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Retro-Inverso Tripeptide Renin Inhibitors

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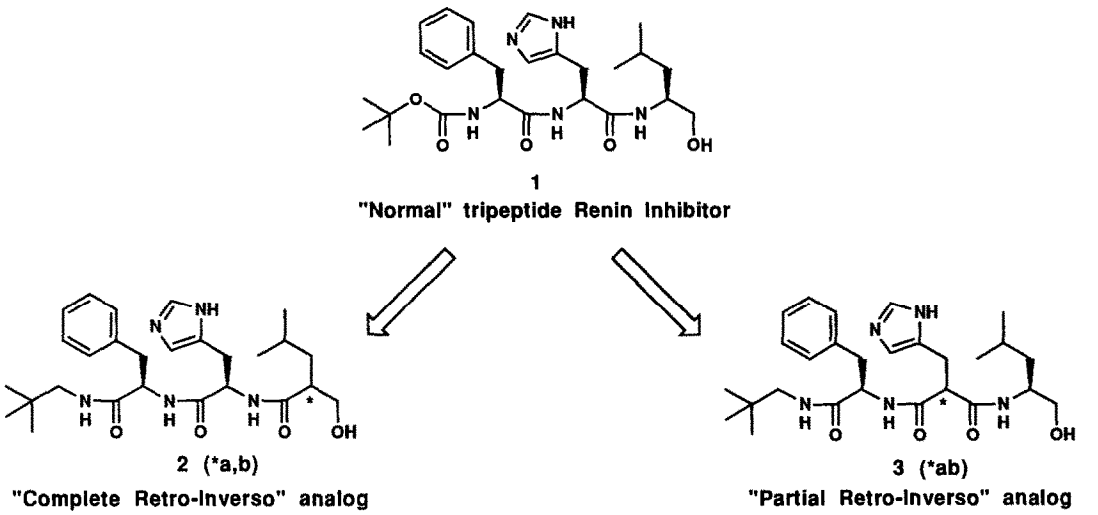
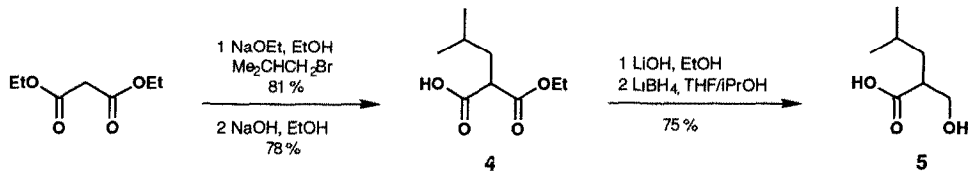
Abstract: *Application of the retro-inverso peptide backbone modification concept to the tripeptide alcohol renin inhibitor Boc-Phe-His-Leucinol* ***1*** *(I_{50} = 16 uM) is described. While the diastereomeric mixture of partial retro analogs* ***3ab*** *was substantially less active (I_{50} = 1200 uM), the complete retro-inverso modification was well tolerated, as evidenced by the equipotency of* ***2b*** *(I_{50} = 20 uM) to parent compound* ***1****.*

Pharmacological intervention of the renin-angiotensin system (RAS) through inhibition of the aspartyl proteinase renin is a viable alternative to the currently existing therapy of blockade of angiotensin-converting enzyme (ACE)[1] for the treatment of hypertension and congestive heart failure. During our own efforts in this highly popular and intense research area,[2] we became interested in investigating the retro-inverso modification[3] of some of our lead tripeptide based renin inhibitors. Besides enabling us to assess the relative importance of side chain vs. backbone structure of our inhibitors, these structurally novel analogs also offered the possibility of exhibiting enhanced stability towards proteolytic enzymatic degradation.[4] As a starting point, we chose to study this modification in the simple primary alcohol tripeptide **1**.[5]

