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Discovery of DS-8108b, a Novel Orally Bioavailable Renin Inhibitor

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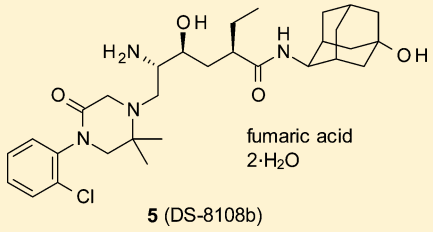
Supporting Information

ABSTRACT: A novel orally bioavailable renin inhibitor, DS-8108b (**5**), showing potent renin inhibitory activity and excellent in vivo efficacy is described. We report herein the synthesis and pharmacological effects of **5** including renin inhibitory activity in vitro, suppressive effects of ex vivo plasma renin activity (PRA) in cynomolgus monkey, pharmacokinetic data, and blood pressure-lowering effects in an animal model. Compound **5** demonstrated inhibitory activities toward human renin (IC_{50} = 0.9 nM) and human and monkey PRA (IC_{50} = 1.9 and 6.3 nM, respectively). Oral administration of single doses of 3 and 10 mg/kg of **5** in cynomolgus monkey on pretreatment with furosemide led to dose-dependent significant reductions in ex vivo PRA and sustained lowering of mean arterial blood pressure for more than 12 h.



5 (DS-8108b)

KEYWORDS: *renin inhibitor, hypertension, plasma renin activity, 4-aminoadamantan-1-ol*

The renin−angiotensin−aldosterone system (RAAS) plays an important role in regulating blood pressure and extracellular fluid volume.[1,2] Chronic stimulation of the RAAS leads to tissue inflammation and fibrosis with end organ dysfunction, particularly of the kidney.[3,4] The aspartyl protease renin, secreted from kidneys, is the first and rate-limiting enzyme of the RAAS system and cleaves angiotensinogen at the N terminus to form the decapeptide angiotensin (Ang) I. Ang I is further converted by angiotensin converting enzyme (ACE) to give an octapeptide, Ang II, which binds to the angiotensin receptor type 1 (AT_1), leading to vasoconstriction, chronic stimulation, inflammation, and fibrosis. While two major classes of RAAS blockers, ACE inhibitors and AT_1 receptor blockers (ARBs), are already on the market, it is expected that a direct renin inhibitor would be valuable as it would not only become an ideal antihypertensive agent for end organ protection but also cause fewer mechanism-based adverse events than ACE inhibitors and ARBs.[5−7]

Although renin inhibitors have been considered to be desirable antihypertensive drugs, identification of orally active, low molecular weight compounds have proven to be a very challenging task. During the 1980s, all of the first generation renin inhibitors were peptides or peptidomimetics that incorporated peptide hydrolysis transition state isosteres. However, because of their poor oral bioavailability, none of these inhibitors was successfully developed as a drug.[8] Beginning in the middle of the 1990s, several novel nonpeptidic renin inhibitors were reported and have entered human clinical trials, such as aliskiren hemifumarate (**1**),[9] ACT-077825 (MK-8141) (**2**),[10] and VTP-27999 (**3**)[11] (Figure 1). Despite significant research investments from the pharmaceutical industry directed toward the discovery of renin inhibitors suitable for clinical development,[12,13] only aliskiren has been launched to the market for the treatment of hypertension to date.[14,15]

We recently discovered a novel class of nonpeptidic renin inhibitors such as **4** characterized by a 2,2-dimethyl-4-phenylpiperazin-5-one moiety as the P_3−P_1 pharmacophore. Inhibitor **4** showed an IC_{50} value of 2.0 nM in purified human renin and 18.5% oral bioavailability in cynomolgus monkey.[16] On the basis of these encouraging results, we selected **4** as a new lead compound and started further modifications to acquire more promising compounds. In earlier work with related compounds, our approach to improve efficacy and oral bioavailability was to introduce a lipophilic moiety into the molecule. However, increasing the lipophilicity of the compounds caused several drawbacks such as interactions with CYPs and cardiac safety problems. These problems also have been reported by other research groups.[17−19] Thus, we replaced the N-terminal butyl side chain of **4** with various substituents incorporating additional polar functionalities to reduce the above undesirable concerns while retaining excellent efficacy. As a result, the introduction of *trans*-4-amino-adamantan-1-ol to the N-terminal portion led to the identification of clinical candidate DS-8108b (**5**) ((2*R*,4*S*,5*S*)-5-amino-6-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-

