Dipeptide Renin Inhibitors Containing a Bis[(1-naphthyl)methyl]acetyl Group as the *N*-Terminal Component

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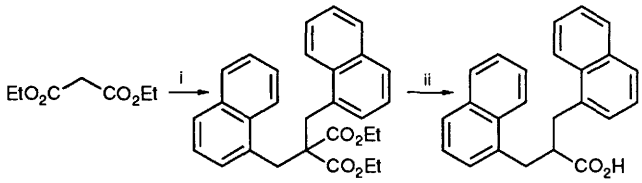
The syntheses and biological activities of potent dipeptide renin inhibitors containing a bis[(1-naphthyl)methyl]acetyl group as the *N*-terminal component are described.

The renin–angiotensin system is implicated in the regulation of blood pressure. The first and rate-limiting step of the cascade involves the aspartic proteinase renin; therefore, the development of renin inhibitors is expected to provide effective antihypertensive agents. Numerous approaches to the design of renin inhibitors have been investigated:[1] one of the most notable attempts has been based on the concept of a transition-state analogue, statine [(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid][2] **1**, in place of the scissile site of Leu-Val. Statine is an unusual β-hydroxy-γ-amino acid that is recognized as a key component of low-molecular-weight aspartic proteinase inhibitors.[3]

Our previous report described a new potent renin inhibitor, *N*-Cbz-Nal(1)-His-Sta-2(*S*)-methylbutylamide† **2** which contains the statine residue.[4] Structure–activity studies with **2** as a prototype have demonstrated that replacement of the *N*-terminal component at the P_4–P_3 (Pro-Phe) site in the angiotensinogen sequence gave potent renin inhibitors that are metabolically stable *in vitro*. It is also well known that the *N*-terminal component interacts with a large hydrophobic subsite in a model three-dimensional structure of renin. We have designed the bis[(1-naphthyl)methyl]acetyl (BNMA) group as an *N*-terminal component, because this component is expected to be able to enhance binding with renin.

The synthesis of BNMA **4**‡ is shown in Scheme 1. Treatment of diethyl malonate with sodium ethoxide and (1-naphthyl)methyl chloride afforded **3**, hydrolysis of which over KOH in aq. Bu^{n}OH at 180 °C provided **4** in good yield (m.p. 172–174 °C). Inhibitors having a BNMA group as the *N*-terminal component were synthesized as depicted in Scheme 2. Deprotection of the t-butoxycarbonyl (Boc) group of *N*-Boc-statine ethyl ester **5** by 4 mol dm^{-3} HCl in dioxane, followed by coupling with *N*-Cbz-histidine hydrazide[5] by the azide method, gave *N*-Cbz-His-Sta-OEt **6** in 62% yield. Reaction of the hydrazide of **6** with 2(*S*)-methylbutylamine



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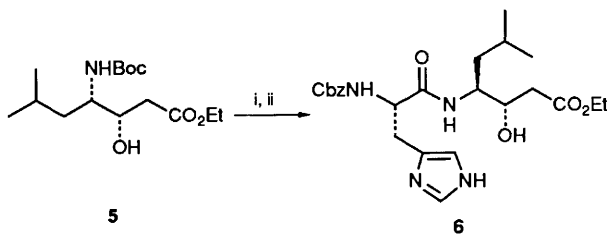
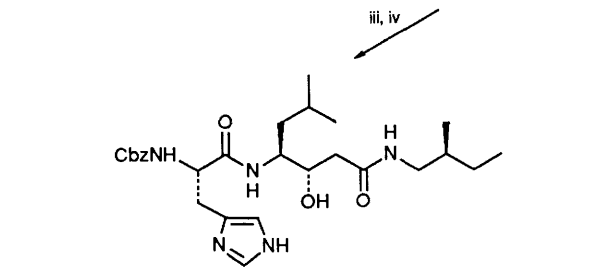
Scheme 1 *Reagents and conditions*: i, NaOEt, (1-naphthyl)methyl chloride, EtOH, room temperature, 75%; ii, KOH, Bu^{n}OH–H_2O, 180 °C, 98%



5 **6**



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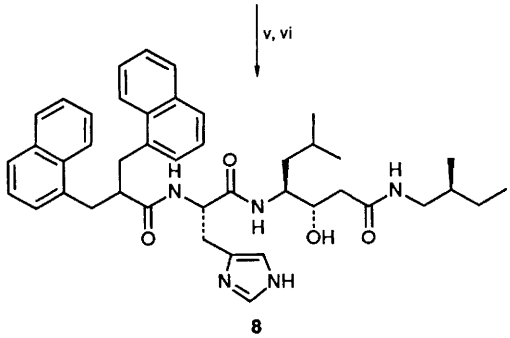

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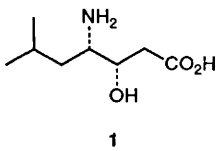
Scheme 2 *Reagents and conditions*: i, 4 mol dm^{-3} dioxane, ii, *N*-Cbz-His-N_2H_3, azide method, 62%; iii, N_2H_4–H_2O, 74%; iv, 2(*S*)-methylbutylamine, azide method, 60%; v, 10% Pd–C, $MeONEt_3$; vi, **4**, DEPC, DMF, 23%



