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Short Communication

Parallel synthesis of α-hydroxy β-amino amide containing peptide derivatives as structural analogues of *Bestatin*†

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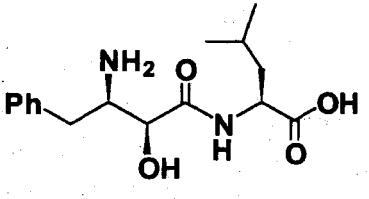
Abstract

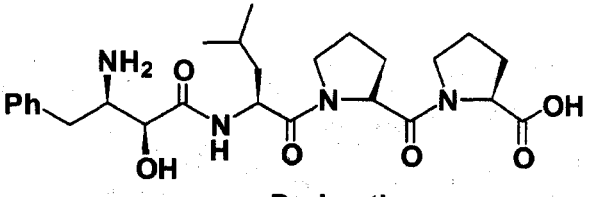
A solution-phase polyaniline-supported cobalt(II) salen-catalyzed synthesis of libraries of α-hydroxy β-amino amide containing dipeptide derivatives was developed from *N*-cinnamoyl peptides as versatile synthon in parallel synthesis. These peptides are structural analogues of amino peptidase inhibitor *bestatin*.

Keywords: Parallel synthesis, peptides, drug discovery.

The increasing demand for new chemical entities has paved the way for the emergence of parallel synthesis[1] in the arena of drug discovery. Parallel synthesis circumvents the disadvantages associated with the synthesis of compound mixtures and promises to provide an efficient protocol for the preparation of a single compound in solution. In connection with our work on new drug discovery, we required a procedure which may allow access to single-compound libraries from well-known chemical transformations. Our attention was focused on libraries containing peptides having α-hydroxy-β-amino acid residue.[2] This residue is prominent in bioactive molecules such as amino peptidase inhibitors *bestatin*[3] and *probestin*[4]. This paper describes the synthesis of β-phenylisoserine-(L)-leucine-(L)-proline containing tripeptide derivatives (**3**), as structural analogues of aminopeptidase inhibitor *bestatin* and *probestin*, from *N*-cinnamoyl dipeptides by a one-pot cobalt-catalyzed conversion using a combined protocol involving epoxidation and subsequent reaction with aniline derivatives (Scheme 1). These peptides were



Bestatin



Probestin

†Dedicated to Prof. S. C. Bhattacharyya.

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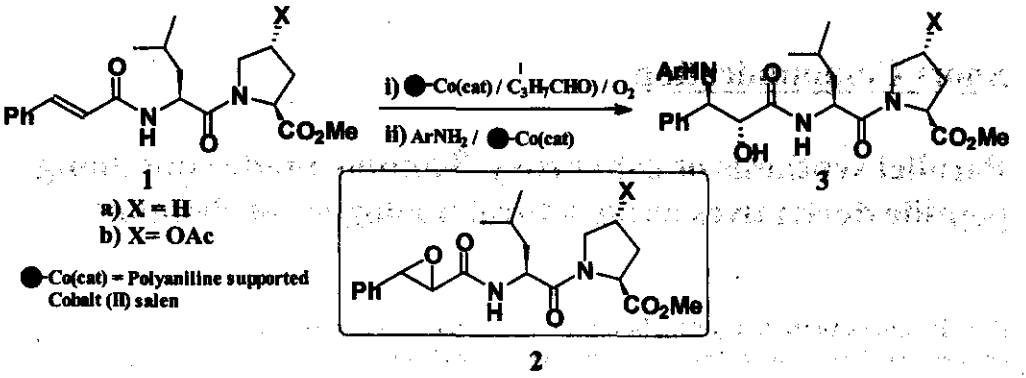
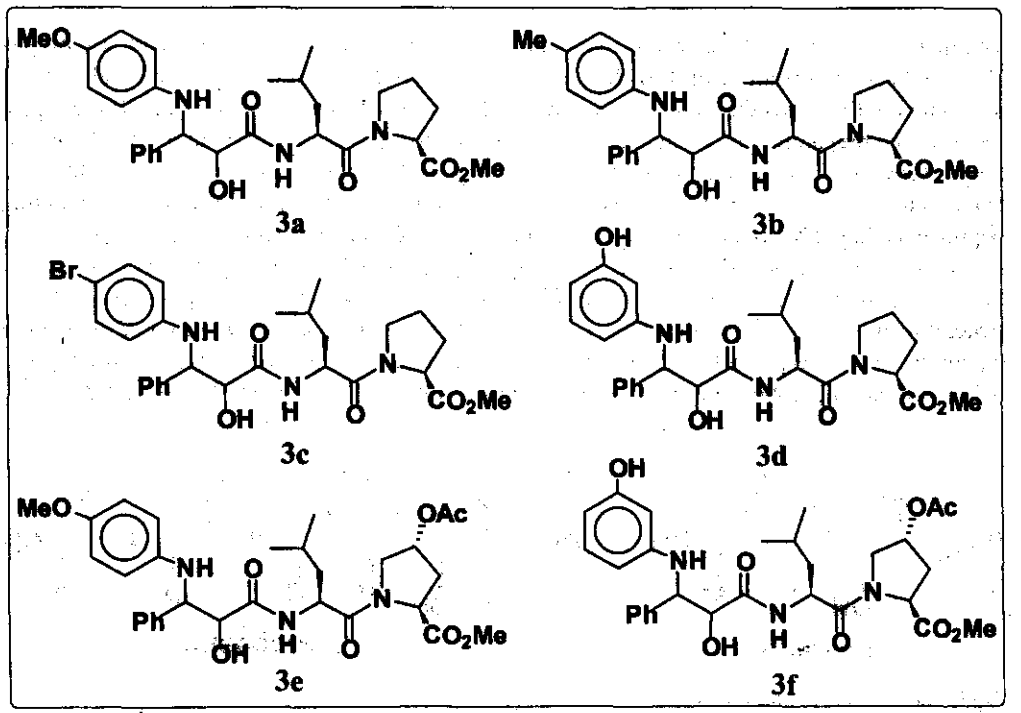


