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Discovery of renin inhibitors containing a simple aspartate binding moiety that imparts reduced P450 inhibition

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ABSTRACT

Discovery of potent renin inhibitors which contain a simplified alkylamino Asp-binding group and exhibit improved selectivity for renin over Cyp3A4 is described. Structure-function results in this series are rationalized based on analysis of selected compounds bound to renin, and the contribution of each molecular feature leading to the reduced P450 inhibition is quantified.

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As the first and rate-limiting enzyme in the renin-angiotensin system, renin has been heralded as an optimal target for the regulation of hypertension, and clinical success in this area has recently been achieved with aliskiren, the first FDA approved renin inhibitor.[1] Although aliskiren effectively reduces blood pressure at levels comparable to the ARBs and ACE inhibitors, and is capable of producing additional positive blood pressure effects in combination with these agents, the drug suffers from the drawbacks typically associated with renin inhibitors (poor bioavailability, cost of synthesis).[1] As a result of these limitations, efforts to develop alternative renin inhibitors continue across the pharmaceutical industry in both the clinical and pre-clinical settings.[2]

A series of biphenylpiperidinylcarbinol renin inhibitors (**1**, Fig. 1) derived from structure-based design was previously disclosed by Vitae Pharmaceuticals with whom we partnered to discover new renin inhibitors within this class.[3] The more active members of this class feature three common motifs: 1) a substituted biphenyl group which occupies both the S1 and S3 hydrophobic binding pockets of renin, 2) a methyl propyl carbamate moiety that fills and forms hydrogen bonds within the deep, narrow $S3^{sp}$ binding site, and 3) an alkylamino functionality that forms a hydrogen-bonded salt bridge with the catalytic aspartate residues (Asp32 and Asp215) of renin.[4] By design, a (1*R*,3*S*)-3-aminocyclopentyl moiety was selected to display the Asp-binding amino group in this series, as structural evidence suggested that the cyclopentane ring would present the amino group in an optimal alignment for Asp binding without inducing unfavorable conformations. Impressively, this analogue design produced exceptionally potent renin inhibitors (e.g. **1b**, renin $IC_{50} < 1$ nM, PRA $IC_{50} < 5$ nM based on GSK assays, see Supporting Information) which are on par with aliskiren. However, the prototypical members of this series contain shortcomings that could limit their usefulness in clinical development of new anti-hypertensive agents. Of particular concern is the potent inhibition of cytochrome P450 3A4 (Cyp3A4) that accompanies this class, the synthetic complexity required to assemble these molecules, and their poor oral bioavailability.

Herein, we disclose the discovery of potent renin inhibitors derived from compound **1** which contain simplified alkylamino Asp-binding groups. The optimal compounds in the series, which inhibit renin activity at levels comparable to **1a**, exhibit 43-fold greater selectivity against Cyp3A4 when measured under identical assay conditions (see Supporting Information). A comparison of key analogues reveals that the moderate P450 activity arises in part from N-methylation (~2-fold effect) and to a greater extent

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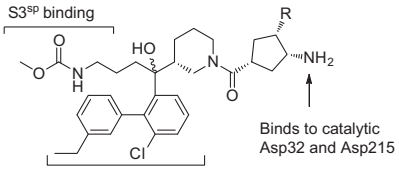


Compd	R	Renin IC_{50}, nM	PRA IC_{50}, nM	Cyp3A4 IC_{50}, nM
1a	H	3.1	8.4	34
1b	OH	0.3	1.8	250

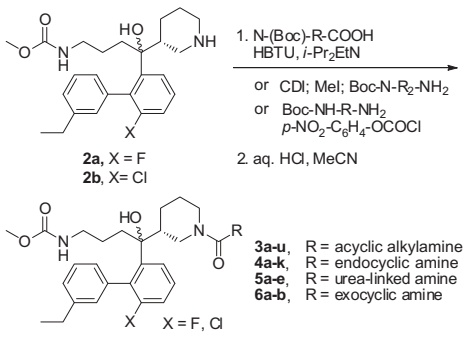
Fig. 1. Biphenylpiperidinylcarbinol renin inhibitors.

from the reduced lipophilic nature (~20-fold effect) of this compound series. Structures of selected compounds bound to renin are presented and used to rationalize the structure-function information generated during the course of the investigation.

