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Microwave assisted stereospecific synthesis of (*S*)-3-substituted 2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido-[3,4-*b*]indole-1,4-diones☆

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Abstract—A new easy way of preparing (*S*)-3-substituted 2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-diones, an important intermediate compound, is described using microwave irradiation supported on silica gel. The reaction is generalised and good to excellent yields of enantiomerically pure products are obtained.

1. Introduction

The class of indolyl diketopiperazine alkaloids is found to be tremorgenic mycotoxins, interfering with the mechanisms responsible for the release of neurotransmitters in the CNS,[1] as well as inhibitory effects on the mammalian cell cycle.[2,3] Also, indolyl diketopiperazine analogues have been studied as potential tools in the CNS receptor studies,[4] as candidates for cancer chemotherapy,[2,3] and as a source for providing molecular probes useful in elucidating regulatory mechanisms of the cell cycle.[2,3] The current interest of this class of compounds also lies in their use as MDR (multidrug resistance) reversal agents,[5] and as cGMP-phosphodiesterase inhibitors in the treatment of impotence.[6]

Reduction of keto group to pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole in itself represents an interesting intermediate compound and grafting of a suitable pharmacophore at pyrazino 4′ position (N atom) could lead to compounds having antihistaminic, anxiolytic and antipsychotic activities.[7–10]

In view of the above we decided to build up tetracyclic lactams having variations at the 3 position of the pyrazino ring. We proceeded through traditional solution phase chemistry, although solid phase organic synthesis including combinatorial chemistry[11–13] is currently in fashion, by linking methyl 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate and Boc protected amino acids followed by the final step which is common to all strategies, deprotection and in situ simultaneous cyclisation to provide stable six-membered cyclic amides or bis lactams. The traditional removal of the Boc group by neat trifluoroacetic acid (TFA) or TFA in dichloromethane followed by neutralisation gave the final products in fair to good (60–75%) yields. It has been very recently reported[14] that the Boc group can be very easily and rapidly (1–3 min) removed by microwave irradiation supported by flash column silica gel (250–400 mesh). Herein we report for the first time the preparation of 3-substituted pyrazino[1′,2′:1,6]-pyrido[3,4-*b*]indole-1,4-diones by this method in very good to excellent (>85%) yields.

2. Results and discussion

The key intermediate, *S*-(−)-methyl 1,2,3,4-tetrahydropyrido[3,4-*b*]indole-3-carboxylate (**2**) required for condensation to generate *N*-Boc protected amino acid (**4a**–**g**) was prepared[7g,15] via Pictet–Spengler cyclisation of the imine derivative of L-tryptophan methyl ester hydrochloride (Scheme 1). The imine derivative was prepared with the condensation of formaldehyde with the methyl ester hydrochloride of L-tryptophan according to the standard reported procedure under protic conditions. The *N*-Boc protected glycine, alanine and tryptophan (**4a**–**c**) were prepared according to the literature procedure[16] via modified Schotten–Baumann reaction of respective amino acids (**3a**–**c**) with di-*t*-butylcarbonate, $(Boc)_2O$ at 0°C in a basic medium (Scheme 1).

The condensation of **2** with **4a,b** in presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) at

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Keywords: microwave heating; stereospecific; Pictet–Spengler reaction; pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione.

