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The Design and Synthesis of Cyclic Renin Inhibitors

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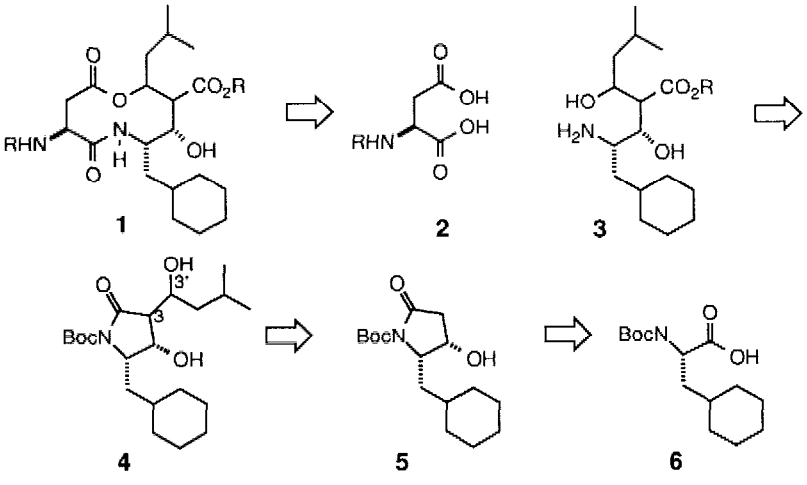
Abstract: A prototype cyclic renin inhibitor was designed through a combined effort between Discovery and Computer Aided Molecular Design. Synthesis of the prototype structure provided compounds which showed weak inhibitory activity of the enzyme renin.

Renin is a highly specific aspartic acid proteinase that catalyzes the proteolytic cleavage of the polypeptide angiotensinogen to the decapeptide angiotensin I. Angiotensin I, which has no known biological activity, is cleaved in a subsequent step by angiotensin converting enzyme (ACE) to produce the vasoactive octapeptide angiotensin II. ACE inhibitors have long been known to be useful drugs in the treatment of hypertension and congestive heart failure. Because renin catalyzes the first and rate-limiting step in the renin-angiotensin-aldosterone system (RAAS) and its only known function is the cleavage of angiotensinogen to angiotensin I, interruption of the RAAS at this point may offer advantages over the ACE inhibitors whose target enzyme acts upon several physiological substrates.[1]



Scheme 1.

A large number of potent renin inhibitors are known.[1a] Most resemble the natural substrate angiotensinogen and incorporate a nonhydrolyzable transition-state mimic at the site of action. Thus, they are

peptidic in nature and are plagued by the problems of limited oral absorption and short pharmacologic duration of action, properties that may exclude their use in therapy. Cyclic renin inhibitor structures might possess certain advantages relative to acyclic compounds, among these are potential stabilization toward proteolytic enzymes and increased binding affinity due to a restriction in the number of available conformations.

The computer model of the active site of renin suggested that cyclization between the P_2 and P_1' sidechains could be accommodated. Although cyclic renin inhibitors were known,[2,3] the concept of cyclizing the acyclic molecules through the P_2 and P_1' sidechains was unique.[4] We concentrated on maintaining hydrogen bonds and hydrophobic interactions in the P_2 to P_1' span that have been implicated as requisite structural features for binding to the enzyme.[5] Overlay of the low energy conformers of prototype inhibitor **1** with known potent acyclic renin inhibitors in the computer model of the enzyme's active site suggested a high correlation both along the carbon backbone and with the important binding elements. The isobutyl and cyclohexylmethyl moieties occupied the P_1' and P_1 hydrophobic pockets in the active site (Figure 1). The P_2 and P_3 amide NH's acted as hydrogen bond donors to Gly 217 and Thr 77 respectively and the P_2 carbonyl as a hydrogen bond acceptor of Thr 77 sidechain. The P_1 hydroxyl was well positioned between the key aspartate residues (32 and 215).

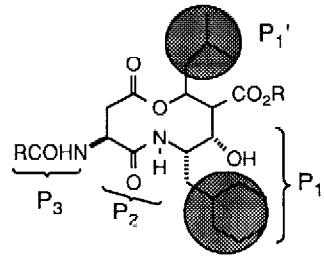
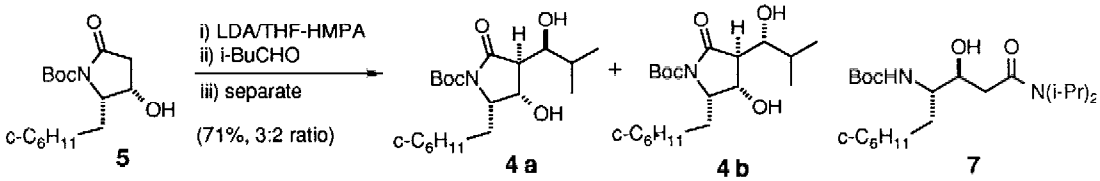


