HETEROCYCLES, Vol.53, No.7, 2000, p.1559 - 1568, Received, 1st March, 2000

SYNTHESES OF BIS(3'-INDOLYL)-2(1*H*)-PYRAZINONES

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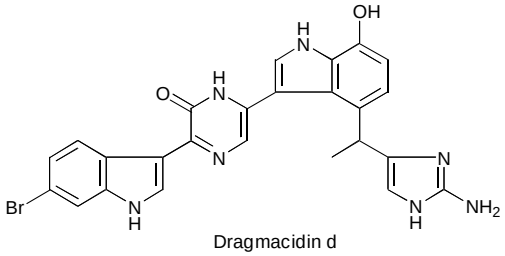
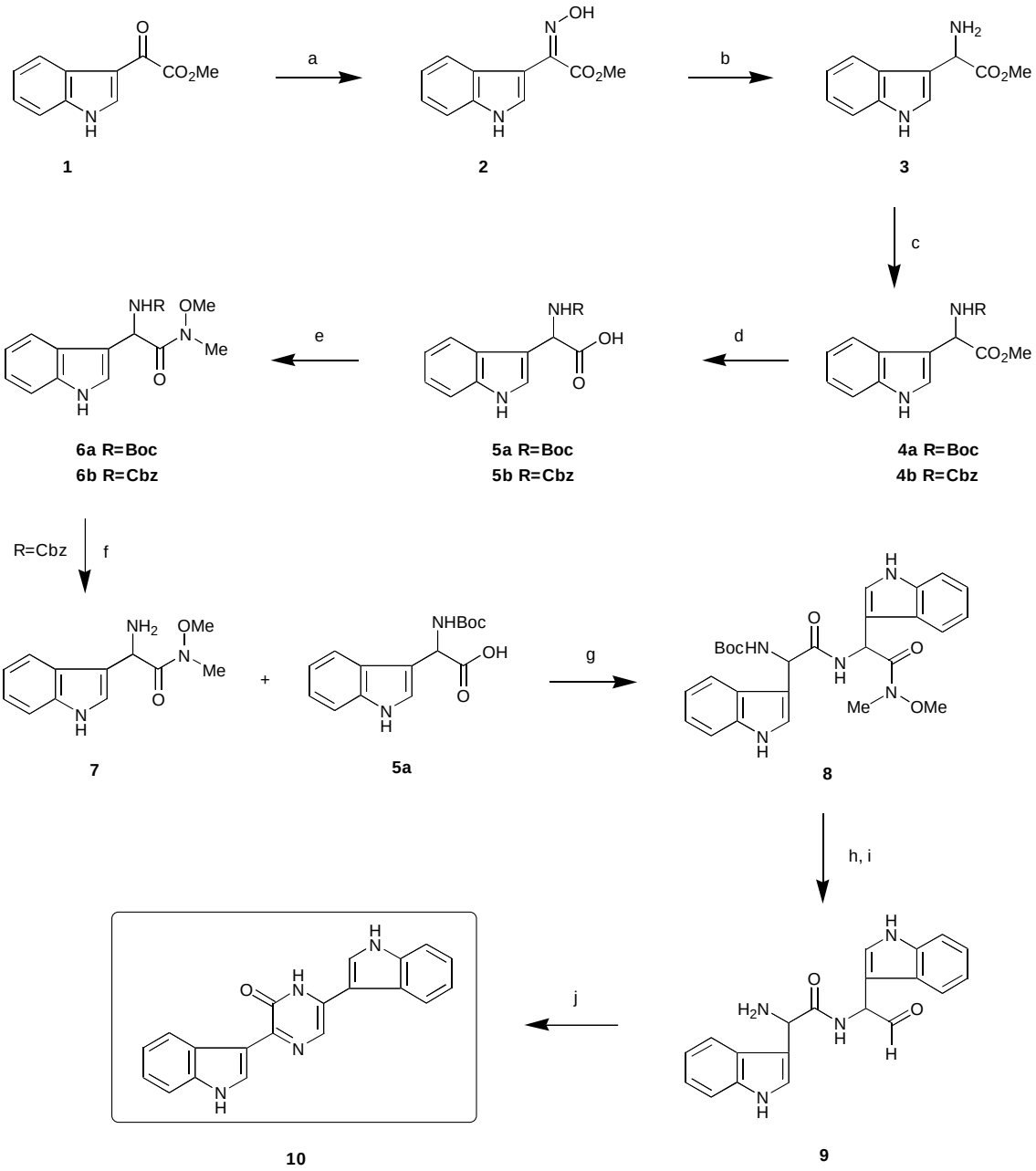
Abstract - The syntheses of 3,6-bis(3'-indolyl)-2(1*H*)-pyrazinone and 3,5-bis(3'-indolyl)-2(1*H*)-pyrazinone were described. Syntheses of 3,6-bis(3'-indolyl)-2(1*H*)-pyrazinone proceeded through the condensation of *N*-Boc-indolylglycine with indol-3-yl-*N*-methyl-*O*-methoxyglycinamide, and followed by reduction with $LiAlH_4$ and cyclization of the resulting bisindolyl aldehyde-amine. 3,5-Bis(3'-indolyl)-2(1*H*)-pyrazinone was synthesized by cyclization of bisindolyl ketone amine in excess of ammonia under pressure.