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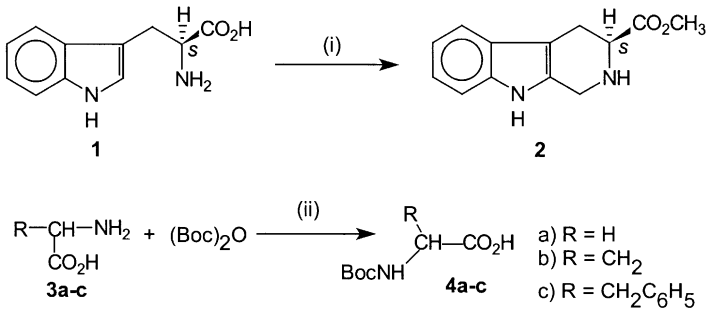
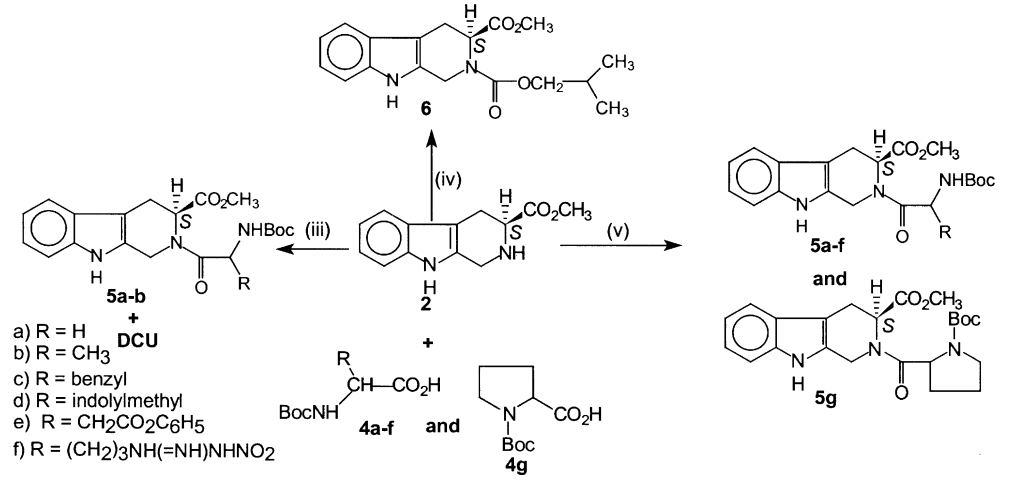


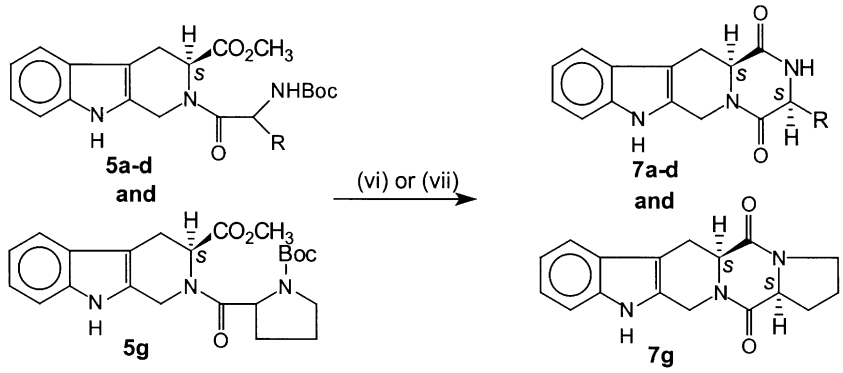
Scheme 1. (i) (a) thionyl chloride, dry methanol, −10 to 30°C, (b) HCHO, H_2O: methanol (1:10), 30°C, (c) sat. soln. of $NaHCO_3$; (ii) (a) 2 M NaOH, H_2O, dioxane, (b) citric acid, 30°C.

0 to 30°C, resulted in the formation of the corresponding *S*-(−)-methyl 2-(*N*-*t*-butoxycarbonyl)aminoacetyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**5a**) and *S*-(-)-methyl 2-α-(*N*-*t*-butoxycarbonyl)-aminopropionyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**5b**). However, condensation of other *N*-Boc protected amino acids (**4c-g**) with **2** did not give the expected compound of type **5** and only the starting material **2** along with dicyclohexylurea (DCU) was recovered. The reaction did not occur by increasing the temperature or time, or both, even in the presence of the commonly used catalyst 4-dimethylaminopyridine (DMAP) (Scheme 2). In the next strategy, therefore, starting materials **2** and **4a** were condensed in presence of isobutyl chloroformate (*i*-BuOCOCl) and dry triethylamine at −40°C, but as there was no reaction, the temperature was raised to 0°C which resulted in the formation of a product different from both the starting material (**2**) and anticipated product (**5a**). The product obtained showed clear triplet (appeared by merging of two doublets of protons of two methyl groups of *iso*-butyl fragment) at chemical shift (δ) value 0.97 ppm having a coupling constant of 7.2 Hz for six protons due to vicinal coupling with another proton. Had the structure of product obtained been in accordance with **5a** a singlet for nine protons at δ value 1.5 ppm due to *tert*-butoxy group would have been observed. Also, the product obtained showed multiplet pattern at δ value 3.94–4.02 ppm, which is the region of O/N-methyl groups whereas for the product **5a** there should be no such peak.

