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Renin inhibitors for the treatment of hypertension: Design and optimization of a novel series of tertiary alcohol-bearing piperidines

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ABSTRACT

The design and optimization of a novel series of renin inhibitor is described herein. Strategically, by committing the necessary resources to the development of synthetic sequences and scaffolds that were most amenable for late stage structural diversification, even as the focus of the SAR campaign moved from one end of the molecule to another, highly potent renin inhibitors could be rapidly identified and profiled.

Despite the fact that anti-hypertensive medications with distinct mechanisms of action have become broadly available in the past two decades, hypertensive heart disease remains one of the leading causes of mortality in the developed world.[1] As a result, there continues to be a demand for the discovery of more efficacious therapeutic agents that can be used either as monotherapy or in combination with existing anti-hypertensive agents. In this regard, one attractive research strategy involves the design and synthesis of new molecules capable of inhibiting renin, an enzyme responsible for the rate-limiting conversion of angiotensinogen into angiotensin I (Fig. 1).[2] Although numerous pharmaceutical companies have embraced this strategy, to date, aliskiren is the only direct renin inhibitor that has been approved by the FDA for the treatment of mild to moderate hypertension.[3]

We have previously reported that piperidines substituted at the 4-position with an *N*-methyl pyridone (**1**, Table 1) can serve as highly potent renin inhibitors.[4] During this SAR campaign, it was observed that the pyridone functionality engages in two key stabilizing interactions with the renin enzyme: (1) formation of a H-bond between the pyridone carbonyl and indole NH of Trp45, (2) formation of a π-stack between the pyridone ring and phenol residue of Tyr83. Even though we believed these pyridone-bearing renin inhibitors possessed all the properties necessary for clinical

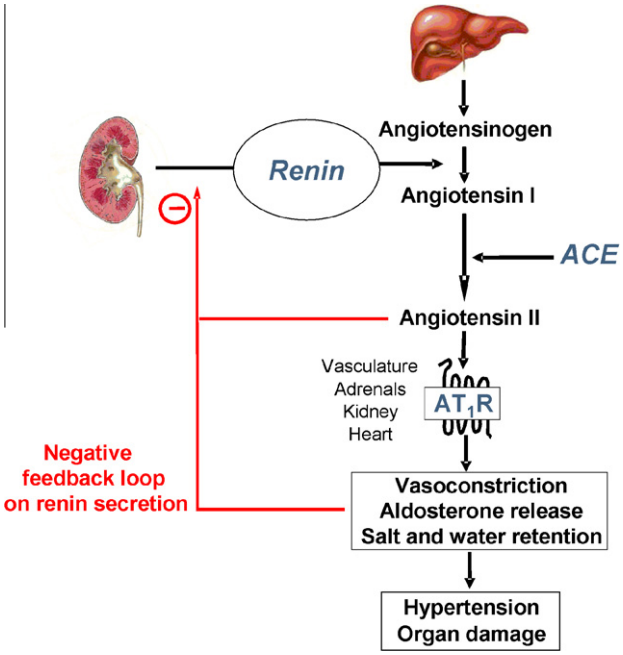

Figure 1. The renin–angiotensin–aldosterone system.

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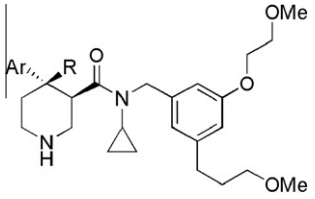
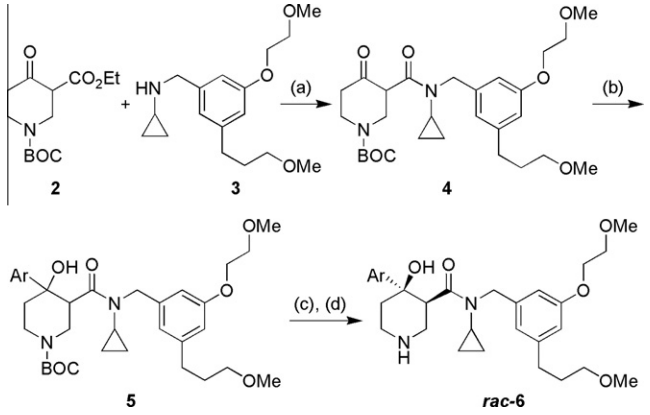
Table 1
SAR of select renin compounds: Northern modifications



Ar									
R	H	OH	OH	OH	OH	OH	OH	OH	OH
	1	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Renin buffer IC_{50}[a] (nM)	12	318	139	54	62	13	9	13	23
Renin plasma IC_{50}[a] (nM)	31	990	467	960	479	135	120	97	230

[a] Average of at least two replicates. All compounds were tested as a racemic mixture. See Ref. 8 for assay protocols.



