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Syntheses and in vitro evaluation of arylsulfone-based MMP inhibitors with heterocycle-derived zinc-binding groups (ZBGs)

Yue-Mei Zhang,* Xiaodong Fan, Shyh-Ming Yang, Robert H. Scannevin, Sharon L. Burke, Kenneth J. Rhodes and Paul F. Jackson

East Coast Research and Early Development, Johnson & Johnson Pharmaceutical Research and Development, Welsh & McKean Roads, Spring House, PA 19477, USA

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Abstract—Several classes of arylsulfone-based MMP-2/-9 inhibitors utilizing 6- to 8-membered heterocyclic rings as zinc-binding groups (ZBGs) have been synthesized and their enzyme inhibitory activities were evaluated. Although a number of 6- and 7-membered heterocycles were effective, the most potent arylsulfone inhibitors are based on the rigid 1- or 3-hydroxypyridone ZBG.

Over-expression of matrix metalloproteinases (MMP) has been implicated in a variety of disease states involving matrix degradation such as cancer, arthritises, cardiovascular diseases, and neurological disorders.[1] Therefore, MMPs have become valid therapeutic targets and many MMP inhibitors (MMPIs) have been developed over the last two decades. However, none of these compounds has successfully completed clinical trials due to the lack of efficacy and long-term dose-limiting side effects in diseases such as cancer and arthritis.[2] Despite these shortcomings, MMP inhibition is still believed to be a valid therapeutic approach. More recently, it has been suggested that MMPIs might have efficacy in the acute clinical setting, in the treatment of disorders such as ischemic stroke, aneurysm, and myocardial rupture.[3]

Typically, an active site MMP inhibitor consists of a Zn-binding group (ZBG) and a recognition motif that binds to the protein. The vast majority of synthetic MMPIs generally fall into four classes (categorized by ZBGs): hydroxamic acids, carboxylic acids, thiols, and tetracyclines. To overcome the limitations of these frequently used ZBGs, the effort to discover other ZBG moieties has been reported.[4] Recently, hydroxypyridinones (HOPOs) and pyrones have emerged as novel ZBGs in MMPI research.[5] Previously, we disclosed a novel series of aryl sulfonamide MMP-2/-9 inhibitors containing *N*-hydroxy-2-pyridinone as the ZBG, with excellent MMP-2/-9 inhibitory activity and in vivo efficacy in a mouse transient middle cerebral artery occlusion (tMCAO) model (Fig. 1, **1**).[6] As part of a continuing effort to explore heterocycle-based ZBGs in our MMP program, herein we report the discovery of a novel series of α- or β-arylsulfone-based MMP-2/-9 inhibitors containing 6- to 8-membered heterocycles as ZBGs

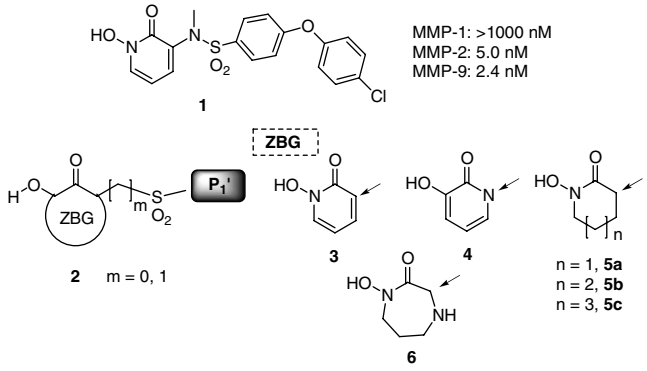

Figure 1. MMPIs with heterocycles as ZBGs.

Keywords: Matrix metalloproteinase inhibitor; Arylsulfone; MMP-2; MMP-9; Zinc-binding group.
* Corresponding author. Tel.: +1 609 409 3498; fax: +1 609 655 6930; e-mail addresses: yzhang5@prdus.jnj.com; xufangymz@yahoo.com