In addition, the parent ion peak (M^+) for the product was observed at 330 units having more than 80% intensity, whereas for **5a** the parent ion peak should appear at 387 units. These data suggested that the structure of product obtained was *S*-(−)-methyl 2-isobutyloxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**6**) (Scheme 2). Based on the formation of **6** it was thought that time required for the formation of mixed anhydride intermediate with the BocGly (**4a**) and *i*-BuOCOCl was not sufficient before the addition of **2** and free *i*-BuOCOCl reacted with starting material **2** instead of **4a** resulting in the formation of **6** by simple condensation. Hence in another experiment sufficient time (2 h) was provided for the reaction between **4a** and *i*-BuOCOCl before adding **2** at −40°C, but again the product **6** was obtained instead of **5a,** which might be due to steric reasons. So lastly, **2** and **4a**–**g** were condensed in presence of benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (BOP) and triethylamine in DMF or acetonitrile to give the required products (**5a**–**g**) (Scheme 2). These products (**5a**–**g**) showed the expected IR and FAB mass spectra, however, these compounds exist as rotamers[17] and their ^1H NMR spectrum showed the presence of two sets of signal for each proton in variable ratios (major and minor) due to the restricted rotation of the carboxamide group at the N atom of the tetrahydropyrido ring of pyrido[3,4-*b*]indole nucleus. In the ^1H spectrum two signals for each proton in the range 2–6 ppm were clearly distinguished, but the peaks below a δ value of 2.0 (i.e. for *t*-butoxy group) and above δ value 6.0 (i.e. for aromatic



Scheme 2. (iii) DCC, HOBt, DMAP, 0°C to reflux, dry THF; (iv) *i*-BuOCOCl, dry Et_3N, −40°C to reflux, dry THF; (v) BOP, Et_3N, 30°C, DMF or CH_3CN.



Scheme 3. (vi) trifluoroacetic acid, CH_2Cl_2, 0 to 30°C; (vii) Flash column silica gel (250–400 mesh), Microwave irradiation, 5 min at 500 W.

regions) were too complex to be resolved into two sets. The complexity in ^{1}H NMR in such cases has also been reported earlier.[5]

In the next step, the compounds **5a–d** and **5g** were treated with TFA in CH_2Cl_2 to remove the Boc group to obtain the products[18] **7a–d** and **7g** through *in situ* intramolecular cyclisation to afford stable six-membered bis lactams by the loss of one mole of methanol (Scheme 3). Also when the reaction was conducted at elevated temperature (200°C) for half an hour in absence of TFA a low yield (5%) of the product of type **5b** was reported[5] along with major quantity (30%) of side product and starting material. Now we report for the first time that if the same reaction is conducted in a microwave oven one can get higher yields of the product of type **7** within 5 min of irradiation (Scheme 3). We have also generalised this method and have obtained more than 85% yield of **7a–d** and **7g**. This also represents one of the fastest, easiest and ecofriendly reaction conditions and can be of much use to prepare important drug intermediates of type **7**. The chiral purity, enantiomeric excess (ee) of the compounds **5a–g** and **7a–d**, **7g** was checked on chiral HPLC column, *chiradex*® (Merck), where (ee) of these compounds were found to be more than 95%.

3. Conclusion

The targeted compounds (*S*)-3-substituted 2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-diones have been prepared with microwave heating which has the advantage over other methods not only in terms of efficacy, but also if the compounds contains acid or base vulnerable groups. Also, the prepared targeted compounds contain diverse substituents at the 3-position and the template can be exploited synthetically for medicinal purposes.