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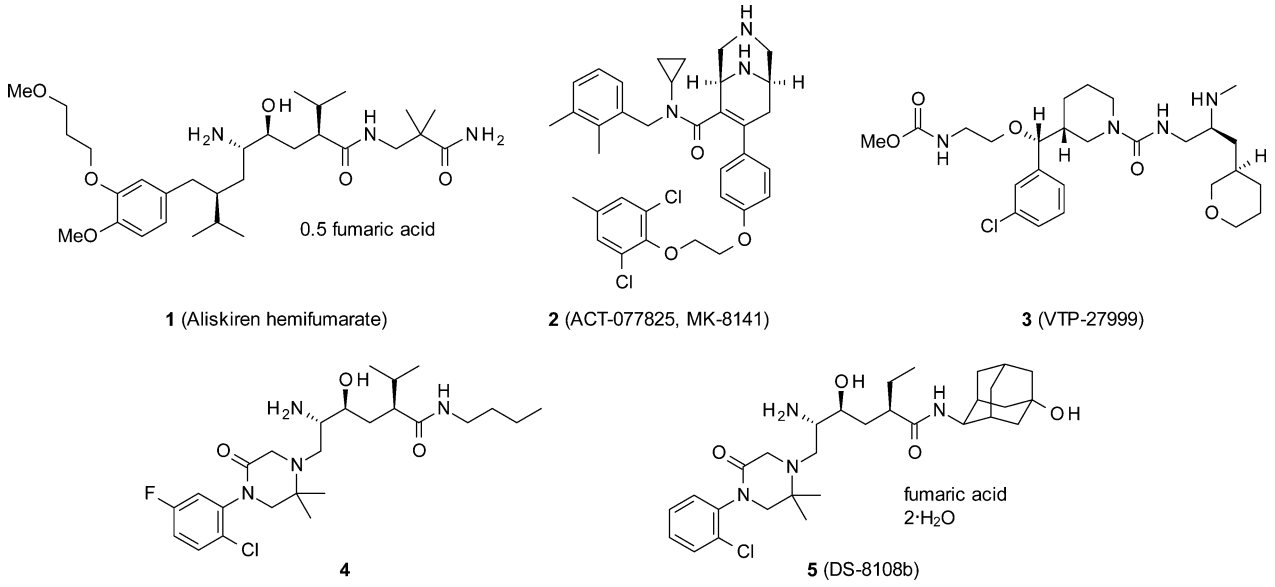
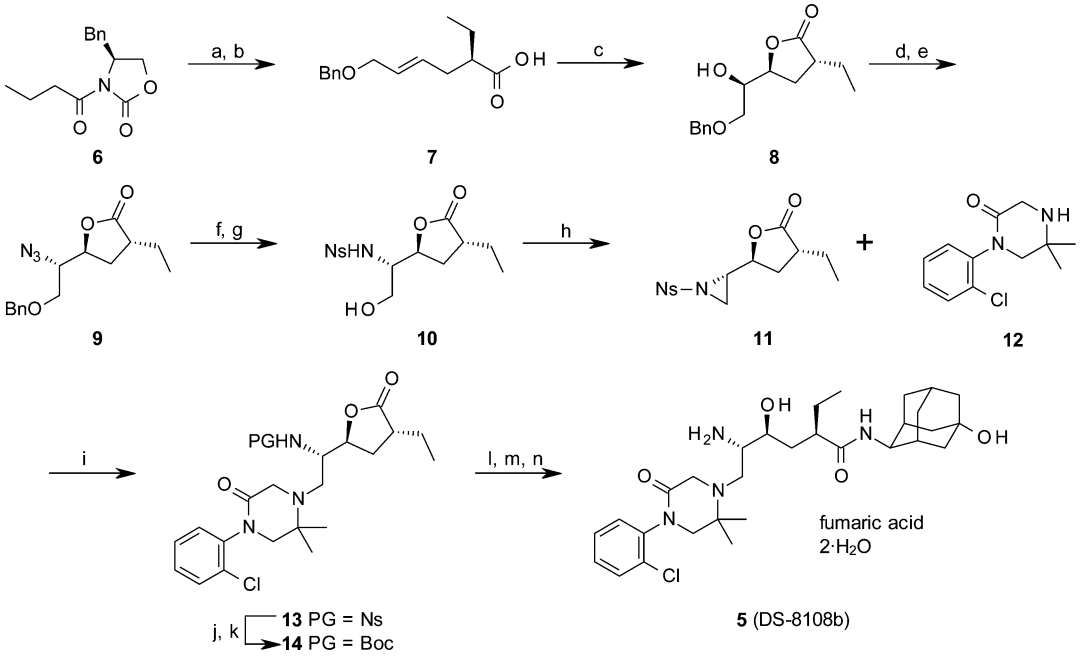