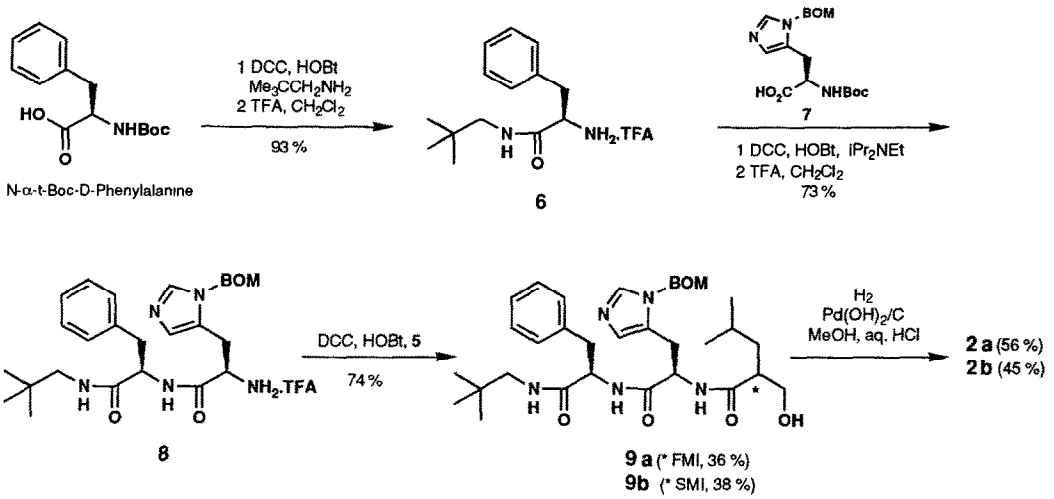


The hydroxyl group of **1** is supposedly interacting with the aspartyl residues at the active site of the enzyme, and was thus retained in all the analogs. Compound **2** is a complete retro-inverso analog involving inversion of all the peptide linkages of **1**, including the replacement of N-terminal t-butoxycarbonyl (Boc) group by a reversed neopentyl amide group.[6] Alternatively, **3** is a partial retro-inverso analog in which the Boc group and the Phe-His amide bond are retro inverted, whereas the His-Leu amide bond is retained in a normal fashion.[7]

Scheme 1



Scheme 2

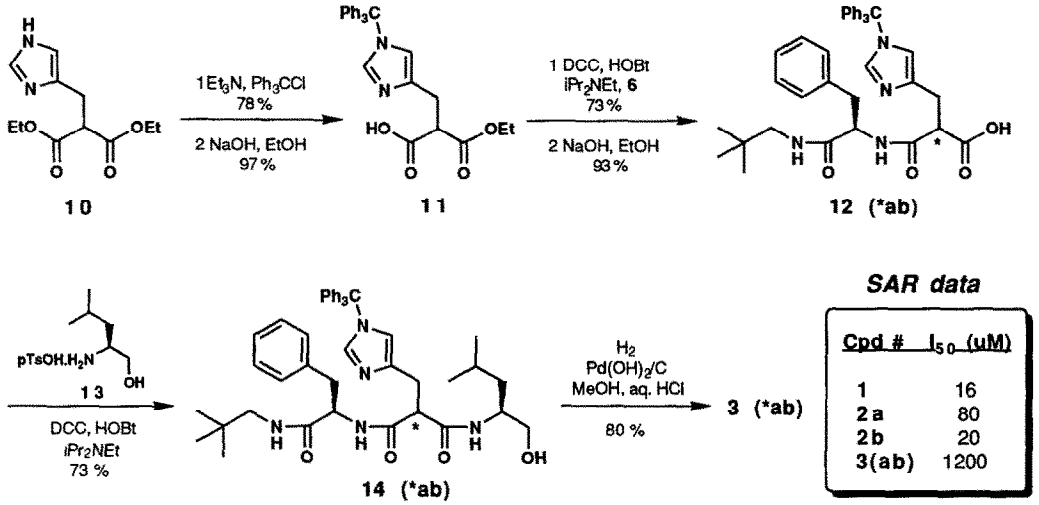


Monoalkylation of diethyl malonate with isobutyl bromide followed by base hydrolysis provided the monoester monoacid **4**, whose ester group was chemoselectively reduced by treatment with lithium borohydride[8] to yield the alcohol **5** in good overall yields (Scheme 1). DCC/HOBt mediated coupling of Boc protected D-phenylalanine with neopentyl amine followed by treatment with TFA/dichloromethane gave **6**, the retro fragment of N-α-t-Boc-L-phenylalanine. Amine **6** was coupled with acid **7**[9] and the resulting dipeptide deprotected in a straightforward manner to yield **8**. Condensation of **8** with the β-hydroxy acid **5** gave the tripeptide alcohol **9** as a separable mixture of diastereomers. The individual diastereomers were then treated with hydrogen in the presence of Pearlmans catalyst to afford the complete retro-inverso analogs **2a** and **2b**.[10] The presence of HCl was critical for efficient and clean removal of

the benzyloxy methoxy (BOM) group in the final hydrogenolysis step.

For preparation of partial retro-inverso analog **3**, the imidazole ring of **10**[11] was protected with a trityl group and the corresponding diester monohydrolyzed to acid **11**. Coupling of **11** with the retro fragment **6** followed by hydrolysis provided the malonyl acid **12** as an inseparable mixture of two diastereomers. Coupling with L-leucinol **13** gave the N-trityl protected tripeptide **14** which was subsequently hydrogenolyzed to afford **3**.[10]

Scheme 3



SAR data

Cpd #	I_{50} (uM)
1	16
2a	80
2b	20
3(ab)	1200

As shown in the table in Scheme 3, the complete retro-inverso analog **2b** was found to be equipotent to the parent tripeptide alcohol **1**. Such a result was quiet impressive, especially in view of the drastic modification of reversal of two amide bonds and a Boc group involved in **2b**. The less active analog **2a** may be the one with incorrect D stereochemistry of the leucinol group, although assignment of absolute stereochemistry was not attempted. In contrast to the equipotency of **2b** to **1**, the diastereomeric mixture of the corresponding partial retro-inverso analogs **3ab** suffered a 75 fold loss in activity, suggesting that a malonyl type residue around the histidine center might not be compatible with these inhibitors.

