock, B. H.; Stone, K. L.; Miller, K. D.; Sledge, G. W.; Hutchins, G. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2217.
15. (a) Buttery, C. D.; Knight, D. W.; Nott, A. P. *Tetrahedron Lett.* **1982**, *23*, 4127; (b) Sharshira, E. M.; Horaguchi, T. *J. Heterocyclic Chem.* **1997**, *34*, 1837.
16. Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.
17. D'Sa, B. A.; Kisanga, P.; Verkade, J. G. *Synlett* **2001**, *5*, 670.
18. Masubuchi, M.; Kawasaki, K.-I.; Ebiike, H.; Ikeda, Y.; Tsujii, S.; Sogabe, S.; Fujii, T.; Sakata, K.; Shiratori, Y.; Aoki, Y.; Ohtsuka, T.; Shimma, N. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1833.
19. Topolski, M. *J. Org. Chem.* **1995**, *60*, 5588.
20. Yamaguchi, S.; Yamamoto, K.; Ueda, T.; Morikawa, T.; Kawase, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 4066.
21. Salvi, V. S.; Sethna, S. *J. Indian Chem. Soc.* **1968**, *45*, 439.