Scheme 1.

isolated by circumventing the column chromatography via a solvent extraction technique. The *in-situ* synthesis of epoxides (**2**) from *N*-cinnamoylpeptides (**1**) can be obtained in a stereoselective manner by polyaniline-supported cobalt(II) salen-catalyzed[5] aerobic epoxidation as reported by us earlier (Scheme 1).

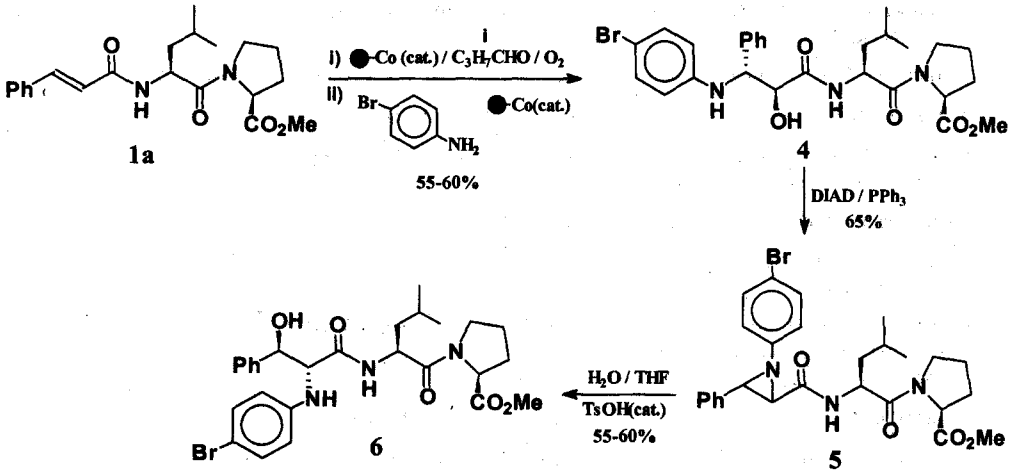
Table I
Tripeptide derivatives (3) as structural analogues of *Bestatin*[a, b]



(a) The tripeptides were obtained as a 1:4 mixture of diastereomers in which the antidiastereomer was obtained as the major product, (b) The isolated yields of the tripeptides were ~60–70% and the HPLC purities ~80–90%.

