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Discovery of TAK-272: A Novel, Potent, and Orally Active Renin Inhibitor

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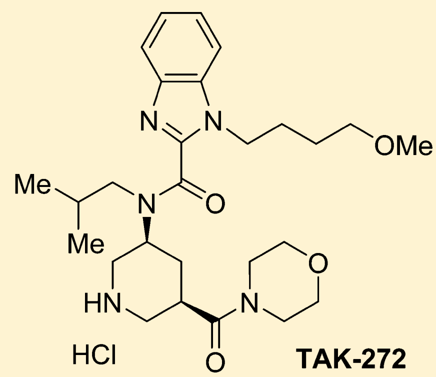
Supporting Information

ABSTRACT: The aspartic proteinase renin is an attractive target for the treatment of hypertension and cardiovascular/renal disease such as chronic kidney disease and heart failure. We introduced an S1′ site binder into the lead compound **1** guided by structure-based drug design (SBDD), and further optimization of physicochemical properties led to the discovery of benzimidazole derivative **10** (1-(4-methoxybutyl)-*N*-(2-methylpropyl)-*N*-[(3*S*,5*R*)-5-(morpholin-4-yl)carbonylpiperidin-3-yl]-1*H*-benzimidazole-2-carboxamide hydrochloride, TAK-272) as a highly potent and orally active renin inhibitor. Compound **10** demonstrated good oral bioavailability (BA) and long-lasting efficacy in rats. Compound **10** is currently in clinical trials.



TAK-272

KEYWORDS: *Renin inhibitor, TAK-272, benzimidazole, hypertension, SBDD, dTg rat*

The renin–angiotensin–aldosterone system (RAAS) is a well-known pathway regulating blood pressure and body fluid homeostasis.[1] Several agents that block the RAAS cascade are available and effective for the control of blood pressure.[2] A number of clinical studies using angiotensin-converting-enzyme inhibitors and angiotensin-II-receptor blockers revealed that treatment of RAAS cascade blockers is beneficial for organ protection such as diabetic nephropathy and heart failure besides antihypertensive effect.[3] The aspartic proteinase renin is the rate-limiting and the first step of the RAAS cascade and considered as an attractive therapeutic strategy to block the whole RAAS cascade.[4,5] Despite renin being discovered as a hypertensive substance more than 100 years ago[6] and the numerous efforts made to discover potent renin inhibitors in many pharmaceutical companies since early 1980s, no product has been launched over more than two decades.[7−9] In 2007, aliskiren was approved as the first orally bioavailable direct renin inhibitor for the treatment of hypertension.[10,11]

We have already found an attractive lead compound **1** with an IC_{50} value of 4.6 nM against human plasma renin by our fragment-based (FBDD) and structure-based drug design (SBDD) efforts.[12] The X-ray cocrystal structure of compound **1** bound to renin was examined in detail as the starting point for our next round of SBDD efforts (Figure 1). The contiguous lipophilic S3 and S1 sites are occupied by the *tert*-butylpyrimidine and isobutyl moieties with the flap *β*-hairpin in a closed conformation.[13,14] The piperidine NH group makes a salt bridge with the residues of Asp32 and Asp215, and the $S3^{sp}$ site is occupied by the furfurylamine moiety. The amino group at the pyrimidine 4-position forms a hydrogen bonding interaction with backbone of Gly217. However, the S1′ site was not utilized by our renin inhibitor **1** in contrast to aliskiren.[10,11] Additionally, it has been demonstrated by others that occupation of the S1′ site can lead to enhancement of potency.[13,14] Thus, we investigated the introduction of additional substituents directed toward the S1′ site to enhance potency.

PK studies revealed that compound **1** has better oral bioavailability in rats than aliskiren (**1**, 13.8%; aliskiren, 2.4%).[10−12] The reasons for this difference were thought to arise from improved physiochemical characteristics such as MW (414 and 552), topological polar surface area (TPSA) (82 and 146), and number of rotatable bonds (nRB) (9 and 20, respectively) which are known as important predictors for BA.[15,16] However, compound **1** possesses the furan moiety, which could potentially be oxidized by CYP to form toxic metabolites.[17,18] We sought to replace this moiety with metabolically stable substituent through chemical modification.