Figure 1. Structures of renin inhibitors.

Scheme 1[a]



[a]Reagents and conditions: (a) $NaN(TMS)_2$, (*E*)-$BnOCH_2CH{=}CHCH_2Br$, THF, −78 to −40 °C, 81%. (b) LiOH, 30% aqueous H_2O_2, THF−H_2O (3:1), 0 °C to rt. (c) 1,2:4,5-Di-*O*-isopropylidene-*β*-D-*erythro*-2,3-hexodiulo-2,6-pyranose, Oxone, K_2CO_3, aqueous $Na_2(EDTA)$, $Na_2B_4O_7{\cdot}10H_2O$, dimethoxymethane−MeCN (2:1), 0 °C, 70% (two steps). (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 96%. (e) NaN_3, DMPU, 60 °C, 93%. (f) Cat. Pd−C, H_2, HCl, EtOH, rt. (g) (i) NsCl, Et_3N, THF−H_2O (10:1), rt; (ii) crystallization in diisopropylether−AcOEt (1:2), 59% (two steps). (h) DEAD, PPh_3, THF, 0 °C, 92%. (i) Toluene, 110 °C, 96%. (j) PhSH, Cs_2CO_3, MeCN, rt, 90%. (k) Boc_2O, $NaHCO_3$, AcOEt−H_2O (1:1), 96%. (l) *trans*-4-Aminoadamantan-1-ol, cat. 2-hydroxypyridine, 90 °C, 72%. (m) TFA, CH_2Cl_2, rt. (n) (i) Fumaric acid, MeOH, rt; (ii) crystallization in 95% aqueous MeCN and 98% aqueous AcOEt (77%, three steps).

yl]-2-ethyl-4-hydroxy-*N*-[(2*s*,5*s*)-5-hydroxyadamantan-2-yl]-hexanamide monofumarate dihydrate).

We report herein the synthesis and pharmacological effects of **5** including its renin inhibitory activity in vitro, ex vivo PRA suppressive effects in monkey, and the blood pressure-lowering effects in an animal model and also report the pharmacokinetic (PK) profiles in monkey.

The synthetic route of DS-8108b (**5**) is shown in Scheme 1. The *N*-(2-nitrobenzenesulfonyl) (Ns)[20] protected key intermediate aziridine **11** was prepared according to a similar procedure reported recently.[21] Asymmetric alkylation of **6** with benzyl (2*E*)-4-bromobut-2-en-1-yl ether[22] to construct the C-2 chiral center of **5** proceeded smoothly, and the oxazolidinone group was removed with LiOH and 30% aqueous H_2O_2 to afford the carboxylic acid (2*R*,4*E*)-**7** in good yield. To construct chirality centers at the C-4 and C-5 of **5**, Shi's asymmetric epoxidation method was employed.[23] Epoxidation of (2*R*,4*E*)-**7** followed by one-pot intramolecular lactonization produced