Scheme 1. Synthesis of **6**. Reagents and conditions: (a) 0.2 equiv DMAP, 140 °C, 79%; (b) 3 equiv LiCl, 3 equiv ArMgBr, THF, rt, 1 h; (c) chromatographic resolution; (d) 30 equiv 4 M HCl in dioxane, rt, 1 h or 10 equiv $ZnBr_2$,CH_2Cl_2.

development, we were intrigued by whether the above favorable interactions could be maintained or enhanced by another suitably-functionalized aromatic plate.

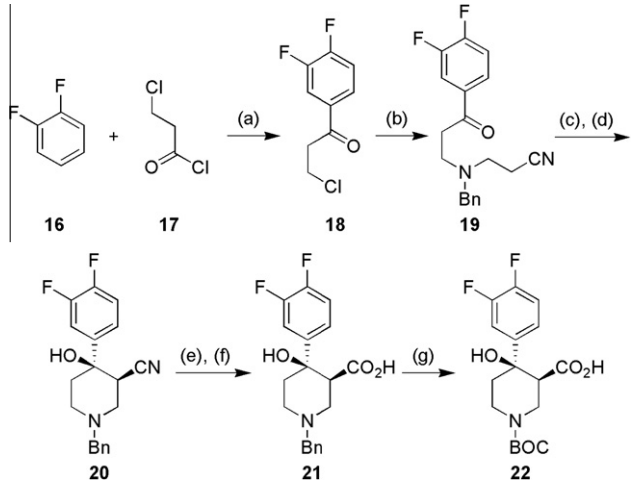
Since the chemistry developed previously for the synthesis of compound **1** necessitated the installation of the pyridone handle at an early stage, an alternative approach that would allow for end stage structural diversification at the 4-position of the piperidine ring was highly desirable. In this regard, the addition of aryl organometallics to 4-oxo-piperidine-3-carboxamides[5] developed by Bezençon et al. proved to be the most ideal solution (Scheme 1). Briefly, β-ketoester **2**[4] was first converted to β-ketoamide **4** by heating with amine **3**[6] in the presence of catalytic quantities of 4-dimethylamino-pyridine. Subsequent LiCl-mediated addition of an aryl Grignard reagent to amide **4** afforded the corresponding alcohol **5**, albeit as a ~1:1 mixture of diastereomers. Following the isolation of the desired *cis*-isomer via repeated column chromatography, the final cleavage of the BOC-protecting group could be readily accomplished either in the presence of a large excess of 4 M HCl in dioxane or with zinc(II) bromide in CH_2Cl_2.[7]

Using compound **7** with its naked benzene as a reference point, the addition of a methoxy group at the *meta*-position (i.e., **8**) to

Table 2
Key profiles of compound **15**

Renin IC_{50}[a,b] (nM)	Buffer		6.4
	Plasma		42
PK in SD rat (5 mpk I.V.)	*F* (%)	0.3 mpk P.O.	17
		3 mpk P.O.	29
		30 mpk P.O.	18
	Cl (mL/min/kg)		36
	$T_{1/2}$ (h)		1.5
	V_{dss} (L/kg)		5
Efficacy in dTGR (10 mpk P.O.)	Max. BP ↓ (mm Hg)		0
	Duration (h)		0
Off-target profile	hERG K_i (μM)		4.5
	CYP 3A4 Inhibition IC_{50} (μM)		0.9

[a] See Ref. 8 for assay protocols.
[b] Average of at least two replicates.



Scheme 2. Synthesis of **22**. Reagents and conditions: (a) 1.2 equiv $AlCl_3$, CS_2, 45 °C, 20 h, 95%; (b) 1 equiv $BnNH(CH_2)_2CN$, 2.5 equiv NEt_3, THF, 22 °C, 0.5 h, >99%; (c) 1.5 equiv KO^{t}Bu, THF, 30 °C, 89%; (d) chiral resolution, AD column, 7:1:1 hexanes/EtOH/*i*PrOH; (e) 2.5 equiv LiOH, 5 equiv 30% aq H_2O_2, DMSO, 45 °C; (f) KOH, ethanol, 80 °C, 10 h; (g) 0.2 equiv $Pd(OH)_2$ on carbon, 1.2 equiv di-*tert*-butyldicarbonate, 1 equiv 200 psi H_2, ethanol, 22 °C, 2 h, 70% over three steps.