On the basis of this analysis, our optimization of compound **1** began with the introduction of a variety of substituents at the piperidine 3-position directed toward the S1′ site to increase renin inhibitory activity.[13,14,19] Due to the low MW of the

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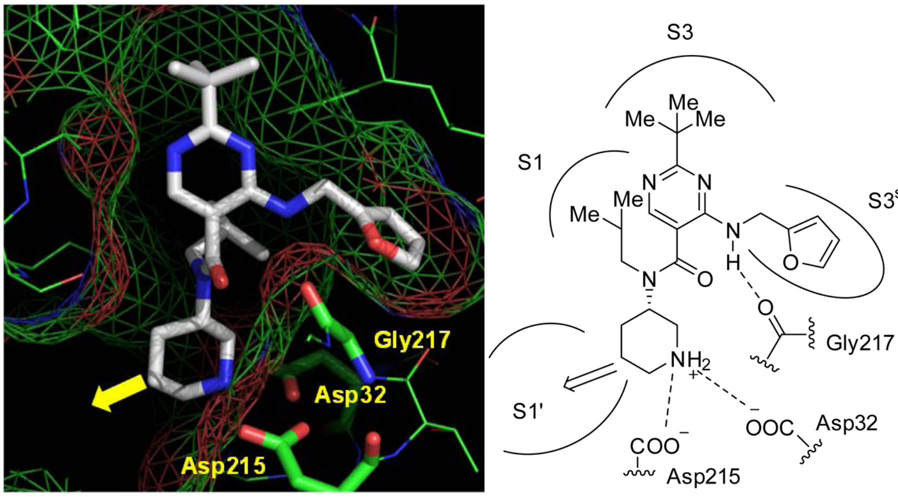
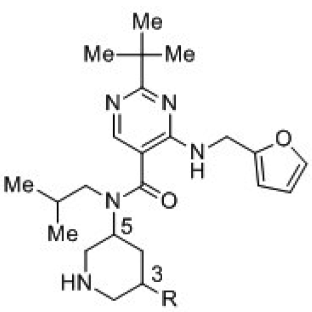


Figure 1. X-ray crystal structure (left) and binding mode (right) of **1** with renin. Our optimization strategy is indicated by the arrow.

Table 1. In Vitro Activities of 1−5, along with Their clogP, LE, and LLE[a]



cmpd	R	Stereo	renin IC_{50} (nM)[b] rh-renin	renin IC_{50} (nM)[b] hPRA	clogD pH7.4	LE	LLE
1	H	S	0.58 (0.39–0.84)	4.6 (2.6–7.6)	3.0	0.31	6.3
2	CO_2Me	cis	0.44 (0.25–0.79)	1.4 (0.85–3.7)	3.3	0.28	6.1
3	CO_2Me	trans	3.3 (2.3–4.9)	10 (7.7–13)	3.3	0.25	5.2
4	CO_2Me	3*S*, 5*R*	1.2 (0.91–1.6)	>10	3.3	0.26	5.6
5	CO_2Me	3*R*, 5*S*	0.039 (0.034–0.044)	0.35 (0.22–0.54)	3.3	0.31	7.1

[a] IC_{50} values shown as the mean values of duplicate measurements. [b] IC_{50} values and 95% confidence limits are calculated from the concentration−response curves generated by GraphPad Prism.

compound **1** (414), we thought that the additional substituent could be added without deleterious effects on PK (Figure 1). In particular, sp^3-rich substituents that could increase receptor/ligand complementarity and enhance potency and selectivity against off-target effects were employed.[20] Subsequently, modification of metabolically liable groups, such as the furfurylamine moiety, was undertaken. Finally, guided by physicochemical parameters, optimization of substituents binding at the S3 and $S3^{sp}$ sites was conducted to discover orally bioavailable renin inhibitors. In this letter, we describe the discovery of a novel, potent, and orally active renin inhibitor **10**, which has been selected as a clinical candidate.

The synthesis of compounds **2−10** is detailed in the Supporting Information. Compounds **1−10** were evaluated for the inhibition of recombinant human renin (rh-renin). Inhibitory activity of these compounds against endogenous renin in human plasma (human plasma renin activity, hPRA) was also measured and is shown as IC_{50} values. The ligand efficiency (LE = (rh-renin pIC_{50})/(heavy atom count)) and ligand lipophilicity efficiency (LLE = (rh-renin pIC_{50}) − clogD (pH 7.4)) are also shown.[21−23] LLE is an important parameter for estimating the potential of the binding interaction without the contribution of lipophilicity.