4. Experimental

4.1. General methods and materials

All chemicals used were of reagent grade unless stated otherwise. In High Performance Liquid Chromatography (HPLC), solvents were used directly from HPLC grade OmniSolv® sureseal bottles. Melting points were determined in open capillaries on an electrically heated melting point apparatus and are otherwise uncorrected. Thin layer chromatography (TLC) was run on self-made plates of silica gel G (Acme Synthetic Chemicals, SRL®, Qualigens®, India) or 0.25 mm ready-made plates of silica gel $60F_{254}$ (Kieselgel $60F_{254}$, E. Merck, Darmstadt, Germany) and detection was acheived by iodine vapours/spraying with Dragondroff spray reagent or by UV radiation. Column chromatography was performed with silica gel (Acme Synthetic Chemicals, SRL®, Qualigens®, India; 60–120 mesh). Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on Bruker AVANCE DPX 200 MHz or Bruker AVANCE DRX 300 MHz spectrometer at 298 K using $CDCl_3$ or DMSO-d_6 as the solvent. Proton chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS, 0.00 ppm). Coupling constants (*J*) are reported in Hertz (Hz), and s, d, t, q, qn, m, br and ex refer to singlet, doublet, triplet, quartet, quintet, multiplet, broad and exchangeable, respectively. Infrared spectra (IR) were recorded on a Shimadzu FTIR model PC spectrophotometer (ν_{max} in cm^{-1}). Electron Impact Mass Spectra (EIMS) and Fast Atomic Bombardment Mass Spectra (FABMS) were recorded on JEOL-JMSD-300 and JEOL-JMS-SX102 spectrometers, respectively. Microanalyses (C, H, N) were performed on a Carlo Erba instruments CHNS-O EA1108 Elemental Analyser. Optical rotations were determined on Autopol III Automatic polarimeter using the sodium D-line (c in g/100 mL). Synthetic reactions were carried out in a commercial microwave oven (IFB, 10 L capacity) with 500 W of power output. Chiral HPLC was performed on an analytical Lachrom Merck, Hitachi System and the column used was LiChroCART® 250-4 ChiraDex® (244×4 mm) of Merck, with a L-7455 Diode Array Detector (DAD) set for 200–400 nm range using MeOH/H_2O (30/70) solvent system with flow rate set at 0.8 mL/min having a pressure of 174 psi at 293 K.

4.1.1. *S*-(−)-Methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]-indole-3-carboxylate (2). Formaldehyde (38 wt% solution in water, 11 mL) was added to a solution of L-tryptophan methyl ester hydrochloride of **1** (22 g, 0.86 mol) in aq. methanol (154 mL; ratio 10:1) during 30 min. The reaction mixture was stirred for 4 h at room temperature, concentrated and cooled to give *S*-(−)-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate hydrochloride which

was basified with sodium bicarbonate to give **2**. Yield 11.4 g (57%) as colourless crystals (methanol); M.P. 165–166°C; $[\alpha]_D^{25}$ −71.0 (c 0.6, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.83–2.96 (m, 1H, CH_2), 3.16 (dd, *J*= 4.6 and 15.3, 1H, CH_2), 3.80 (s, 4H, OCH_3 and CH), 4.13 (bs, 2H, NCH_2), 7.06–7.19 (m, 2H, ArH), 7.30 (d, *J*=7.1, 1H, ArH), 7.47 (d, *J*=8.2, 1H, ArH), 7.83 (brs, 1H, indole NH); FTIR (KBr, cm^{-1}): 738, 820, 866, 1004, 1056, 1128, 1190, 1234, 1302, 1346, 1442, 1504, 1590, 1626, 1740, 1916, 2312, 2752, 2938, 3058, 3150, 3324; MS (EI): *m/z* 230 (M^+). Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C 67.81; H 6.13; N 12.17%. Found: C 67.85; H 6.14; N 12.26%.

4.1.2. *S*-(−)-Methyl 2-α[*N-t*-butoxycarbonyl]amino-propionyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (5b, R=CH_3). Procedure A: *S*-(−)-Methyl 1, 2, 3, 4-tetrahydro-9*H*-pyrido[3, 4-*b*]indole-3-carboxylate **2** (0.23 g, 1.0 mmol) dry triethylamine (0.28 mL, 2.0 mmol) and BOP (0.48 g, 1.1 mmol) was added to a stirred solution of α [*N-t*-butoxycarbonyl]aminopropionic acid (0.21 g, 1.1 mmol) in dry DMF (5 mL) and stirring was continued for further 2 h at 30°C. It was diluted with water (20 mL) and crude solid product **5b** separated was filtered, washed with water and purified over silica gel column using 0.5% methanol in chloroform as an eluant. Yield 0.35 g (87%).

Colourless crystals (methanol); M.P. 92–93°C; $[\alpha]_D^{25}$ +56.1 (c 0.31, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 & 1.46 (s, 12H, CH_3 & $OC(CH_3)_3$), 1.65 (ex, brs, 1H, NH), 2.70–2.80 (m, 1H, CH_2), 3.34 (d, *J*=15.8, 1H, CH_2), 3.52 & 3.59 (s, 3H, OCH_3), 4.50–5.28 (m, 2H, NCH_2), 5.13 & 5.88 (d, *J*=5.4, 1H, CH), 5.53–5.64 (m, 1H, CH), 7.07–7.47 (m, 4H, ArH), 8.28 (brs, 1H, indole NH); FTIR (KBr, cm^{-1}): 746, 1167, 1242, 1448, 1512, 1651, 1740, 2980, 3340; MS (FAB): *m/z* 401 (M^+), 402 (M^++H). Anal. Calcd. for $C_{21}H_{27}N_3O_5$: C 62.83; H 6.78; N 10.46%. Found: C 62.68; H 6.82; N 10.32%.