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alcohol **8** as a mixture of stereoisomers (ca. 97:3). The slow addition of Oxone and K_2CO_3 in aqueous Na_2(EDTA) solution over a period of 4 h to the reaction mixture of **7** and 1,2:4,5-di-*O*-isopropylidene-*β*-D-*erythro*-2,3-hexodiulo-2,6-pyranose (1 equiv) was necessary to complete the reaction. Mesylation of **8** with MsCl and triethylamine and subsequent S_N2 substitution of the methanesulfonyloxy group with an azide group was accomplished by treatment with sodium azide in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) to obtain **9**. Then, hydrogenation of **9** in the presence of HCl and the subsequent reaction with 2-nitrobenzenesulfonyl chloride (NsCl)[20] under the Schotten−Baumann conditions, followed by crystallization gave *N*-Ns alcohol **10** as a single diastereomer in 59% yield from **9**. *N*-Ns-protected **11** was formed by the Mitsunobu reaction of **10** with diethyl azodicarboxylate (DEAD) and Ph_3P in 92% yield. The ring opening of aziridine **11** with 4-(2-chlorophenyl)-2,2-dimethylpiperazin-2-one (**12**)[16] proceeded smoothly in toluene at 110 °C to afford lactone **13** in excellent yield. After replacement of the Ns group with the Boc group, sequential N-terminal amide bond formation with *trans*-4-aminoadamantan-1-ol under neat conditions at 90 °C in the presence of 2-hydroxypyridine as a catalyst,[24] deprotection of the Boc group with trifluoroacetic acid (TFA) in CH_2Cl_2, and treatment with fumaric acid afforded the desired DS-8108b (**5**).

Table 1. In Vitro Renin Inhibition

compd	IC_{50} (nM)[a,b]		
	human renin	human PRA	monkey PRA
aliskiren hemifumarate (**1**)	1.5	2.9	8.0
DS-8108b (**5**)	0.9	1.9	6.3

[a]Assay protocols are provided in the Supporting Information. [b]Assay results are the average of at least two replicates.

Inhibitory activities of **5** toward human and cynomolgus monkey renin are shown in Table 1. Aliskiren hemifumarate (**1**) was included for comparison. Compound **5** demonstrated potent inhibitory activity against human renin (IC_{50} = 0.9 nM), comparable to that of aliskiren hemifumarate (IC_{50} = 1.5 nM). Inhibitory effects on human and monkey plasma renin activity (PRA) were also evaluated, and the IC_{50} values were 1.9 and 6.3 nM, respectively. In addition, **5** showed excellent selectivity for renin over four other aspartyl proteases: human cathepsin D, cathepsin E, pepsin, and HIV protease (IC_{50} = >10 μM), and **5** also exhibited relatively weak inhibitory activities against CYP enzymes and against a panel of 68 receptors, ion channels, and enzymes with IC_{50} values >10 μM.[25] Furthermore, **5** did not affect the hERG and hNav 1.5 channel currents at a concentration of 100 μM. Compound **5** was nonmutagenic in the Ames assay when tested in either the presence or the absence of S9 mix.

The X-ray crystal structure of **5** bound to human renin was obtained (PDB code: 3VUC; Figure 2). The general binding mode and specific interactions observed in the complex were as expected based on the previously published X-ray crystal structure of compound **4** (PDB code: 3VSX).[16] Both X-ray crystal structures of **4** and **5** in complex with renin provided evidence that their P_3 phenyl groups of compound **4** and **5** penetrate deeper into the S_3 pocket than the phenyl ring of aliskiren and that both compounds do not utilize the S_3^{sp} pocket. The chloro atom points toward the opposite site of S_3^{sp}

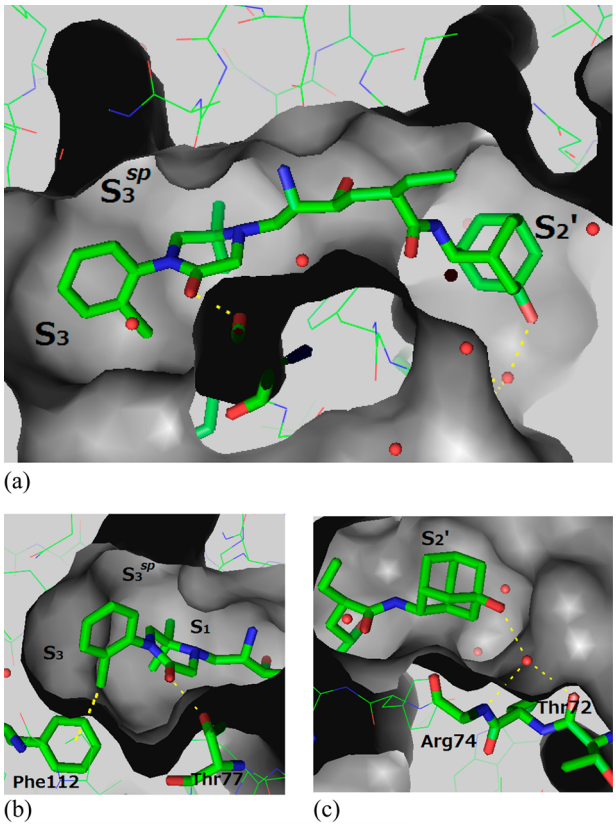

Figure 2. X-ray crystal structure of **5** in complex with human renin (PDB code: 3VUC). Water molecules are shown as red dots. (a) Overview, (b) S_1−S_3 region, and (c) S_2' region.