In order to enhance the potency, a methoxycarbonyl group was introduced at the piperidine 3-position, which was expected to interact with the S1′ site surrounded by both lipophilic and hydrophilic amino acids. Additionally, this functionality was thought to be easily modifiable for latter optimization. The structure−activity relationships of stereoisomers at the piperidine 3- and 5-positions was investigated in detail (Table 1). The *cis*-racemic mixture **2** showed more potent renin inhibitory activity than that of *trans*-racemic mixture **3**. Among the *cis*-isomers, the 3*R*,5*S*-enantiomer **5** was about 30-fold more potent toward renin than its enantiomer **4**, measured either in rh-renin assay (IC_{50} = 0.039 nM vs 1.2 nM) or in hPRA assay (IC_{50} = 0.35 nM vs >10 nM). These results indicated that the stereochemistry at the piperidine 3- and 5-positions is important in determining renin inhibitory activity. Compared to **1**, the renin inhibitory activity of **5** was increased dramatically by introducing the methoxycarbonyl group on the piperidine ring with moderate increase in MW (increased by 58). Although LE values generally decrease with increase in

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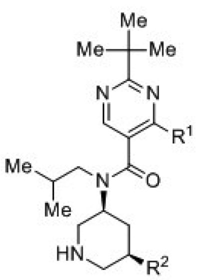
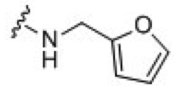
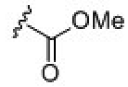
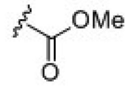
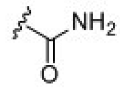
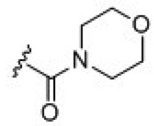
Table 2. In Vitro Activities of 5−8, along with Their clogP, LE, and LLE[a]



cmpd	R^1	R^2	renin IC_{50} (nM)[b] rh-renin	renin IC_{50} (nM)[b] hPRA
5			0.039 (0.034–0.044)	0.35 (0.22–0.54)
6			2.6 (1.4–5.1)	5.2 (3.6–7.4)
7			1.4 (0.97–2.0)	4.5 (3.3–6.1)
8			1.5 (0.60–3.6)	0.79 (0.61–1.0)

[a] IC_{50} values shown as the mean values of duplicate measurements. [b] IC_{50} values and 95% confidence limits are calculated from the concentration−response curves generated by GraphPad Prism.

molecular size, compound **5** retained the same LE value as that of compound **1**, indicating that the methoxycarbonyl group efficiently interacts at the S1′ site. This conclusion was also supported by the increase in LLE value from compound **1** (6.3) to **5** (7.1) despite the increase in clogD value (3.0 and 3.3, respectively).

Modification of the metabolically liable furan moiety of compound **5** and optimization of the methoxycarbonyl moiety were then undertaken (Table 2). In the course of these modifications, the methoxypropylamino group was found as an alternative $S3^{sp}$ site binder with a 10-fold decrease in renin inhibitory activity relative to the furfurylamine moiety (**6**, hPRA IC_{50} = 5.2 nM). The related methoxypropyloxy side chain is a well-known binding motif of the renin $S3^{sp}$ site, present in aliskiren and in other renin inhibitors.[12,15,16] Next, optimization of the methoxycarbonyl moiety of compound **6** was conducted. While carbamoyl derivative **7** showed comparable renin inhibitory activity to **6**, morpholinocarbonyl derivative **8** exhibited potent inhibitory activity (hPRA IC_{50} = 0.79 nM) as well as **5**, suggesting that occupation of the S1′ site would be effective for obtaining strong potency in hPRA assay, since introduction of the morpholinamide might induce the decrease of the human plasma protein binding.

The X-ray cocrystal structure of compound **8** bound to renin was obtained and revealed that the piperidine and amino-pyrimidine moieties are bound to renin protein in the same manner as observed for compound **1**[12] and that the methoxypropylamino moiety was indeed located in the $S3^{sp}$ site (Figure 2). The morpholinocarbonyl group occupies the S1′ site, as we predicted.[13,14,19] Furthermore, its carbonyl oxygen atom forms a hydrogen bond with the backbone amino group of Ser76 on the flap being in a closed conformation.[13,14] These interactions would be expected to contribute to the improvement in renin inhibitory activity.