Procedure B: *S*-(−)-Methyl 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **2** (0.23 g, 1.0 mmol), dry triethylamine (0.28 mL, 2.0 mmol) and BOP (0.48 g, 1.1 mmol) was added to a stirred solution of α [N-*t*-butoxycarbonyl] aminopropionic acid (0.21 g, 1.1 mmol) in fresh acetonitrite (10 mL) and stirring was continued for further 4 h at 30°C. Brine (30 mL) was added to the reaction mixture and extracted with chloroform (3×20 mL). The organic layer was washed with 2N HCl (3×20 mL), distilled water (3×20 mL) and dried over sodium sulphate. Chloroform was evaporated under reduced pressure and product **5b** was obtained after triturating with ether-hexane and was found to be pure enough for the next step. Yield 0.32 g (80%).

The compounds (**5a, c–g**) were synthesised by the above procedure by reacting with appropriate α [*N-t* butoxycarbonyl]amino acids.

4.1.3. *S*-(−)-Methyl 2-[*N-t*-butoxycarbonyl]aminoacetyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (5a, R=H). Yield 72% as colourless crystals (methanol); M.P. 100–102°C; $[\alpha]_D^{25}$ +62.7 (c 0.30, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9*H*, $OC(CH_3)_3$), 3.00–3.17 & 3.42–3.54 (m, 2H, CH_2), 3.60 & 3.63 (s, 3H, OCH_3), 4.00–4.24 (m, 2H, CH_2), 4.47 & 5.23 (d, *J*=17.0 & 16.3, 1H, NCH_2), 4.61–4.76 (m, 1H, NCH_2), 4.83 & 5.86 (d, *J*=4.5 & 5.2, 1H, CH), 5.59 (ex, brs, 1H, NH), 7.08–7.19 (m, 2H, ArH), 7.3–7.36 (m, 1H, ArH), 7.49 (d, *J*=7.1, 1H, ArH), 8.14 (brs, 1H, indole NH); FTIR (KBr, cm^{-1}): 747, 1167, 1240, 1443, 1508, 1661, 1703, 2976, 3335, 3396; MS (FAB): *m/z* 387 (M^+), 388 (M^++H). Anal. Calcd. for $C_{20}H_{25}N_3O_5$: C 62.0; H 6.50; N 10.85%. Found: C 61.82; H 6.46; N 10.92%.

4.1.4. *S*-(−)-Methyl 2-α[*N-t*-butoxycarbonyl]amino-β-phenyl propionyl-1,2,3,4-tetra-hydro-9*H*-pyrido[3,4-*b*]-indole-3-carboxylate (5c, R=$CH_2C_6H_5$). Yield 79% as amorphous; M.P. 74–76°C; $[\alpha]_D^{25}$ +55.0 (c 0.20, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 & 1.52 (s, 9*H*, $OC(CH_3)_3$), 2.98–3.23 (m, 2H, CH_2), 3.57 & 3.60 (s, 3H, OCH_3), 4.40–5.10 & 5.85–5.95 (m, 5H, NCH_2, CH, CH_2Ar), 5.35–5.50 (m, 2H, CH, NH), 7.10–7.49 (m, 9*H*, ArH), 8.12 (ex, brs, 1H, indole NH); FTIR (KBr, cm^{-1}): 745, 986, 1169, 1242, 1292, 1433, 1649, 1703, 1742, 2959, 3319; MS (FAB): *m/z* 478 (M^++H). Anal. Calcd. for $C_{27}H_{31}N_3O_5$: C 67.90; H 6.54; N 8.80%. Found: C 67.78; H 6.68; N 8.68%.