A number of bis(indole) alkaloids isolated from the marine organism show significant anti-tumor and anti-inflammatory activity,[1] many of that have a structure of central heterocyclic ring linked to two indole rings. For example, anti-tumor active dragmacidin d isolated from *spongosorites* sp. has a 2(1*H*)-pyrazinone moiety existing between the two indole rings,[2] cytotoxic anti-fungal active nortopsentin from *spongosorites ruetzler* has a imidazole moiety,[3] and both biologically active hamacanthin A and hemacanthin B from deep water sponge of the genus *hamacantba* have a dihydropyrazinone moiety.[4] The remarkable feature of their biological activity and novel structure made bisindole alkaloids as an attractive target and leading compound in discovery of new drugs for both organic chemist and medicinal chemist.[5] As our ongoing program to discover new anti-tumor drugs using natural marine indole alkaloids as leading compounds,[6] we are interested in the syntheses of marine bis(indole) alkaloids and their analogues. In this paper, the syntheses of bis(3'-indolyl)-2(1*H*)-pyrazinones, the core and analogues of the cytotoxic marine bisindole alkaloids dragmacidin d, is described.



Dragmacidin d

Several kinds of methodologies have been developed in the synthesis of 3,6-dialky substituted 2(1*H*)-pyrazinone for past years. One of more practical and efficient approach is the cyclization of dipeptidyl chloromethyl ketone or dipeptidyl aldehyde.[7,8] Retrosynthetically, the 2(1*H*)-pyrazinone ring in dragmacidin d was derived from the cyclization of 2-(3-indolyl)glycine. However, the 2-(3-indolyl)glycine derivatives which were prepared by direct hydrolysis of the corresponding indolyl-aminoacetonitrile was approved not to be successful.[9,10]



Reagents and conditions: a. $NH_2OH.HCl$, NaOAc, MeOH-H_2O, reflux, 8 h; b. H_2, 10%Pd/C, con.HCl, MeOH, 6 h. c. for Boc protection: $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 2 h; for Cbz protection: CbzCl, Et_3N, CH_2Cl_2, rt, 3 h; d. 20%NaOH, MeOH, reflux, 3 h, e. N,O-dimethylhydroxyamine hydrochloride, BOP, Et_3N, CH_2Cl_2, rt, 6 h; f. Cyclohexene, 10%Pd/C, MeOH, reflux; g. BOP, Et_3N, CH_2Cl_2, rt, 4 h, h. $LiAlH_4$, THF, -10 ^oC, 1 h; i. AcCl/MeOH, rt, 4 h; j. MeCN, rt, 2 d.