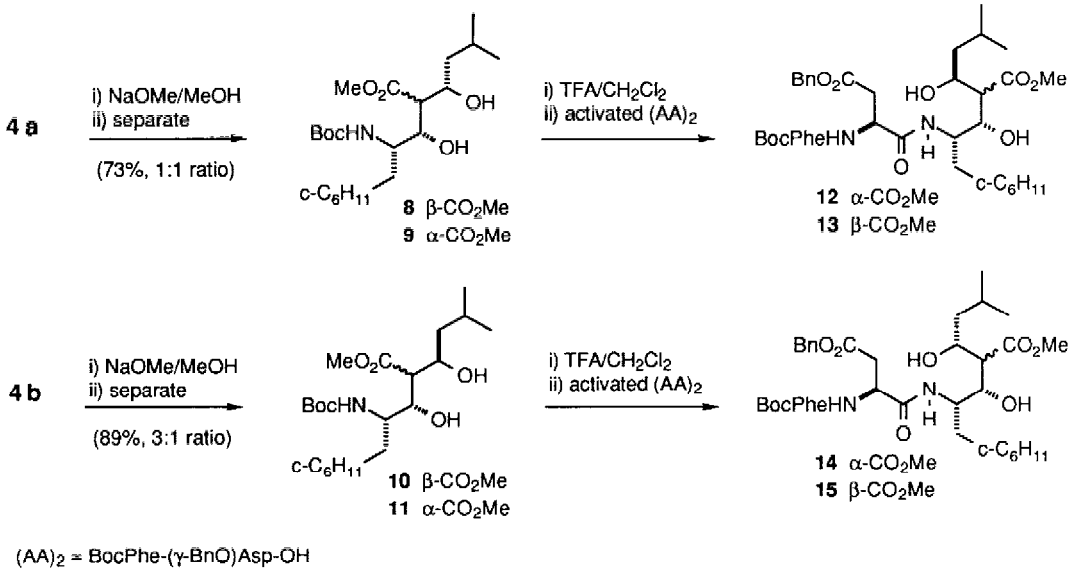
Figure 1. Potential binding elements of prototype inhibitor

A retrosynthetic analysis is depicted in Scheme 1. Because the prototype **1** was designed with an eye toward synthesis, an obvious disconnection bisected the molecule. The western partner **2** is a N-substituted aspartic amino acid. The eastern half **3** contains most of the stereochemical complexity. Cyclization gave **4** which was recognized as a 3-substituted cyclic "ACHPA" ((3S,4S)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid) derivative. The substituent was introduced through an aldol reaction between isovaleraldehyde and the enolate of cyclic "ACHPA" derivative **5**. The stereochemistry at C3 and C3' in **4** is a result of the aldol reaction. Control and flexibility at these centers would be a very desirable aspect to the synthesis as the optimal stereochemical disposition of substituents about the macrocycle **1** was unknown. Details for the preparation of **5** from the N-Boc amino acid **6** were published.[6]



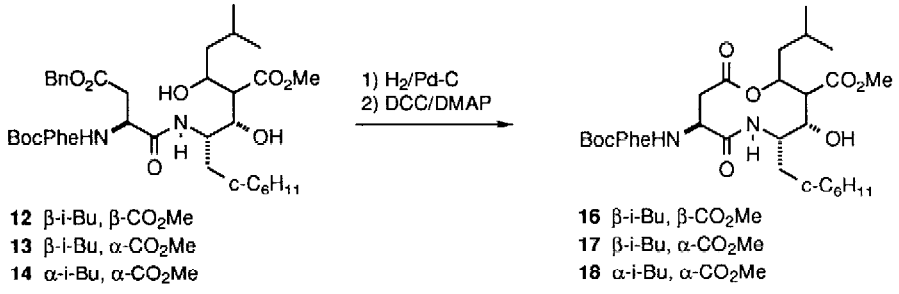
Scheme 2.

Treatment of the lithium dianion of **5** with isovaleraldehyde resulted in the formation of the diastereomeric aldol products **4a** and **4b** accompanied by substantial amounts (20-25%) of the carbonyl addition product **7**[7] (Scheme 2). Lactam ring opening was accomplished by the method of Grieco[8] and produced mixtures of diastereomers in each of the aldol product series allowing preparation of all four of the prototype C3, C3' diastereomers **8-11** (Scheme 3). N-Boc removal and treatment with the activated dipeptide esters (either by standard mixed anhydride or EDAC/HOBT protocol[9]) produced the ω-hydroxy benzyl esters **12-15**.



Scheme 3.

Following hydrogenolysis, three of the ω-hydroxy acids **12-14** cyclized to the desired cyclic compounds in moderate yield (25-50%) by treatment with 1,3-dicyclohexylcarbodiimide (DCC) under high dilution (5 mM) conditions (Scheme 4). DCC was found to be the only reagent of those surveyed (2,2'-dipyridyl disulfide-Ph_3P[10], 2-chloro-1-methyl pyridinium iodide[11]) to effect this capricious transformation.[12] Unfortunately the fourth diastereomer **15** failed to provide any indentifiable cyclic product. In the cases of **12** and **13** some epimerization occurred (presumably at the Phe and Asp side chains) under the prolonged reaction times required to bring about reasonable conversion.



Compounds **16** and **18** proved to be weak inhibitors of purified human renin (IC_{50} @ pH 6.0 of 6.9 μM and 13 μM respectively) and validated our original hypothesis that P_2-P_1' sidechain cyclization could be tolerated. The lower binding affinity of these ten membered ring compounds for the enzyme relative to the recently reported potent P_2-P_1' cyclic inhibitors probably reflects the inability of these compounds to adopt an optimum geometry within the active site due the constraints of the smaller ring.[13]

Acknowledgement: We are grateful to our collaborators Herman H. Stein, Jerome Cohen, and Vered Klinghofer for their work in performing the biological assays and to the Analytical Chemistry Department of Abbott Laboratories for spectral determinations.

References and Notes

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