The *N*-cinnamoyl peptides were used as synthons in a one-pot vicinal hydroxyamination reaction in parallel and we have prepared a 150-member library. Some representative examples of this library are shown in Table I. Thus, the one-pot conversion[6,7] of *N*-cinnamoyl peptides (**1a** or **b**) to the corresponding peptide derivatives (**3a–f**), respectively, was achieved by first polyaniline-supported cobalt(II) salen-catalyzed aerobic epoxidation followed by the opening of the epoxides with various aniline derivatives (i.e. *p*-methylaniline, *p*-methoxyaniline, *p*-bromoaniline and *m*-aminophenol) in the presence of the same catalyst. The peptides (**3**) were obtained as mixture of diastereomers in 60–70% yields in which the *anti* isomer (4:1) was found to be the major product. The peptides (**3**) were isolated by filtering the cobalt catalyst and removing the acetonitrile followed by washing of the residue in carbon tetrachloride: hexane (1:3) which resulted in their precipitation as powder. The excess amine and any unreacted epoxide were retained in the mother liquor and this process afforded >80% pure desired peptides.

Because of the difference in the solubility of peptides (**3**) and aniline derivatives, the solvent extraction procedure for the isolation of these peptides is very simple, as it does not require any aqueous work up or column chromatography. Interestingly, the conversion using **1a** or **b** and *meta* aminophenol afforded the corresponding peptides **3d** or **f**, respectively, mainly as *anti* diastereomer and no product arising due to opening of the epoxide with phenolic oxygen was observed in the reaction mixture (Table I). The *anti* stereochemistry of the major diastereomers was assigned based on the ^{1}H NMR coupling constant[8] between the methine protons and also by converting them to the corresponding aziridine on treatment with diisopropyl azodicarboxylate (DIAD) and PPh_3. Accordingly, the one-pot conversion of **1a,** by epoxidation and opening protocol with *p*-bromoaniline, afforded the mixture of the corresponding diastereomer (**3c**) which was subjected to column chromatography to isolate the *anti* tripeptide (**4**) in good yields (Scheme 2). The peptide (**4**) was smoothly transformed to the corresponding *anti* aziridine peptide (**5**) on treatment with DIAD and PPh_3. *On the other hand, the corresponding syn diastereomer remained unreactive on treatment with DIAD and PPh_3 under*



Scheme 2.

similar conditions. The aziridine peptide (**5**) is an useful intermediate as it was transformed, on treatment with catalytic amount of *p*-toluenesulfonic acid in aqueous THF, to a mixture of the corresponding β-hydroxyphenylalanine containing peptide derivatives from which the major *anti* diastereomer (**6**) was isolated by column chromatography. The *anti* stereochemistry for (**6**) was assigned based on the large coupling constant ($J = 4.8$ Hz) compared with the corresponding *syn* diastereomer ($J = 3.5$ Hz).

In conclusion, the polyaniline-supported cobalt(II)salen-catalyzed one-pot parallel synthesis of β-phenylisoserine-(L)-leucine-(L)-proline-derived peptides is an useful protocol for access to structural analogues of aminopeptidase inhibitor *bestatin* and *probestin*.

Acknowledgement

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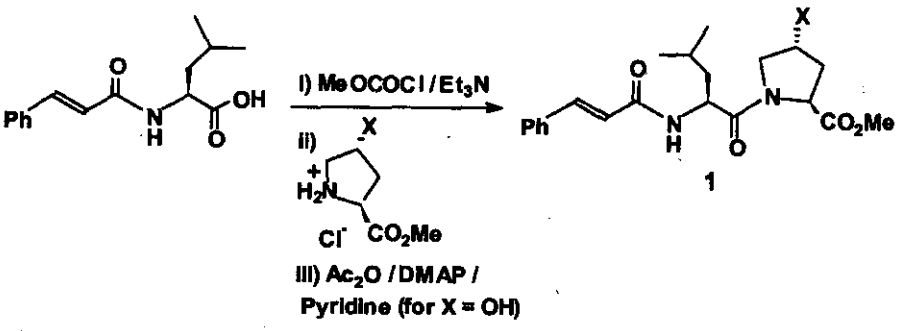
6. Amides **1** were prepared in high yields (~80%) from *N*-cinnamoyl luecine according to the following procedure:



7. **General procedure for the synthesis of tripeptide derivatives (3)**: Amides **1** (5 mmol), 2-methylpropanal (15 mmol) and cobalt(II) salen-polyaniline (~10 mg) were stirred in acetonitrile (20 ml) at ambient temperature for 15–16 h under dioxygen balloon. The balloon was removed and following the addition of aniline derivatives (6 mmol), the stirring was continued for further 17–18 h. The catalyst was filtered and the acetonitrile was removed under vacuum. The residue was successively washed with hexane–CCl_4 (3:1) to afford the peptide derivatives (**3**) as amorphous solids in high purity 80–90%(HPLC). Further purification of **3** was achieved by crystallization from ethyl acetate–hexane. **Synthesis of *N*-arylaziridine (5)**: β-Phenylisoserine derivative **4** (5 mmol), DIAD (15 mmol) and triphenylphosphine (15 mmol) were stirred in acetonitrile (25 ml) at ambient temperature for 20 h. The solvent was removed under vacuum to afford a residue which was subjected to column chromatography (silica gel; hexane/ethyl acetate) to afford the aziridine (**5**) as gum. **Synthesis of β-hydroxyphenylalanine derivative (6)**: *N*-arylaziridine (**5**) (2 mmol) was taken in THF/water (8:2) mixture (10 ml) and a catalytic amount of *p*-toluenesulphonic acid was added to it and the mixture was stirred for 6 h at ambient conditions. The solvent was evaporated under vacuum and the residue was taken in ethyl acetate and washed with saturated solution of sodium bicarbonate (3 × 10 ml) and water (3 × 5 ml). Drying (Na_2SO_4) and evaporation of solvent gave a residue which was subjected to column chromatography (silica gel; hexane/ethyl acetate) to afford **6** as gum.

8. **Spectral data for some compounds**: **4**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.29 (m, 3H), 7.28–7.21 (m, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.97 (m, 1H), 6.47 (d, J = 8.4 Hz, 2H), 4.85 (dd, J = 11.4 and 3 Hz, 1H), 4.76 (dd, J = 14.4 and 4.5 Hz, 1H), 4.50–4.47 (m, 1H), 4.39 (dd, J = 8.4 and 3 Hz, 1H), 3.78–3.71 (m, 1H), 3.69 (s, 3H), 3.51–3.49 (m, 1H), 2.22–2.14 (m, 1H), 2.09–1.92 (m, 3H), 1.53–1.47 (m, 1H), 1.45–1.43 (m, 1H), 1.23 (ddd, J = 21, 14.1 and 7.2 Hz, 1H), 0.93 (d, J = 6 Hz, 3H), 0.886 (dd, J = 6 and 3 Hz, 3H) Mass: (*m/z*)560 (M^+), 299, 261, 128, 211. **5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.19 (m, 7H), 7.12–7.07 (m, 1H), 6.66 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 4.93 (ddd, J = 21.2, 8.4 and 5.2 Hz, 0.5H), 4.82 (ddd, J = 19.2, 10.4 and 5.2 Hz, 0.5H), 4.51 (dd, J = 8.8 and 2.8 Hz, 1H), 3.76 (s, 3H), 3.74 (d, J = 2.8 Hz, 1H), 3.62–3.50 (m, 2H), 3.28 (d, J = 2.8 Hz, 1H), 2.06–1.97 (m, 3H), 1.56–1.53 (m, 1H), 1.30–1.15 (m, 3H), 0.97 (dd, J = 10. 6 and 3 Hz), 0.90 (t, J = 6 Hz, 3H). **6**: ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.35–7.32 (m, 4H), 7.30–7.23 (m, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 1H), 6.40 (d, J = 8.8 Hz, 2H), 5.01 (t, J = 4.8 Hz, 1H), 4.80 (dt, J = 8.8 and 5.2 Hz, 1H), 4.47 (dd, J = 8.8 and 4.4 Hz, 1H), 4.30 (d, J = 5.6 Hz, 1H), 3.97 (t, J = 6 Hz, 1H), 3.80 (m, 1H), 3.70 (s, 3H), 3.54–3.44 (m, 1H), 2.22–2.13 (m, 1H), 2.11–1.91 (m, 3H), 1.75 bs, 1H), 1.50–1.38 (m, 1H), 1.35 (m, 2H), 0.88 (d, J = 5.6 Hz, 3H), 0.79 (dd, J = 6 and 3.6 Hz, 3H); Mass: (*m/z*) 560 (M^+), 501, 453, 297, 107.