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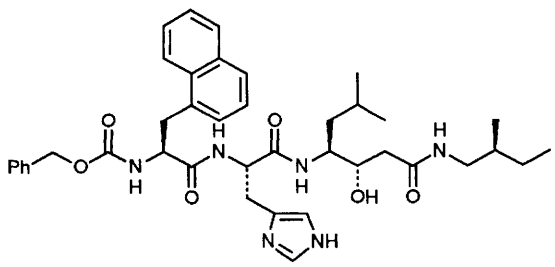

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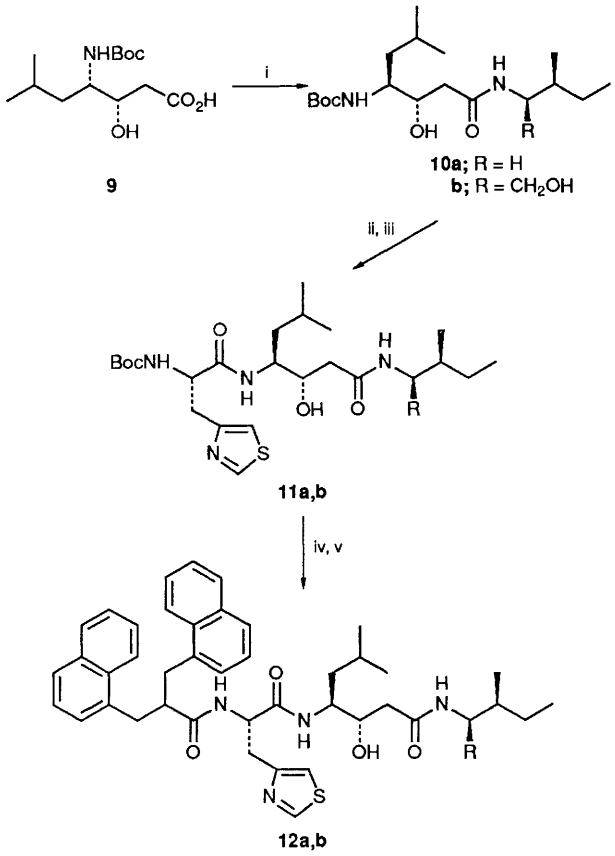
† Abbreviation; Cbz = benzyloxycarbonyl, Nal(1) = 3-(1-naphthyl)-L-alanine, His = L-histidine, Sta = statine.

‡ All new compounds gave satisfactory spectral data and elemental analyses.



Scheme 3 *Reagents and conditions*: i, 2(*S*)-methylbutylamine or isoleucinol, DEPC, NEt_3, THF, 93 and 90%; ii, 4 mol dm^{-3} HCl–dioxane; iii, *N*-Boc-3-(4-thiazolyl)-L-alanine, DEPC, NEt_3, THF, 84 and 85%; iv, 4 mol dm^{-3} HCl–dioxane; v, **4**, DEPC, NEt_3, THF, 70 and 82%

gave **7**. After deprotection of the Cbz group of **7** by hydrogenation over 10% Pd–C, the product was coupled with **4** using diethylphosphoryl cyanide (DEPC),[6] to give the desired compound **8** {m.p. 130–135 °C, $[\alpha]_D^{25}$ −66.0° (*c* 0.1, MeOH)}.

While histidine is the amino acid at the P_2 site in angiotensinogen, 3-(4-thiazolyl)alanine[7] was used for synthetic ease and to enhance activity. The inhibitors containing 3-(4-thiazolyl)alanine at the P_2 site were prepared as shown in Scheme 3. Condensation of 2(*S*)-methylbutylamine or isoleucinol with *N*-Boc-statine **9** gave **10a,b** in good yield. After removal of the Boc group, acylation with *N*-Boc-3-(4-thiazolyl)-L-alanine yielded **11a,b**. Furthermore, deprotection of **11a,b** and coupling with **4** using DEPC afforded **12a** {$[\alpha]_D^{25}$ −50.2° (*c* 1, MeOH)} and **12b** {$[\alpha]_D^{25}$ −50.4° (*c* 1, MeOH)} respectively.

The inhibitory potencies against human renin were determined by radioimmunoassay with a human renin–sheep substrate assay system. The compounds **8**, **12a** and **12b** are potent inhibitors of human renin with IC_{50} of 9.2, 0.7 and 1.3 nmol dm^{-3} respectively. Furthermore, these inhibitors showed excellent enzyme specificity; they did not inhibit cathepsin D, pepsin, trypsin, chymotrypsin, angiotensin converting enzyme (ACE) or urinary kallikrein at a concentration of 10^{-5} mol dm^{-3}.[8]

In conclusion, structure–activity studies with tripeptide **2** as a prototype led to the potent dipeptide inhibitors **8**, **12a** and **12b**.

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