and interacts with Phe112 (Figure 2b). To our knowledge, this is the first example of a halogen-*π* interaction reported for aspartyl protease inhibitors. The carboxamide oxygen of the 2,2-dimethyl-4-phenylpiperazin-5-one moiety participates in a hydrogen bond to Thr77. In addition, the hydroxyl group of adamantane located in the S_2' pocket forms a hydrogen-bonding network involving the backbone atoms of Thr72, Arg74, and a water molecule (Figure 2c).

In another series of experiments, the ex vivo PRA suppressive effects of **5** were investigated in cynomolgus monkey (Figure 3). Vehicle or 1, 3, and 10 mg/kg of **5** were orally administered to cynomolgus monkey after pretreatment with furosemide. Compound **5** showed PRA suppressive effects in a dose-dependent manner at a dose of 1, 3, and 10 mg/kg, and more than 65% of the PRA suppressive effects as compared with the predose values were sustained over a period of 24 h for the 3 and 10 mg/kg groups. Thus, as compared with aliskiren hemifumarate (data not shown), **5** demonstrated at least a three times more potent PRA suppressive effect in cynomolgus monkey at either the dose or the exposure level.

Next, the antihypertensive efficacy of **5** was investigated in cynomolgus monkey (Figure 4). Vehicle or 1, 3, and 10 mg/kg of **5** were orally administered. Compound **5** showed significant reduction in mean arterial blood pressure (MAP) in a dose-dependent manner sustained over a period of at least 12 h.

The PK of **5** was evaluated in cynomolgus monkey. The PK parameters after a single oral administration are shown in Table 2. The C_{max} at doses of 3 and 10 mg/kg in monkey was 102 and 399 ng/mL, and the t_{max} was 3.0 and 2.3 h postdose, respectively. The terminal half-life ($t_{1/2}$) values in monkey at

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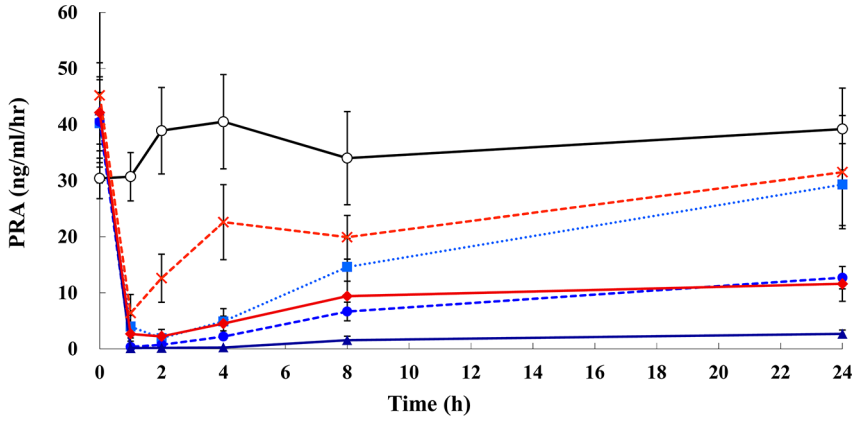

Figure 3. Ex vivo PRA suppressive effects of DS-8108b (**5**) and aliskiren hemifumarate (**1**) in cynomolgus monkey on pretreatment with furosemide. Note that vehicle (1% MC solution, white circle); 1 (light blue square), 3 (blue circle), and 10 mg/kg (dark blue triangle) of **5**; and 3 (red times sign) and 10 mg/kg (dark red tilted square) of **1** were orally administered to cynomolgus monkey after pretreatment with furosemide. PRA was measured 1, 2, 4, 8, and 24 h after oral administration. Assay protocols are provided in the Supporting Information.