A rat cassette dosing study indicated that compound **8** possessed poor oral exposure (*F*, <1%; AUC_{po}, not detected; CL 5539 mL/h/kg; Table 3). The physicochemical properties of **8** were analyzed to improve its poor oral absorption. Compared to orally bioavailable compound **1**, the MW and TPSA values of **8** are notably higher. We assumed that improvement of oral absorption could be achieved by control of these physicochemical properties. However, to occupy each binding site, a somewhat higher MW is required for this scaffold. Thus, reduction of the TPSA value was alternatively performed by converting the methoxypropylamino moiety into the corresponding carbon analogue. The *n*-hexyl derivative **9** showed improved *F*, AUC_{po}, and CL values and markedly reduced TPSA value with a 20-fold decrease in renin inhibitory activity (Table 3). This decrease in renin inhibitory activity was interpreted as arising due to the loss of interaction with Gly217 observed in compound **8**.

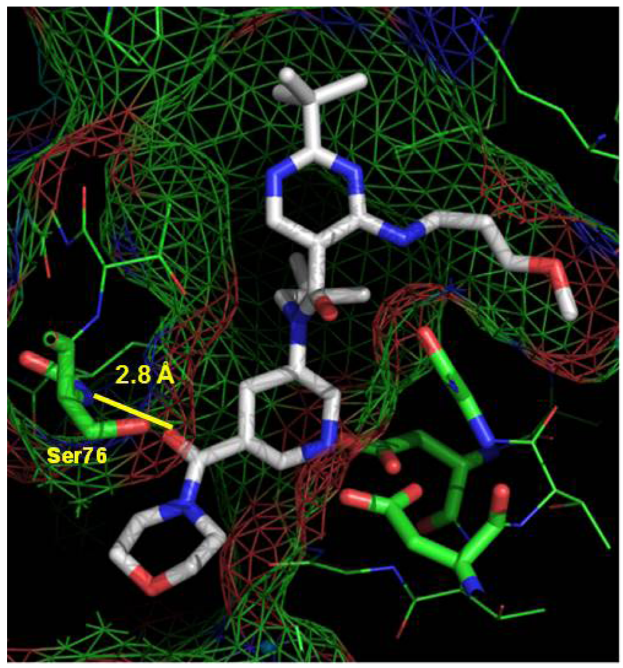


Figure 2. X-ray crystal structure of **8** with renin.

On the basis of the observations discussed above, further investigation was focused on the S3 and $S3^{sp}$ site binding moieties in order to recover decreased potency and improve the PK profiles of compound **9**. Extensive modifications involving

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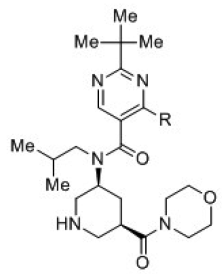
Table 3. In Vitro Activities and PK Profiles of 8–9[a]



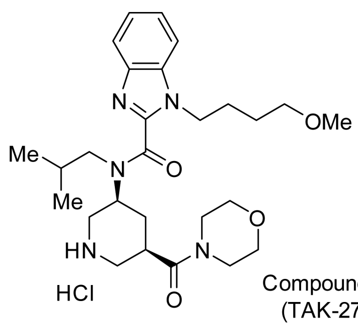
cmpd	R	renin IC_{50} (nM)[b]		MW	TPSA	CL[c] (mL/h/kg)	AUCpo[c] (ng h/mL)	F[d] (%)
		rh-renin	hPRA					
8		1.5 (0.60–3.6)	0.79 (0.61–1.0)	519	109	5539	ND[e]	<1
9		29 (22–38)	> 10	516	88	2407	20.9	5.0

[a]IC_{50} values shown as the mean values of duplicate measurements. [b]IC_{50} values and 95% confidence limits are calculated from the concentration–response curves generated by GraphPad Prism. [c]Rat cassette dosing at 0.1 mg/kg, i.v., and 1 mg/kg, p.o. (n = 3). [d]F means bioavailability. [e]Not detected.

the introduction of the fused and nonfused heteroaromatic ring as replacements for the *t*-butylpyrimidine scaffold led to the discovery of benzimidazole derivative **10** and will be reported elsewhere.