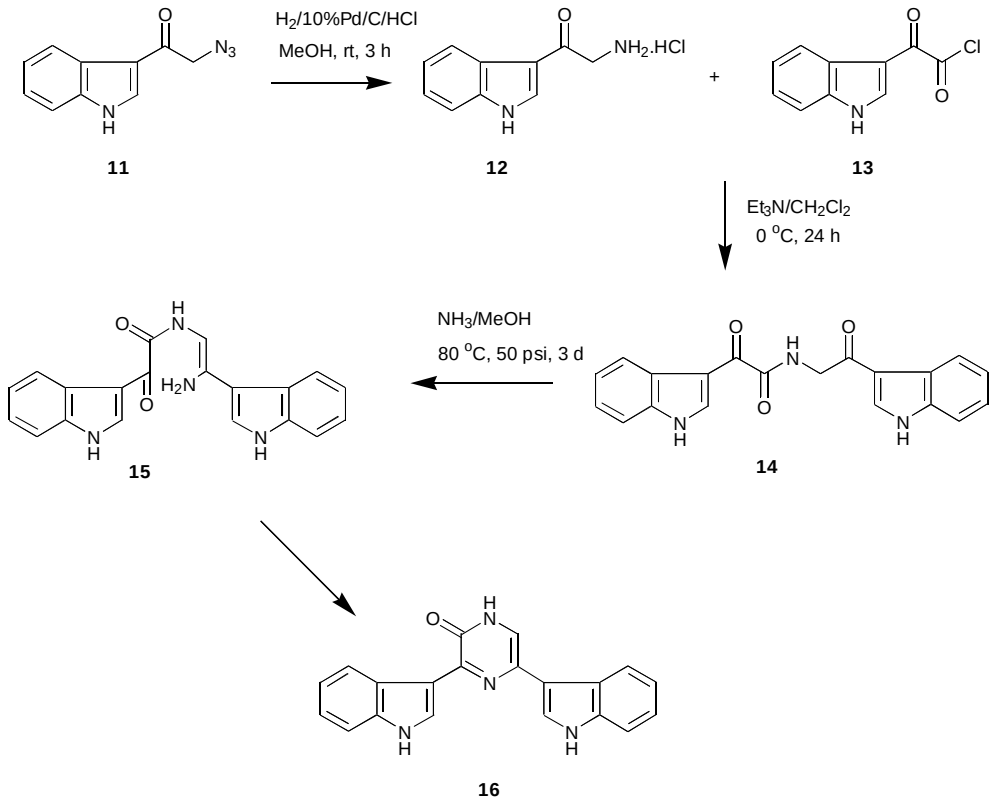
Scheme 1

Our laboratory work testified that conversion of 3-indolylgloxylic acid to its corresponding oxime followed by hydrogenation would be a straightforward method for preparation of 2-(3-indolyl)glycine. As shown in **Scheme 1**, the methyl indolylglycinate (**3**) was given in good yield by hydrogenation of methyl indolylgloxylate oxime (**2**)**,** which was prepared from indolylgloxylate[11,12] by treatment with hydroxylamine hydrochloride.[13]

Initially, $(Boc)_2O$ was the preferred protective group to give *N*-Boc-indolylglycinate (**4a**) in 98% yield, which was converted through 20% aqueous sodium hydroxide in refluxing methanol to *N*-Boc-indolylglycine (**5a**). Condensation of **5a** with *N,O*-dimethylhydroxylamine (DMA) hydrochloride[14] using benzotriazole-1-yloxytris(dimethylamino)phosphonium hexfluorophosphate (BOP Reagent)[15] as condensing agent gave Weinreb amide (**6a**) in 88% yield. Attempting to remove the Boc protective group in **6a** with 50% TFA in CH_2Cl_2, AcCl/MeOH[16] or $Ce(NH_4)_2(NO_3)_6/CH_3CN$[17] was failed. Thus we had to be back to select other effective protective group replacing Boc. It was found that Cbz was a more practical protective group and could be removed selectively by cyclohexene in methanol over 10%Pd/C,[18] which was verified by the following process.

Methyl indolylglycinate (**3**) was treated with benzyl chloroformate and triethylamine in CH_2Cl_2 to give *N*-Cbz-indolylglycinate (**4b**) in 86% yield. **4b** was converted to **6b** under similar condition for **6a** mentioned above. Compound (**6b**) in methanol was heated with cyclohexene over 10% Pd/C to afford Weinreb amide (**7)** as a sole product. The unstable compound (**7**) was immediately coupled with **5a** using BOP Reagent[19] to obtain the key dipeptide (**8**) in 67% yield. Finally, selective reduction of Weinreb amide in **8** with $LiAlH_4$ in THF at -10 °C and removal of *N*-Boc protective group with acetyl chloride in methanol gave its corresponding aldehyde-amine (**9**), which was cyclized in acetonitrile at room temperature for two days to afford 3,6-bis(3'-indolyl)-2(1*H*)-pyrazinone (**10**) in no need of any further purification of compound (**9**).