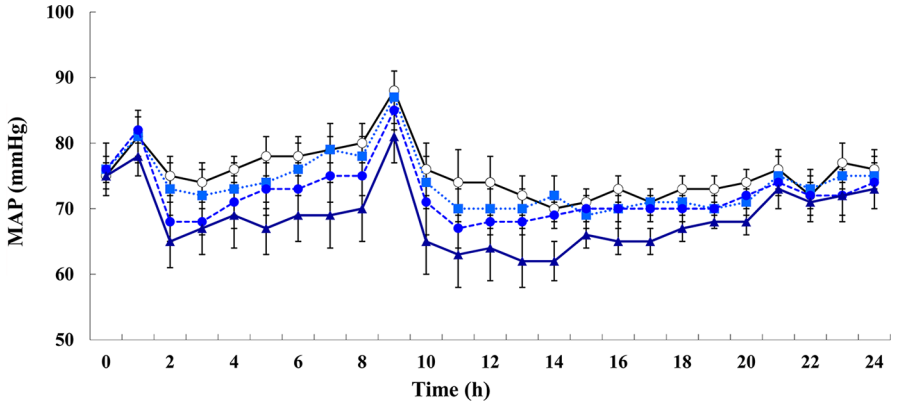

Figure 4. MAP responses to DS-8108b (**5**) in cynomolgus monkey on pretreatment with furosemide. Note that vehicle (1% MC solution, white circle) and 1 (light blue square), 3 (blue circle), and 10 mg/kg (dark blue triangle) of **5** were orally administered to cynomolgus monkey. Data are expressed as means ± SEMs. Assay protocols are provided in the Supporting Information.

Table 2. PK Parameters of DS-8108b (5) in Cynomolgus Monkey

dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng h/mL)	$t_{1/2}$ (h)	F (%)	CL (mL/min/kg)	Vss (L/kg)
3[a]	102 ± 60	3.0 ± 1.7	685 ± 452	5.1 ± 0.7	4.1 ± 0.6		
3[b]			15500 ± 8200	7.8 ± 2.6		3.59 ± 1.74	1.12 ± 0.52
10[a]	399 ± 177	2.3 ± 1.5	2880 ± 1710	5.4 ± 0.7	5.3 ± 1.0		

[a]po administration (n = 3). [b]iv administration (n = 3).

oral doses of 3 and 10 mg/kg and an intravenous dose of 3 mg/kg were 5.1, 5.4, and 7.8 h, respectively. The oral bioavailability at doses of 3 and 10 mg/kg was 4.1 and 5.3%, respectively. The low bioavailability of **5** in monkey is similar to that of aliskiren hemifumarate (**1**) (data not shown).

Finally, we evaluated **5** in a cardiac safety study in telemetered cynomolgus monkey. After administration of a single oral dose of 1000 mg/kg of **5**, the QRS width and QTc interval over 24 h oral postdose were not impacted. These data support that the potential cardiac toxicity risk of compound **5** is considered to be low.

In summary, we present DS-8108b (**5**), a structurally novel renin inhibitor possessing potent and selective renin inhibitory activity with a profile suitable for further development. Oral administration of single doses of 3 and 10 mg/kg of **5** in cynomolgus monkey after pretreatment with furosemide elicited sustained reductions in PRA and MAP in a dose-dependent manner.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details for the synthesis and characterization of DS-8108b (**5**), biological assays, animal studies, and crystallography procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

Y.N., T.F., Y.O., C.S., S.M., K.T., and T.N. contributed to the design and synthesis of DS-8108b (**5**); M.T. and Y.M.

contributed to the X-ray crystal structures; T.N., K.M., and M.M. contributed to the in vitro, ex vivo, and in vivo studies; N.M. contributed to the PK studies; and K.C. contributed to the cardiac study in cynomolgus monkey.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

TMS, trimethylsilyl; DEAD, diethyl azodicarboxylate; DMPU, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; TFA, trifluoroacetic acid

■ REFERENCES

(1) Zaman, M. A.; Oparil, S.; Calhoun, D. A. Drugs targeting the renin-angiotensin-aldosterone system. *Nat. Rev. Drug Discovery* **2002**, *1*, 621−636.