In summary, we have demonstrated that a complete retro-inverso modification is well tolerated with tripeptide primary alcohol based renin inhibitors like **1**. This promising data has encouraged us to undertake similar modifications with several other more potent classes of tripeptide based renin inhibitors.

Acknowledgements :

We wish to thank Dr. E. W. Petrillo for helpful discussions, and Dr. Charles A. Free and Ms. Sandra A. Smith for the biological evaluation of compounds **1**, **2a**, **2b** and **3**.

Notes and References :

1 Petrillo, E. W. Jr.; Ondetti, M. A. *Med. Res. Rev.* **1982**, *2*, 1.

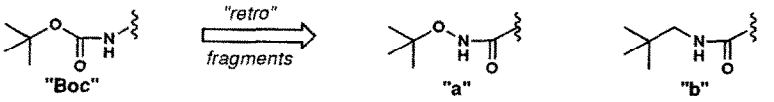
2 Greenlee, W. J. *Med. Res. Rev.* **1990**, *10*, 173.

3 Retro-inverso compounds are structural analogs of parent peptides with identical topology i.e. absolute side chain stereochemistry, but reversed amide linkages. For an excellent review, see Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1.

4 Since these modifications involve the replacement of the natural L-amino acids with their D-enantiomer or non-amino acid (malonyl or gem-diamino) residues, they may possess enhanced stability towards proteolytic enzymatic degradation.

5 Compound **1** was prepared by S. Natarajan and E. Sabo at Bristol-Myers Squibb. It involved a DCC/HOBt mediated coupling Boc-Phe-His(BOM)-OH with L-leucinol followed by hydrogenolysis to effect the removal of BOM group from the coupled product.

6 Although the hydroxamic ether group **a** would be a more appropriate retrofragment of the Boc group, the neopentylamide group **b** was chosen for convenience.

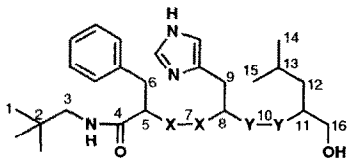


7 The Phe-His bond is suspected to be prone to proteolytic degradation. Peptide backbone modifications like N-methylation of the Phe-His amide bond with other classes of renin inhibitors have resulted in analogs with higher metabolic stability and prolonged duration of action. See Thaisrivongs, S.; Pals, D. T.; Harris, D. W.; Kati, W. M.; Turner, S. R. *J. Med. Chem.* **1986**, *29*, 2088.

8 Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702.

9 The D-acid **7** was prepared following the procedure reported for the preparation of its L enantiomer. See Brown, T.; Jones, J. H.; Richards, J. D. *J. Chem. Soc. Perkin Trans. I*, **1982**, 1553.

10 All compounds were characterized by MS, ^{1}H & ^{13}C NMR..



Compound 2a [CD_3OD, 67.5 MHz] : 22.4, 23.5 (C-14,15), 27.3 (C-13), 27.7 (C-1), 29.4 (C-9), 33.2 (C-2), 37.8, 38.7 (C-6,12), 51.7 (C-3), 54.8, 55.6, 56.6 (C-5,8,11), 65.8 (C-16), 127.8, 129.5, 130.1, 136.3, 138.6 (aromatics), 173.3, 173.5 (C-4,7), 178.3 (C-10). **Compound 2b** [CD_3OD, 67.5 MHz] : 22.6, 23.6 (C-14,15), 27.0 (C-13), 27.7 (C-1), 29.8 (C-9), 33.1 (C-2), 38.7, 39.0 (C-6,12), 51.7 (C-3), 54.8, 56.4 (C-5,8,11), 64.9 (C-16), 127.8, 129.5, 130.3, 134.0, 136.1, 138.3 (aromatics), 172.9, 173.3 (C-4,7), 177.4 (C-10). **Compounds 3ab** [CD_3OD, 67.5 MHz] : 22.2, 23.7 (C-14,15), 25.8, 25.9 (C-13), 27.7 (C-1), 27.8 (C-9), 33.1 (C-2), 39.0, 40.9 (C-6,12), 51.7 (C-3), 50.9, 54.7, 56.3 (C-5,8,11), 65.8 (C-16), 112.7, 127.8, 129.5, 130.2, 130.3, 138.3 (aromatics), 171.0, 171.3, 173.2, 173.5 (C-4,7,10).

11 For preparation of **10**, see Chaturvedi, N.; Goodman, M., Bowers, C. *Int. J. Pept. Protein. Res.* **1981**, 17, 72.