3,5-Bis(3'-indolyl)-2(1*H*)-pyrazinone (**16**) was synthesized as shown in **Scheme 2**. The azidoacetylindole (**11**) derived from indole[20, 21] was hydrogenated over 10% Pd/C to give the amino-acetylindole hydrochloride (**12**) in presence of 35% HCl. Reaction of **12** with 3-indolylglyoxylic chloride (**13**)[22] gave the key precursor of bisindolyl diketone amide (**14**) in 67% yield. Attempting to form pyrazinone by heating compound (**14**) with ammonium acetate in ethanol[23] or acetic acid[24] was failed. Finally, the formation of pyrazinone ring in compound (**16**) was successfully carried out by heating compound (**14**) in excess of liquid ammonia at 80 °C under 50 psi for three days to afford 3,5-bis(3'-indolyl)-2(1*H*)-pyrazinone (**16**) in 63% yield. The mechanism for the formation of the pyrazinone ring could be proceeded through cyclization of ketone-amine. One of carbonyl groups in diketone (**14**) was reacted with ammonia to give enamine (**15**). The amino group in **15** attached second carbonyl group of indolylglyoxyamide moiety to form the pyrazinone ring.[11]



11 **12** **13** **14** **15** **16**

Scheme 2

In summary, we have achieved the first step of syntheses of the 3,6-bis(3'-indolyl)-2(1*H*)-pyrazinone and 3,5-bis(3'-indolyl)-2(1*H*)-pyrazinone, the core of cytotoxic bisindole alkaloid dragmacidin d. The methodology of construction of bis(indole)pyrazinone is valuable for syntheses of the analogues of bis(indole)pyrazinone alkaloid of dragmacidin d in medicinal chemistry.

EXPERIMENTAL

Melting points were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer with Me_4Si as an internal standard. Coupling constants, J values, were given in Hz. IR spectra were taken on a Shimadzu IR-440 spectrophotometer. MS and HRMS were run respectively on a Finnigan 4021 GC MS/DC and Varian MAT 21 instrument with an ionizing voltage of 70eV.

Methyl indol-3-ylglyoxylate oxime (**2**):

To a solution of methyl indol-3-ylglyoxylate[11, 12] (8.0 g, 39.4 mmol) in methanol (150 mL) was added NaOAc (32.8 g, 0.4 mmol) and a solution of hydroxylamine hydrochloride (27.8 g, 40 mmol) in water (60 mL). The mixture was heated at reflux for 6 h. Solvent was removed by distillation. The mixture was extracted with ethyl acetate (3x80 mL). The extracts were washed with water and dried over Na_2SO_4. After removal of solvent, a pale yellow solid **2** (8.46 g, 95%) was obtained. Recrystallized from ethyl

acetate/n-hexane. mp 170-170.8 ^{o}C. ν_{max}(KBr)/cm^{-1} 3399 (NH), 3251 (NOH), 1668 (CO_2CH_3), 1649 (C=N); δ_H (acetone-d_6), 8.22 (1H, s, 2-H), 7.51(1H, d, $J_{4,5}$ 7, 4-H), 7.49(1H, d, $J_{6,7}$ 8.1, 7-H), 7.17 (1H, dd, $J_{5,6}$ 7.4, $J_{6,7}$ 8.1, 6-H), 7.09(1H, dd, $J_{4,5}$ 7, $J_{5,6}$ 7.4, 5-H), 3.89 (3H, s, OCH_3); *m/z* (EI) 218(M^+, 78%), 158(22), 142(100). Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.49; H, 4.63; N, 12.98.

Methyl indol-3-ylglycinate (3):

Methyl indol-3-ylglyoxylate oxime (**2**) (301 mg, 1.38 mmol) in methanol (30 mL) containing 35% HCl (1 mL) was hydrogenated over 10% Pd/C (50 mg) under 60 psi for 5 h. After the catalyst was filtered, the filtrate was condensed under reduced pressure. The residue was dissolved in water (10 mL) and neutralized with 5% NaOH to pH=8, following extraction with ethyl acetate (3x10 mL). The extracts was worked up as usual to afford **3** (213mg, 74%) in form of orange powder. Recrystallized from ethanol. mp 116-118 ^{o}C. ν_{max}(KBr)/cm^{-1} 3374 and 3127(NH), 1741(CO_2CH_3), 1591(C=N); δ_H (CD_3OD) 7.83(1H, d, $J_{4,5}$ 7.7, 4-H), 7.54(1H, d, $J_{6,7}$ 8.1, 7-H), 7.46(1H, s, 2-H), 7.25 (1H, dd, $J_{5,6}$ 7.11, $J_{6,7}$ 8.1, 6-H), 7.18(1H, dd, $J_{4,5}$ 7.7, $J_{5,6}$ 7.1, 6-H), 5.05(1H, s, $NCHCO_2$), 3.54(3H, s, OCH_3); *m/z* (EI) 204(M^+, 3.6%), 188(8), 145(100), 118(48). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.65; H, 5.92; N, 15.67. Found: C, 64.45; H, 5.87; N, 15.77.