(2) Schmieder, R. E.; Hilgers, K. F.; Schlaich, M. P.; Schmidt, B. M. W. Renin-angiotensin system and cardiovascular risk. *Lancet* **2007**, *369*, 1208−1219.

(3) Remuzzi, G.; Perico, N.; Macia, M.; Ruggenenti, P. The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease. *Kidney Int.* **2005**, *68*, S57−S65.

(4) Ruiz-Ortega, M.; Rupérez, M.; Esteban, V.; Rodríguez-Vita, J.; Sánchéz-López, E.; Carvajal, G.; Egido, J. Angiotensin II: A key factor in the inflammatory and fibrotic response in kidney diseases. *Nephrol., Dial., Transplant.* **2006**, *21*, 16−20.

(5) Weber, M. A. Clinical experience with the angiotensin II receptor antagonist losartan: A preliminary report. *Am. J. Hypertens.* **1992**, *5*, 247S−251S.

(6) Norris, K.; Vaughn, C. The role of renin-angiotensin-aldosterone system inhibition in chronic kidney disease. *Expert Rev. Cardiovasc. Ther.* **2003**, *1*, 51−66.

(7) Cooper, M. E. The role of the renin-angiotensin-aldosterone system in diabetes and its vascular complications. *Am. J. Hypertens.* **2004**, *17*, 16S−20S.

(8) Tice, C. M.; McGeehan, G. M.; Claremon, D. A. In *Burger's Medicinal Chemistry, Drug Discovery, and Development*, 7th ed.; Abraham, D. J., Rotella, D. P., Eds.; Wiley: Hoboken, NJ, 2010; Vol. *4*, pp 239−266.

(9) Rahuel, J.; Rasetti, V.; Maibaum, J.; Rüeger, H.; Göschke, R.; Cohen, N.-C.; Stutz, S.; Cumin, F.; Fuhrer, W.; Wood, J. M.; Grütter, M. G. Structure-based drug design: The discovery of novel nonpeptide orally active inhibitors of human renin. *Chem. Biol.* **2000**, *7*, 493−504.

(10) Bezençon, O.; Bur, D.; Weller, T.; Richard-Bildstein, S.; Remeň, L.; Sifferlen, T.; Corminboeuf, O.; Grisostomi, C.; Boss, C.; Prade, L.; Delahaye, S.; Treiber, A.; Strickner, P.; Binkert, C.; Hess, P.; Steiner, B.; Fischli, W. Design and Preparation of Potent, Nonpeptidic, Bioavailable Renin Inhibitors. *J. Med. Chem.* **2009**, *52*, 3689−3702.

(11) Jia., L.; Simpson, R. D.; Yuan, J.; Xu, Z.; Zhao, W.; Cacatian, S.; Tice, C. M.; Guo, J.; Ishchenko, A.; Singh, S. B.; Wu, Z.; McKeever, B. M.; Bukhtiyarov, Y.; Johnson, J. A.; Doe, C. P.; Harrison, R. K.; McGeehan, G. M.; Dillard, L. W.; Baldwin, J. J.; Claremon, D. A. Discovery of VTP-27999, an Alkyl Amine Renin Inhibitor with Potential for Clinical Utility. *ACS Med. Chem. Lett.* **2011**, *2*, 747−751.

(12) Webb, R. L.; Schiering, N.; Sedrani, R.; Maibaum, J. Direct Renin Inhibitors as a New Therapy for Hypertension. *J. Med. Chem.* **2010**, *53*, 7490−7520.

(13) Hershey, J. C.; Steiner, B.; Fischli, W.; Feuerstein, G. Renin inhibitors: An antihypertensive strategy on the verge of reality. *Drug Discovery Today: Ther. Strategies* **2005**, *2*, 181−185.

(14) Maibaum, J.; Stutz, S.; Göschke, R.; Rigollier, P.; Yamaguchi, Y.; Cumin, F.; Rahuel, J.; Baum, H.-P.; Cohen, N.-C.; Schnell, C. R.; Fuhrer, W.; Gruetter, M. G.; Schilling, W.; Wood, J. M. Structural Modification of the P_2' Position of 2,7-Dialkyl-Substituted 5(*S*)-Amino-4(*S*)-hydroxy-8-phenyl-octanecarboxamides: The Discovery of Aliskiren, a Potent Nonpeptide Human Renin Inhibitor Active after Once Daily Dosing in Marmosets. *J. Med. Chem.* **2007**, *50*, 4832−4844.