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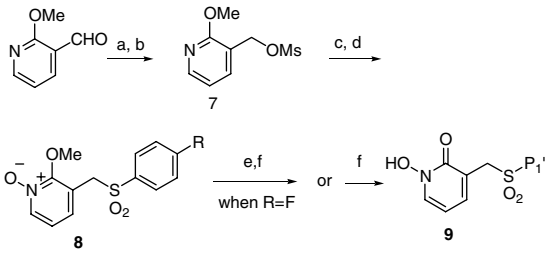
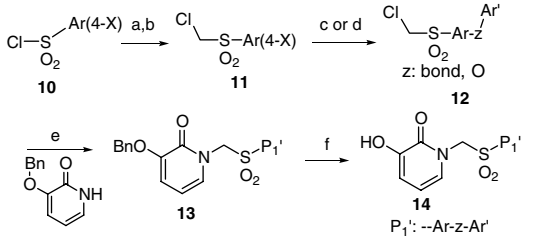


Scheme 1. Reagents and conditions: (a) $NaBH_4$, EtOH, −20 °C, 90%; (b) MsCl, TEA, CH_2Cl_2, 87%; (c) (4-R)PhSH, TEA, $CHCl_3$, 50 °C, 84%; (d) UHP/TFAA (2.1:2), CH_2Cl_2, 0 °C–rt, 54%; (e) (4-OMe)-PhOH, Cs_2CO_3, DMF, 90 °C, 78%; (f) 2 N HCl/MeOH (1:1.5), reflux, 96%.

(Fig. 1, **2**). These ZBGs (Fig. 1, **3**–**6**) were postulated to bind the zinc(II) ion in a bidentate fashion.

Synthesis of the *N*-hydroxy-2-pyridinone-based arylsulfone **9** is outlined in Scheme 1. Reduction of 2-methoxy-3-pyridinecarboxaldehyde with Na BH_4 and subsequent mesylation of the alcohol gave **7**. The P_1' group was then installed by an SN2 displacement reaction with an aryl thiol under basic conditions. Subsequent oxidation with a urea–H_2O_2 complex (UHP) and trifluoroacetic anhydride afforded the fully oxidizded compound **8**. The R substituent can be further elaborated via nucleophilic aromatic displacement of fluorine to obtain a biaryl ether P_1' substituent. The hydrolysis of the 2-methoxypyridine *N*-oxide provided the target compound **9** in high yield.

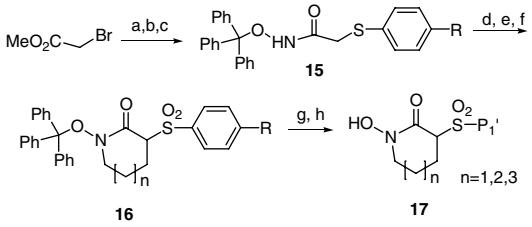
Similarly, Scheme 2 describes the preparation of compounds containing a 3-hydroxy-2-pyridinone ZBG. Chloromethylsulfone **11** was obtained via a one-pot two-step sequence from commercially available sulfonyl chloride **10** and bromochloromethane.[7] Pd-catalyzed Suzuki coupling or Cu(I)-catalyzed Ullmann coupling with an aryl bromide, or alternatively SN2 displacement of an aryl fluoride with an appropriately substituted phenoxide, afforded **12**. The Suzuki or Ullmann coupling needed to be monitored closely as prolonged reaction time increased the formation of the by-product methyl sulfones resulting from chloride reduction. Compound **12** was then reacted with benzyl protected 3-hydroxy-2-pyridinone under basic conditions,[8] followed by benzyl cleavage with neat $MeSO_3H$, to give the final compound **14**.



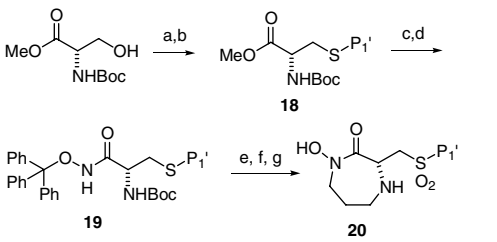
Scheme 2. Reagents and conditions: (a) Na_2SO_3, $NaHCO_3/H_2O$; (b) $BrCH_2Cl$, TBAB (cat.), 60% (two step); (c) when X = Br, 1.2 equiv $Ar'B(OH)_2$, 5 mol% $Pd(dppf)Cl_2$, 2.0 equiv Na_2CO_3 (2 M), 1,4-dioxane/H_2O, 74%; (d) when X = F, 1.1 equiv Ar′OH, K_2CO_3, DMF, 88%; when X = Br, 1.3 equiv. Ar′OH, 10 mol% CuI, 40 mol% 2,2,6,6-tetramethyl-heptane-3,5-dione, Cs_2CO_3, DMF, 100 °C, 66%; (e) Cs_2CO_3, DMF, 85%; (f) $MeSO_3H$, 15 min, 90%.