4.1.5. *S*-(−)-Methyl 2-α[*N-t*-butoxycarbonyl]amino-β-indolepropionyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (5d, R=$CH_2C_8H_6N$). Yield 68% as amorphous; M.P. 122– 25°C; $[\alpha]_D^{25}$ +52.0 (c 0.24, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 & 1.45 (s, 9*H*, $OC(CH_3)_3$), 2.90–3.05 (4H, 2×CH_2), 3.54 & 3.57 (s, 3H, OCH_3), 4.30–4.45 (m, 1H, CH), 4.75–5.20 (m, 2H, NCH_2), 5.40–5.55 (ex, 1H, NH), 5.83 (d, *J*=4.7, 1H, CH), 7.12–4.47 (m, 8H, ArH), 7.68–7.80 (m, 1H, ArH), 7.94–8.08 (ex, brs, 2H, indole NH); FTIR (KBr, cm^{-1}): 748, 1167, 1236, 1364, 1435, 1647, 1695, 1740, 2976, 3327, 3400; MS (FAB): *m/z* 516 (M^+), 517 (M^++H). Anal. Calcd. for $C_{29}H_{32}N_4O_5$: C 67.43; H 6.24; N 10.85%. Found: C 67.40; H 6.20; N 10.81%.

4.1.6. *S*-(−)-Methyl 2-[*N-t*-butoxycarbonyl]pyrrolidone-α-carbonyl-1,2,3,4-tetra hydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (5g). Yield 82% as amorphous; M.P. 197–200°C; $[\alpha]_D^{25}$ +9.0 (c 0.20, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.50 (s, 9*H*, $OC(CH_3)_3$), 1.89–2.00 (m, 2H, CH_2), 2.05–2.30 (m, 2H, CH_2), 3.00–3.20 & 3.50–3.70 (m, 4H, 2×CH_2), 3.52 (s, 3H, OCH_3), 4.50–5.00 (m, 3H, NCH_2, CH), 5.52 & 5.95 (d, *J*=6.2, 1H, CH), 7.04–7.36 (m, 4H, ArH), 9.26 (brs, 1H, indole NH); FTIR (KBr, cm^{-1}): 501, 709, 750, 887, 997, 1032, 1165, 1238, 1296, 1325, 1363, 1400, 1651, 1742, 2976, 3244; MS (FAB): *m/z* 427 (M^+), 428 (M^++H). Anal. Calcd. for $C_{23}H_{29}N_3O_5$: C 64.62; H 6.84; N 9.83%. Found: C 64.54; H 6.80; N 9.77%.

4.1.7. *S*-(−)-Methyl 2-α[*N-t*-butoxycarbonyl]amino-β-benzyloxycarbonyl-propionyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (5e, R=$CH_2CO_2C_6H_5$). Yield 74% as amorphous; M.P. 85–87°C; $[\alpha]_D^{25}$ +19.1 (c 0.22, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38–1.48 (m, 9*H*, $OC(CH_3)_3$), 2.70–2.85 (m, 1H, CH_2), 2.95–3.20 (m, 2H, CH_2), 3.40–3.50 (m, 1H, CH_2), 3.58 & 3.60 (s, 3H, OCH_3), 4.40–4.55, 4.80–5.60 & 5.80–5.90 (m, 7H, 2×CH, OCH_2, NCH_2, NH), 7.10–7.85 (m, 9*H*, ArH), 8.07 & 8.12 (brs, 1H, indole NH); FTIR (KBr, cm^{-1}): 745, 991,

1024, 1167, 1238, 1290, 1445, 1651, 1738, 2970, 3337; MS (FAB): *m/z* 535 (M^+), 536 (M^++H). Anal. Calcd. for $C_{29}H_{33}N_3O_7$: C 65.03; H 6.21; N 7.85%. Found: C 65.0; H 6.18; N 7.80%.

4.1.8. *S*-(−)-Methyl 2-α-[*N*-*t*-butoxycarbonyl]amino-ω[*N*-nitro]-δ-guanidino-n-valeryl-1,2,3,4-tetrahydro-9*H*-pyrido [3,4-*b*] indole-3-carboxylate (5f, R=$(CH_2)_3NH$-C(=NH)$NHNO_2$). Yield 50% as amorphous; M.P. 120–123°C; $[\alpha]_D^{25}$ −16.9 (c 0.32, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9*H*, $OC(CH_3)_3$), 1.88–1.98 (m, 1H, NH), 2.26 (ex, brs, 1H, NH), 2.35–2.55 (m, 2H, CH_2), 2.85–2.95 (m, 1H, CH_2), 3.05–3.20 (m, 1H, CH_2), 3.45–3.60 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.15 (s, 2H, NCH_2), 4.35–4.50 (m, 1H, NH), 4.55–4.75 (m, 2H, NCH_2 (arginyl), 5.19 (d, *J*=8.5, 1H, CH), 5.87 (d, *J*=4.4, 1H, CH), 7.06–7.48 (m, 4H, ArH), 8.10 (ex, brs, 1H, indole NH), 9.52 (ex, brs, 1H, NH); FTIR (KBr, cm^{-1}): 746, 1049, 1101, 1155, 1252, 1364, 1448, 1500, 1608, 1699, 2972, 3346; MS (FAB): *m/z* 531 (M^+), 532 (M^++H). Anal. Calcd. for $C_{24}H_{33}N_7O_7$: C 54.23; H 6.26; N 18.45%. Found: C 54.12; H 6.30; N 18.32%.