(15) Jensen, C.; Herold, P.; Brunner, H. R. Aliskiren: the first renin inhibitor for clinical treatment. *Nat. Rev. Drug Discovery* **2008**, *7*, 399−410.

(16) Nakamura, Y.; Sugita, C.; Meguro, M.; Miyazaki, S.; Tamaki, K.; Takahashi, M.; Nagai, Y.; Nagayama, T.; Kato, M.; Suemune, H.; Nishi, T. Design and Optimization of Novel (2*S*,4*S*,5*S*)-5-Amino-6-(2,2-dimethyl-5-oxo-4-phenylpiperazin-1-yl)-4-hydroxy-2-isopropyl-hexanamides as Renin Inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4561−4566.

(17) Powell, N. A.; Ciske, F. L.; Cai, C.; Holsworth, D. D.; Mennen, K.; Huis, C. A. V.; Jalaie, M.; Day, J.; Mastronardi, M.; McConnell, P.; Mochalkin, I.; Zhang, E.; Ryan, M. J.; Bryant, J.; Collard, W.; Ferreira, S.; Gu, C.; Collins, R.; Edmunds, J. J. Rational design of 6-(2,4-diaminopyrimidinyl)-1,4-benzoxazin-3-ones as small molecule renin inhibitors. *Bioorg. Med. Chem.* **2007**, *15*, 5912−5949.

(18) Chen, A.; Dubé, D.; Dubé, L.; Gagné, S.; Gallant, M.; Gaudreault, M.; Grimm, E.; Houle, R.; Lacombe, P.; Laliberté, S.; Liu, S.; MacDonald, D.; Mackay, B.; Martin, D.; McKay, D.; Powell, D.; Lévesque, J.-F. Addressing time-dependent CYP 3A4 inhibition observed in a novel series of substituted amino propanamide renin inhibitors, a case study. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5074−5079.

(19) Chen, A.; Campeau, L.-C.; Cauchon, E.; Chefson, A.; Ducharme, Y; Dubé, D.; Falgueyret, J.-P.; Fournier, P.-A.; Gagné, S.; Grimm, E; Han, Y.; Houle, R.; Huang, J.-Q.; Lacombe, P.; Laliberté, S.; Lévesque, J.-F.; Liu, S.; MacDonald, D.; Mackay, B.; McKay, D; Percival, M. D.; Regan, C.; Regan, H.; St-Jacques, R.; Toulmond, S. Renin inhibitors for the treatment of hypertension: Design and optimization of a novel series of pyridone-substituted piperidines. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3970−3975.

(20) Fukuyama, T.; Jow, C.-K.; Cheung, M. 2- and 4-Nitrobenzenesulfonamides: Exceptionally versatile means for preparation of secondary amines and protection of amines. *Tetrahedron Lett.* **1995**, *36*, 6373−6374.

(21) Nakamura, Y.; Ogawa, Y.; Suzuki, C.; Fujimoto, T.; Miyazaki, S.; Tamaki, K.; Nishi, T.; Suemune, H. Efficient Synthesis of 5-Amino-6-dialkylamino-4-hydroxypentanamide Derivatives for Renin Inhibitors. *Heterocycles* **2011**, *83*, 1587−1602.

(22) Kottirsch, G.; Koch, G.; Feifel, R.; Neumann, U. *β*-Aryl-Succinic Acid Hydroxamates as Dual Inhibitors of Matrix Metalloproteinases and Tumor Necrosis Factor Alpha Converting Enzyme. *J. Med. Chem.* **2002**, *45*, 2289−2293.

(23) Tu, Y.; Wang, Z.-X.; Shi, Y. An Efficient Asymmetric Epoxidation Method for *trans*-Olefins Mediated by a Fructose-Derived Ketone. *J. Am. Chem. Soc.* **1996**, *118*, 9806−9807.

(24) Openshaw, H. T.; Whittaker, N. The synthesis of emetine and related compounds. Part VII. The utility of bi-functional catalysts in amine-ester interactions. *J. Chem. Soc. (C.)* **1969**, 89−91.

(25) MDS Pharma Services; Lead Profiling Screen.