Beyond HOPOs, we also explored non-aromatic heterocyclic ZBGs with the aryl sulfone scaffold. The preparation of the α-sulfone series with a 'conformationally constrained hydroxamic acid' is outlined in Scheme 3. Bromo methyl acetate was reacted with aryl thiols, followed by ester hydrolysis and peptide coupling with trityl-protected hydroxylamine, to afford **15**. N-Alkylation of **15** with dibromoalkanes, immediately followed by *m*CPBA oxidation and then base treatment of the resulting sulfones, gave the cyclized products **16**. Again, the desired P_1' groups can be obtained by elaborations of the R substituent via a variety of synthetic transformations as described in Scheme 3. Thus, a series of 6- to 8-membered *N*-hydroxy lactam MMP inhibitors were synthesized.

Compound **20** containing 1-hydroxy-[1,4]-diazepin-2-one as a ZBG was synthesized according to the sequence detailed in Scheme 4. (*S*)-*N*-Boc-2-amino-3-hydroxypropionate was converted to the corresponding tosylate and subsequent displacement with an aryl thiol gave **18**. Methyl ester **18** was then converted into trityl-protected hydroxamate **19** via a hydrolysis-peptide coupling sequence. Bis-alkylation of **19** under basic conditions followed by sulfide oxidation and trityl de-protection afforded target molecule **20**.

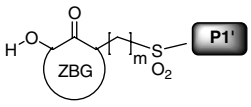


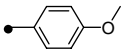
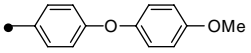
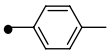
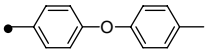
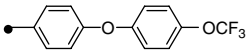
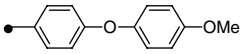
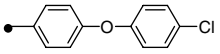
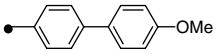
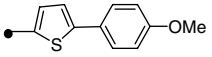
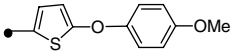
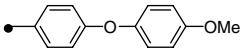
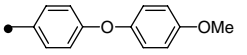
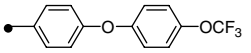
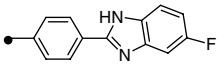
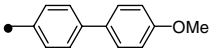
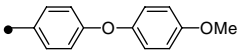
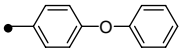
Scheme 3. Reagents and conditions: (a) (4-X)PhSH, TEA, THF, reflux, 90%; (b) KOH, MeOH/H_2O, 95%; (c) *O*-trityl-hydroxylamine, EDCI, NMP, HOBt, DMF, rt, 84%; (d) $BrCH_2(CH_2)_nCH_2Br$, Cs_2CO_3, DMF, rt, 65%; (e) *m*CPBA, CH_2Cl_2, rt, 67%; (f) Cs_2CO_3, THF, 60 °C, 60%; (g) when X = F, ArOH, K_2CO_3, DMF, 100 °C, 69–30%; when X = Br, 5 mol% $Pd(PPh_3)_4$, aq Na_2CO_3 (2 M), 1,4-dioxane, 78%; (h) TFA/CH_2Cl_2 (1:1), rt, 87%.



Scheme 4. Reagents and conditions: (a) TsCl, pyridine, CH_2Cl_2, 0 °C–rt, 85%; (b) HS-P1′, K_2CO_3, DMF, rt, 85%; (c) LiOH, THF/H_2O, 0 °C–rt, 96%; (d) EDC, HOBt, DMAP, TEA, Ph_3CONH_2, $CHCl_3$, rt, 70%; (e) $I(CH_2)_3Cl$, Cs_2CO_3, DMF/MeCN, then NaH, 19%; (f) *m*CPBA, CH_2Cl_2, rt, 84%; (g) TFA, Et_2O, rt, 74%.