4.1.9. *S*-Methyl 2-*i*-butoxycarbonyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (6). Yield 67% as amorphous; M.P. 112–114°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (t, *J*=7.2, 6H, $(CH_3)_2$), 1.98–2.02 (m, 1H, CH), 3.10 (dd, *J*=6.5 & 15.0, 1H, CH_2), 3.40–3.52 (m, 1H, CH_2), 3.62 (s, 3H, OCH_3), 3.94–4.03 (m, 2H, OCH_2), 4.52–4.69 (m, 1H, NCH_2), 4.87–4.98 (m, 1H, NCH_2), 5.28 & 5.45 (d, *J*=6.1, 1H, CH), 7.08–7.20 (m, 2H, ArH), 7.31 (d, *J*=7.7, 1H, ArH), 7.50 (d, *J*=7.3, 1H, ArH), 7.81 and 7.92 (brs, ex, 1H, NH); FTIR (KBr, cm^{-1}): 652, 750, 1022, 1202, 1240, 1292, 1331, 1375, 1412, 1464, 1692, 1734, 2961, 3350; MS (EI): *m/z* 330 (M^+). Anal. Calcd. for $C_{18}H_{22}N_2O_4$: C 65.44; H 6.71; N 8.48%. Found: C 65.32; H 6.50; N 8.32%.

4.1.10. (3*S*,12a*S*)-3-Methyl-1,4-dioxo-1,2,3,4,6,7,12,12a-octahydropyrazino [2′,1′:6,1] pyrido[3,4-*b*]indole (7b, R=CH_3). Procedure A: Trifluoroacetic acid (0.3 mL) was added to a solution of **5b** (0.20 g, 0.5 mmol) in dry dichloromethane (0.6 mL) and stirring was continued for 1–2 h at 30°C. The reaction mixture was basified with ammonia and the crude product obtained was purified over silica gel column using 3% methanol in chloroform as an eluant to give **7b**.Yield 0.08 g (60%).

Amorphous; M.P. 223–226°C; $[\alpha]_D^{25}$ −144.3 (c 0.23, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3), 2.90–3.11 (m, 1H, CH_2), 3.50–3.68 (m, 1H, CH_2), 4.17–4.36 (m, 3H, NCH_2 & CH), 5.50–5.70 (m, 1H, CH), 6.26 (ex, brs, 1H, piperazinyl NH), 7.13–7.50 (m, 4H, ArH), 8.00 (ex, brs, 1H, indole NH); FTIR (KBr, cm^{-1}): 746, 1155, 1223, 1325, 1462, 1659, 2957, 3261; MS (EI): *m/z* 269 (M^+). Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C 66.90; H 5.61; N 15.60%. Found: C 66.72; H 5.48; N 15.46%.

Procedure B: **5b** (0.20 g, 0.5 mmol) was dissolved in dichloromethane (10 mL) and flash chromatography silica gel (250–400 mesh) (2 g) was added. The solvent was evaporated in vacuo and the powdered solid was irradiated in the microwave oven, in an open conical flask for 5 min at 500 W. The resulting baked solid (darkened) was thoroughly washed with methanol and passed through a celite pad and solvent was evaporated under reduced pressure to afford pure **7b** in 95% yield.

Similarly compounds **7a, c, d, g** of the series were synthesised.