Methyl *N*-Boc-indol-3-ylglycinate (4a):

To a solution of methyl indol-3-ylglycinate (**3**) (612 mg, 3 mmol) and $(Boc)_2O$ (725 mg, 3.35 mmol) in dichloromethane (25 mL) was added dropwise triethylamine (0.6 ml, 3.6 mmol) at rt. The mixture was stirred for 2 h and washed with 2N HCl, water, brine and dried over Na_2SO_4. After removal of solvent, the residue was subjected to flash chromatography (eluted solvent petroleum ether: EtOAc=1:1) to afford **4a** (1.01g, 98%), which was recrystallized from ethyl acetate/n-hexane. mp 147.4-148.2 ^{o}C. ν_{max}(KBr)/cm^{-1} 3425 and 3318(NH), 1739(CO_2Me), 1699(Boc); δ_H (acetone-d_6): 8.42(1H, br s, NH), 7.72(1H, d, $J_{4,5}$ 7.7, 4-H), 7.38(1H, d, $J_{6,7}$ 8.1, 7-H), 7.25 (1H, dd, $J_{5,6}$ 7.11, $J_{6,7}$ 8.1, 6-H), 7.18(1H, dd, $J_{4,5}$ 7.7, $J_{5,6}$ 7.1, 6-H), 5.61(1H, d, J 7.23, BocNH), 5.46(1H, d, J 7.23, BocNH*CH*CO), 3.72(3H, s, CO_2CH_3), 1.45(9H, s, Boc); *m/z* (EI) 304(M^+, 0.9%), 248(41), 216(47), 189(100), 145(47). Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.23; H, 6.63; N, 9.25.

Methyl *N*-Cbz-indol-3-ylglycinate (4b):

To a solution of methyl indol-3-ylglycinate (**3**) (1.43 g, 7 mmol) and benzyl chloroformate (2 mL, 14 mmol) in dichloromethane (40 mL) was added dropwise triethylamine (2 mL, 14.3 mmol) at 0 ^{o}C. The mixture was stirred at rt for overnight, followed by washing with water, brine and drying over Na_2SO_4. After removal of solvent, the residue was subjected to flash chromatography (eluted solvent petroleum ether: EtOAc=1:1) to afford **4b** (2.02g, 86%), Recrystallized from ethyl acetate/n-hexane. mp 149.7-150.7 ^{o}C. ν_{max}(KBr)/cm^{-1} 3444 and 3320(NH), 1739(CO_2Me), 1700(Cbz), 1650(Ph);δ_H (DMSO-d_6) 10.03(br s,

1H, NH), 7.49(1H, d, $J_{4,5}$ 7.7, 4-H), 7.31(1H, d, $J_{6,7}$ 8.1, 7-H), 7.25(5H, m, Ph-H), 7.16(1H, s, 2-H), 7.16 (1H, dd, $J_{5,6}$ 7.1, $J_{6,7}$ 8.1, 6-H), 7.0(1H, dd, $J_{4,5}$ 7.7, $J_{5,6}$ 7.1, 6-H), 6.14(1H, d, J 7.13, NHCbz), 5.47(1H, d, J 7.21, CbzNH*CH*CO), 4.94(2H, s, CH_2Ph), 3.53(3H, s, OCH_3). Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.33; N, 8.28. Found: C, 67.55; H, 5.46; N, 8.44.