Table 1. IC_{50} (nM) values and SAR of compounds **9**, **14**, **17**, and **20**



Compound	ZBG	*m*	P_1'	MMP-2 (nM)[a]	MMP-9 (nM)[a]
9a	**3**	**1**		>1000	>1000
9b	**3**	**1**		17.2	7.3
14a	**4**	**1**		468	809
14b	**4**	**1**		16.7	45.8
14c	**4**	**1**		12.6	4.0
14d	**4**	**1**		84.5	56.1
14e	**4**	**1**		10.6	16.4
14f	**4**	**1**		>1000	>1000
14g	**4**	**1**		184	522
14h	**4**	**1**		72.0	13.9
17a	**5a**	**0**		167.5	87.9
17b	**5b**	**0**		95.9	31.0
17c	**5b**	**0**		59.4	21.5
17d	**5b**	**0**		377	846
17e	**5b**	**0**		>1000	>1000
17f	**5c**	**0**		>1000	>1000
20	**6**	**1**		36.8	21.1

[a] Values are means of at least two experiments.

All compounds were tested against the MMP-2 and MMP-9 enzymes and the inhibitory activities are summarized in Table 1. Generally, the compounds with more rigid HOPOs (**3** and **4**) as ZBGs were preferred. Both compounds **9b** and **14c** exhibited single digit nanomolar IC_{50}s against MMP-9. Nevertheless, the 7-membered heterocycles, *N*-hydroxy-azepin-2-one and *N*-hydroxy-[1,4]-diazepin-2-one, were also found to be effective ZBGs (**17b–c** and **20**). These heterocycles have not been reported as ZBGs in the design of MMPI. Compound **17c** with a α-sulfone scaffold and compound **20** with a β-sulfone scaffold showed comparable MMP-9 activity. This demonstrates the versatility of the *N*-hydroxy-lactam functionality as a ZBG in MMPIs with

Table 2. IC_{50}[a] values against selected MMPs of **9b**, **14c**, and **20**

Compound	MMP-1	MMP-2	MMP-3	MMP-9	MMP-13
9b	>1000	17.2	308	7.3	13.4
14c	>1000	12.6	203	4.0	7.3
20	>1000	36.8	964	21.1	11.0

[a] IC_{50} (nM) values are means of at least two determinations.

different scaffolds. Although docking of compound **14c** in an MMP-9 homology model indicates that one of the sulfonyl oxygen atoms forms a H-bond with the backbone –NH of Leu 188, it is unclear whether the corresponding sulfonyl oxygen of **17c** or **20** interacts with the peptide backbone of MMP-9 in a similar fashion. Replacing the *N*-hydroxy-azepin-2-one moiety of **17b** with the smaller *N*-hydroxy-piperidin-2-one of **17a** let to a threefold decrease in inhibitory potency against MMP-9 and a twofold decrease against MMP-2. Surprisingly, the 8-membered *N*-hydroxy-azocin-2-one ZBG (**17f**) was not tolerated. This observation suggests that the size of the *N*-hydroxy-lactam has a significant impact on the optimal-binding mode of the molecules. Table 1 also reveals that the size and geometry of the P_1' group is critical for MMP-2/-9 inhibitory activities. In particular, compounds **9a** and **14a** with shorter P_1' substituents do not exhibit good inhibitory activity. A larger P_1' group is necessary to reach the deeper S_1' pockets of MMP-2 and -9. However, the linear biaryl P_1' groups do not fit well into the S_1' subsite (**14f** and **17e**). This agrees with our previous observation in the 1,2-HOPO-based sulfonamide series (Fig. 1, **1**).[6] Furthermore, some inhibitory activity can be recovered by incorporating an angled P_1' group containing 5-membered heteroaromatic rings, as in compounds **14g** and **17d**. Compounds **9b**, **14c**, and **20** were screened against other MMPs (Table 2) and showed excellent selectivity over MMP-1 and 40- to 50-fold selectivity over MMP-3. These compounds are also potent inhibitors of MMP-13.

In summary, we discovered several classes of MMP inhibitors containing heterocyclic ZBGs which showed good inhibitory activities against the MMP-2 and -9 enzymes and excellent selectivity over MMP-1. Further structural modifications of these MMPIs to pick up additional-binding interactions with the enzyme through the introduction of a P_1 group on the cyclic ZBGs are underway. The compounds disclosed here along with the reported MMP inhibitors containing HOPOs and hydroxypyrones[5] as the ZBGs suggest a new direction for the design of novel ZBGs and MMPIs with improved physico-chemical properties and selectivity.

Acknowledgment

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Supplementary data

Synthetic details of all compounds in Table 1. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.10.049.

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