Compound **10** showed potent inhibitory activity against human renin (IC_{50} = 2.1 nM) in hPRA assay and excellent selectivity against other aspartic proteases, such as pepsin (IC_{50} > 10 μM) and cathepsin D (IC_{50} > 10 μM). As shown in Table 4, compound **10** exhibited a dramatically improved PK profile in rats (F = 25.2%). The antihypertensive efficacy of **10** was examined using human-angiotensinogen and human-renin double transgenic rats (dTg rat) (Figure 3). Compound **10** (3 and 10 mg/kg, p.o.) exhibited potent and long-lasting antihypertensive efficacy in a dose-dependent manner. At the time point of 5 h after oral administration, the antihypertensive efficacy of compound **10** at a dosage of 3 mg/kg was comparable to that of aliskiren at a dosage of 75 mg/kg; the antihypertensive efficacy of compound **10** at a dosage of 10 mg/kg also exceeded that of aliskiren at a dosage of 75 mg/kg at both 5 and 24 h after administration. These studies raised expectations of the potential clinical efficacy of compound **10** and encouraged us to investigate this compound further as a candidate for clinical development as a new agent for treating cardiovascular disease.

Table 4. PK Profile of Compound 10 in Rat[a]



Compound **10**
(TAK-272)

iv		po	
$t_{1/2}$ (h)	1.3	$t_{1/2}$ (h)	3.3
MRT (h)	1.1	C_{max} (μg/mL)	0.017
CL (mL/h/kg)	2335.7	T_{max} (μg/mL)	0.5
$V_{d(ss)}$(mL/kg)	2530.3	$AUC_{0-48\ h}$ (μg h/mL)	0.107
		F[b] (%)	25.2

[a]Compound **10** was administered to rats at 0.2 mg/kg, i.v., or 1 mg/kg, p.o. (n = 3). [b]F means bioavailability.

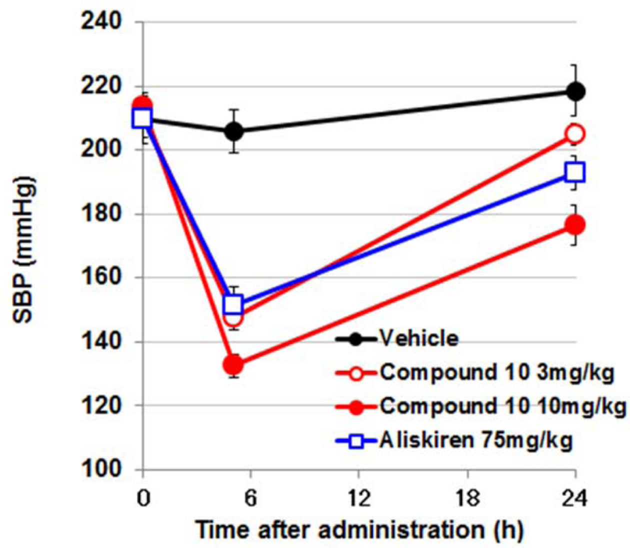


Figure 3. Antihypertensive effect of compound **10** (3 and 10 mg/kg, *po*) and aliskiren (75 mg/kg, *po*) in dTg rat model. Data represent the systolic blood pressure (SBP) measured at 5 and 24 h after administration.

In conclusion, we discovered compound **10**, a structurally novel renin inhibitor showing potent renin inhibitory activity, *in vivo* efficacy in dTg rat model, and a favorable PK profile in rats. In the course of our modifications, the S1′ site was utilized for the enhancement of potency by the introduction of sp^3-rich substituents into the piperidine ring. Optimization of each binding element aimed at improving physicochemical properties succeeded in improving the PK profile. Compound **10** is currently undergoing human clinical trials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00251.

Experimental procedures and characterization, biological assay protocols (PDF)

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Accession Codes

Atomic coordinates and structure factors have been deposited in the Protein Data Bank with codes 5KOQ for **1** and 5KOS for **8**.

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Author Contributions

Y.I., H.T., Y.F., and T.K. contributed design and synthesis of compounds; R.K., Y.K., K.K., and M.K. contributed in vitro and in vivo study; G.S. and C.B. contributed X-ray structures.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

RAAS, renin−angiotensin−aldosterone system; BA (*F*), bioavailability; nRB, number of rotatable bonds; TPSA, topological polar surface area; rh-renin, recombinant human renin; hPRA, human plasma renin activity; LE, ligand efficiency; LLE, ligand-lipophilicity efficiency; SBP, systolic blood pressure

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