***N*-Boc-indol-3-ylglycine (5a):**

Methyl *N*-Boc-indol-3-ylglycinate (**4a**) (800 mg 2.63 mmol) in methanol (15 mL) was hydrolyzed with 20% NaOH (5 mL) under reflux for 3 h . The mixture was acidified with 4N HCl to pH=6. Solvent was removed under reduced pressure. Ethyl acetate (20 mL) was added to the residue. The organic phase was washed with water and dried over Na_2SO_4. After removal of solvent, red foam solid **5a** (743 mg, 97%) was obtained. Recrystallized from ethyl acetate/n-hexane. mp 132.3-132.8 ^oC. ν_{max}(KBr)/cm^{-1} 3410 (CO_2H), 3318(NH), 1719(CO_2), 1699(Boc); δ_H (acetone-d_6): 7.84(1H, d, $J_{4,5}$ 7.7, 4-H), 7.55(1H, d, $J_{6,7}$ 8.1, 7-H), 7.45 (1H, s, 2-H), 7.34 (1H, dd, $J_{5,6}$ 7.11, $J_{6,7}$ 8.1, 6-H), 7.25(1H, dd, $J_{4,5}$ 7.7, $J_{5,6}$ 7.1, 6-H), 5.67(1H, br s, BocNH*CH*CO), 1.65(9H, s, Boc); *m/z* (EI) 290(M^+, 0.6%), 234(18), 216(47), 216(17), 189(37), 59(100). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.95; H, 7.55; N, 10.07.

***N*-Boc-indol-3-yl-*N*-methyl-*O*-methoxyglycinamide (6a):**

Compound (**5a**) (590 mg, 2.0 mmol) in dichloromethane (15 mL) was added to a mixture of triethylamine (0.4 mL, 2.8 mmol) and BOP Reagent (1.06 g, 2.4 mmol) at rt for 15 min, followed by adding *N*,*O*,-dimethylhyroxylamine hydrochloride (240 mg, 2.4 mmol) and triethylamine (0.4 mL, 2.8 mmol). The resulting mixture was then stirred at rt overnight. The mixture was washed with 2N HCl, brine and dried over Na_2SO_4. After removal of solvent, the residue was subjected to flash chromatography (eluted solvent petroleum ether: EtOAc =1:1) to afford **6a** (484 mg, 73%). Recrystallized from ethanol. mp 121.4-122.3 ^oC. ν_{max}(KBr)/cm^{-1} 3315(NH), 1657(CO); δ_H (DMSO-d_6) 11.07(1H, br s, NH), 7.57(1H, d, $J_{4,5}$ 7.7 , 4-H), 7.36(1H, d, $J_{6,7}$ 8.1, 7-H), 7.20(1H, s, 2-H), 7.10 (1H, dd, $J_{5,6}$ 7.0, $J_{6,7}$ 8.1, 6-H), 7.01(1H, dd, $J_{4,5}$ 7.7, $J_{5,6}$ 7.1, 6-H), 6.19(1H, d, J 8, NHBoc), 5.95(1H, d, J 8, BocNH*CH*CO), 3.52(3H, s, $NOCH_3$), 3.08(3H, s, NCH_3), 1.40(9H, s, $OC(CH_3)_3$); *m/z* (EI) 333(M^+, 0.6%), 245(45), 217(17), 189(100). Anal. Calcd for $C_{17}H_{23}N_3O_4$: C, 61.26; H, 6.91; N, 12.61. Found: C, 61.35; H, 7.17; N, 12.77.

***N*-Cbz-indol-3-yl-*N*-methyl-*O*-methoxyglycinamide (6b):**

Methyl *N*-Cbz-indol-3-ylglycinate (**4b**) (1.4 g, 4.14 mmol) in methanol (20 mL) was hydrolyzed with 20% NaOH (10 mL) under reflux for 2 h . The mixture was acidified with 4 N HCl to pH=6. Solvent was removed under reduced pressure. Ethyl acetate (20 mL) was added to the residue. The organic phase was washed with water and dried over Na_2SO_4. After removal of solvent, a red foam solid *N*-Cbz-indol-3-yl-glycine (**5b**) (1.29 g) was obtained. The crude product was used directly for next step.