4.1.11. (12a*S*)-1,4-Dioxo-1,2,3,4,6,7,12,12a-octahydropyrazino [2′,1′:6,1] pyrido[3,4-*b*]indole (7a, R=H). Yield 63% (Procedure A), 88% (Procedure B) as amorphous; M.P. 252–255°C (Lit.[10] M.P. 275–280°C for racemic); $[\alpha]_D^{25}$ −164.8 (c 0.21, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.90–3.10 (m, 1H, CH_2), 3.40–3.55 (dd, *J*=4.5 & 15.5, 1H, CH_2), 4.00–4.30 (m, 4H, 2×NCH_2), 5.56 (m, 1H, CH), 7.00–7.45 (m, 4H, ArH), 8.22 (ex, brs, 1H, indole NH), 10.64 (brs, 1H, piperazinyl NH); FTIR (KBr, cm^{-1}): 754, 1123, 1331, 1458, 1632, 3096, 3219, 3281; MS (EI): *m/z* 255 (M^+). Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C 65.87; H 5.13; N 16.46%. Found: C 65.67; H 5.04; N 16.30%.

4.1.12. (3*S*,12a*S*)-3-Benzyl-1, 4-dioxo-1,2,3,4,6,7,12,12a-octahydropyrazino [2′,1′:6,1] pyrido[3,4-*b*]indole (7c, R=$CH_2C_6H_5$). Yield 63% (Procedure A), 90% (Procedure B) as amorphous; M.P. 74–77°C;$[\alpha]_D^{25}$ −84.9 (c 0.18, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10–1.40 (m, 1H, CH_2), 1.60–1.90 (m, 1H, CH_2), 3.00–3.25 (m, 2H, CH_2), 4.10–4.25 (m, 2H, NCH_2), 4.30–4.45 (m, 1H, CH), 5.55–5.70 (m, 1H, CH), 6.10 (ex, brs, 1H, NH), 7.10–7.50 (m, 9*H*, ArH), 7.90 (ex, brs, 1H, indole NH); FTIR (KBr, cm^{-1}): 700, 748, 1138, 1200, 1338, 1450, 1672, 3067, 3260, 3398; 743; MS (EI): *m/z* 345 (M^+). Anal. Calcd. for $C_{21}H_{19}N_3O_2$: C 73.03; H 5.54; N 12.17%. Found: C 73.0; H 5.50; N 12.10%.

4.1.13. (3*S*,12a*S*)-3-Indolymethyl-1, 4-dioxo-1,2,3,4,6,7, 12,12a-octahydropyrazino [2′,1′:6,1] pyrido[3,4-*b*]indole (7d, R=$CH_2C_8H_6N$). Yield 59% (Procedure A), 90% (Procedure B) as amorphous; M.P. 270–274°C (dec); $[\alpha]_D^{25}$ −126.0 (c 0.20, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.65 (d, *J*=9.3, 2H, CH_2), 3.06 (dd, *J*=4.5 & 16.5, 1H, CH_2), 3.29–3.36 (m, 1H, CH_2), 4.05–4.13 (m, 2H, NCH_2), 4.40 (m, 1H, CH), 5.57 (d, *J*=16.8, 1H, indole CH), 6.20 (ex, brs, 1H, NH), 6.96–7.30 (m, 8H, ArH), 7.57–7.61 (m, 1H, ArH), 9.70 & 9.88 (s, 1H, indole NH); FTIR (KBr, cm^{-1}): 743, 1105, 1194, 1329, 1460, 1649, 2928, 3063, 3275, 3398; MS (EI): *m/z* 384 (M^+). Anal. Calcd. for $C_{23}H_{20}N_4O_2$: C 71.86; H 5.24; N 14.57%. Found: C 71.71; H 5.20; N 14.47%.

4.1.14. (5a*S*,14a*S*)-5,14-Dioxo-1,2,3,5,5a,6,11,12,14,14a-decahydro-5*H*,14*H*-pyrrolo[1′′,2′′:4′,5′]pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole (7g). Yield 65% (Procedure A), 94% (Procedure B) as amorphous; M.P. 266–268°C (dec); $[\alpha]_D^{25}$ −24.6 (c 0.22, DMF); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90–2.20 (m, 4H, 2×CH_2), 2.40–2.55 (m, 1H, CH_2), 2.85–3.05 (m, 1H, CH_2), 3.45–3.9 (m, 3H, NCH_2 & CH), 4.10–4.35 (m, 2H, NCH_2), 5.15–5.30 (m, 1H, CH), 7.10–7.55 (m, 4H, ArH), 8.00 (brs, 1H, indole NH); FTIR (KBr, cm^{-1}): 741, 1155, 1335, 1425, 1655, 2882, 3053, 3273; MS (FAB): *m/z* 295 (M^+), 296 (M^++H). Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C 69.14; H 5.80; N 14.23%. Found: C 69.0; H 5.64; N 14.16%.

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