Each analogue required for the study could be accessed from intermediates **2a** and **2b**, which were synthesized as described previously (Scheme 1).[3] The tertiary alcohol was synthesized as a 1:1 mixture of stereoisomers while the piperidine stereocenter originated from (*R*)-Boc-nipecotic acid. Under certain reaction conditions the stereopurity of the piperidinyl center was observed to erode en route to **2a** and **2b** and attempts were made to avoid this problem.[5] While the enantiomeric purity of each analogue is presumed to be >95% based on starting material input, it should be recognized that some compounds in this report could contain enantiomeric or epimeric impurities based on the observed lability of this stereocenter. Renin inhibitors **1**, **3**, **4**, and **6** were derived through HBTU-mediated coupling (HBTU, *i*-Pr_2EtN, DMF, 25 °C, 2 h) of piperidine **2** with N-Boc protected amino acids followed by Boc removal (2 M aq. HCl, CH_3CN, 25 °C, 2 h). Urea-linked inhibitors (**5**) were prepared by converting **2a** or **2b** to an acylimidazolium adduct (CDI, CH_2Cl_2, Et_3N, 25 °C, 18 h; MeI, 25 °C, 18 h) that was coupled with N-Boc protected diamines (CH_3CN, 50 °C, 18 h). Alternatively, the urea bond could be formed by treating **2a** or **2b** with N-Boc protected diamines (CH_2Cl_2, Et_3N, 25 °C, 3 h) that had been activated as *p*-nitrophenyl carbamates (*p*-NO_2-C_6H_4-OCOCl, Et_3N, 25 °C, 30 min).

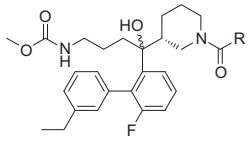
The biological activity of each analogue was assessed in assays utilizing the human renin enzyme in buffer or in the presence of human plasma (PRA, see Supporting Information). Activity against P450s was routinely measured using Cypex bactosome preparations and selected compounds were also assayed against human liver microsomes (HLM) using midazolam as substrate to determine their Cyp3A4 inhibition within a biological matrix (see Supporting Information).

In an effort to decrease the complexity of **1a**, and with the intent of reducing the lipophilicity of the renin inhibitors, *n*-alky-



Scheme 1. Synthetic route to renin inhibitors **3** – **6**.

Table 1
Effect of alkyl chain length.



Compd	R	Renin[a] IC_{50} (nM)	PRA[b] IC_{50} (nM)
3a	CH_2NH_2	63	3800
3b	$CH_2CH_2NH_2$	100	nd[c]
3c	$CH_2CH_2CH_2NH_2$	1.0 ± 0.5	13
3d	$(CH_2)_5NH_2$	3.2	100
3e	$(CH_2)_4NH_2$	2.0	120

[a] Renin values are presented as the mean of n = 2 measurements with average SD of ±0.3 pIC_{50}; where n ≥ 3 was measured, values are presented as mean ± SD.
[b] PRA = plasma renin assay, values are presented as the mean of n = 2 measurements with average SD of ± 0.1 pIC_{50};
[c] nd = not determined.

lamines were screened as potential replacements for the Asp-binding cyclopentylamine moiety (**3a–e**, Table 1). Compounds bearing C1-C5 alkylamines displayed good to moderate activity against renin (IC_{50} = 1–100 nM), and the propylamine group emerged as an effective substitution with **3c** displaying similar potency against renin in isolation (IC_{50} = 1.0 nM) and in a functional setting (PRA IC_{50} = 13 nM) compared to the prototype **1a** (renin IC_{50} = 3.1 nM, PRA IC_{50} = 8.4 nM). Although compounds bearing longer alkyl linkers (**3d**, **3e**) are slightly less potent (3–4-fold) compared to **3c**, their significant binding reflects the conformational flexibility inherent in the alkyl groups. Conversely, analogues projecting the critical amino group through a C1–C2 alkyl chain (**3a**, **3b**) displayed substantially reduced activity (>50-fold), suggesting that these changes force a disrupted binding wherein the amino-Asp, biphenyl-S1/S3, and carbamate-$S3^{sp}$ interactions cannot be simultaneously accommodated.

Consistent with these results, an X-ray crystal structure[6] of an N-methyl propylamine containing compound (**3p**, Table 2) bound to renin (Fig. 2) demonstrates that the propyl chain binds in a fully extended conformation (θ > 150° for each bond) to center the amine appendage between the two Asp carboxylates while fully maintaining the renin binding contacts presented by other elements of the molecule. In this binding mode, shorter alkyl linkers would leave the amino group too distant from the aspartates (≥4 Å) for effective binding while longer linkers must adopt unfavorable conformational angles to appropriately position the amino group between the catalytic residues.

Having defined the optimal chain length for display of the Asp-binding amino group, the effect of substitution of the propyl chain was examined. In keeping with our intent to reduce the lipophilicity and synthetic complexity of the inhibitors, polar substituents that were readily accessible were predominately surveyed (Table 2). In all cases tested, substitution at R^1 and R^3 produced significant reductions in renin inhibition (**3f-3o**, IC_{50} = 6–630 nM) – a result that, in hindsight, is not unexpected given that our subsequent structural analysis (Fig. 2) of this series of ligands indicates that the R^1 and R^3 substituents point inward toward the hydrophobic S1 pocket of renin. In this context, it is noteworthy that lipophilic groups at R^3 (e.g. **3g**, IC_{50} = 25 nM) are tolerated more than polar groups of similar size (e.g. **3i**, IC_{50} = 630 nM). In contrast, substituents at R^2 are expected to project away from the binding site

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