The crude **5b** (1.23 g) in dichloromethane (25 mL) was added to a mixture of triethylamine (0.7 mL, 5

mmol) and BOP Reagent (2.02 g, 1.2 mmol) at rt for 15 min, followed by adding *N,O,*-dimethylhydroxyamine hydrochloride (456 mg, 4.56 mmol) and triethylamine (1.0 mL, 7.1 mmol). The resulting mixture was then stirred at rt overnight. The mixture was washed with 2N HCl, water, brine and dried over Na_2SO_4. After removal of solvent, the residue was subjected to flash chromatography (eluted solvent petroleum ether: EtOAc =2:1) to afford **6b** (963 mg, 69%). Recrystallized from ethyl acetate/n-hexane. mp 160.0-160.4 ^oC. ν_{max}(KBr)/cm^{-1} 3312(NHCbz), 3289(NH), 1700(Cbz), 1655(C=O), 1533 and 1457(C_6H_5); δ_H (DMSO-d_6) 10.65(1H, br s, NH), 7.62(1H, d, $J_{4,5}$ 7.7, 4-H), 7.31(1H, d, $J_{6,7}$ 8.1, 7-H), 7.25(5H, m, Ph-H), 7.15(1H, s, 2-H), 7.06 (1H, dd, $J_{5,6}$ 7.1, $J_{6,7}$ 8.1, 6-H), 6.98(1H, dd, $J_{4,5}$ 7.7, $J_{5,6}$ 7.1, 6-H), 6.67(1H, d, J 7.96, CBzNH*CH*CO), 6.02(1H, br s, NHCbz), 5.02(2H, s, CH_2Ph), 3.45(3H, s, $NOCH_3$), 3.11(3H, s, NCH_3); *m/z* (EI) 367(M^+, 3%), 279(90), 235(33), 171(27), 91(100). Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.49; H, 5.55; N, 11.51.

Indol-3-yl-*N*-methyl-*O*-methoxyglycinamide (7):

N-Cbz-indol-3-yl-*N*-methyl-*O*-methoxyglycinamide (**6b**) (147 mg, 0.4 mmol), cyclohexene (4 mL) and 10% Pd/C (50 mg) in methanol (6 mL) was refluxed for 20 min. The catalyst was filtered out. After removal of solvent under reduced pressure, the crude product was purified by flash chromatography (eluted solvent petroleum ether: EtOAc =2:1.5) to afford **7** (93 mg) as an oil quantitatively. ν_{max}(KBr)/ cm^{-1} 3400(NHCbz), 3289(NH); δ_H (acetone-d_6) 7.74(1H, d, $J_{4,5}$ 7.7 , 4-H), 7.38(1H, d, $J_{6,7}$ 8.1, 7-H), 7.24(1H, s, 2-H), 7.10 (1H, dd, $J_{5,6}$ 7.1, $J_{6,7}$ 8.1, 6-H), 7.00(1H, dd, $J_{4,5}$ 7.7, $J_{5,6}$ 7.1, 6-H), 5.21(1H, br s, NH_2*CH*CO), 3.46(3H, s, $NOCH_3$), 3.12(3H, s, NCH_3); *m/z* (EI) 217(M^+-CH_3, 50%), 157(85), 145(32), 130(26), 118(21).

***N*-Boc-indol-3-yl-glycylindol-3-yl-*N*-methyl-*O*-methoxyglycinamide (8):**

A solution of **5a** (240 mg, 0.8 mmol) in dichloromethane (15 mL) was added to a mixture of BOP Reagent (360 mg, 0.8 mmol) and triethylamine (0.4 mL, 2.85 mmol). After stirring at rt for 20 min, **7** (190 mg, 0.81 mmol) in dichloromethane (5 mL) was added. After stirring for 2 h, the organic solution was washed with brine and dried over Na_2SO_4. After removal of solvent, the residue was purified by flash chromatography on silica gel (eluted solvent petroleum ether: EtOAc=2:1) to give **8** (305 mg, 75%). Recrystallized from ethyl acetate/n-hexane. mp 290 ^oC (decomp). ν_{max}(KBr)/cm^{-1} 3300-3289(br s, NH), 1657(CO); δ_H (acetone-d_6) 11.25(1H, s, NH), 10.95(1H, s, N'H), 8.45(1H, d, J, 12, CONHC), 7.60(1H, d, $J_{4,5}$ 7.7 , 4-H), 7.55 (1H, d, $J_{4'5'}$ 7.7 , 4'-H), 7.40(1H, d, $J_{6,7}$ 8.1, 7-H), 7.35(1H, d, $J_{6',7'}$ 8.1, 7'-H), 7.38 (1H, s, 2-H), 7.25(1H, s, 2'-H), 7.10 (2H, m, 5-H and 5'-H), 6.98(2H, m, 6-H and 6'-H), 6.19(1H, d, J 12, CONCHCO), 5.55(1H, d, J 8, BocNH*CH*CO), 3.62(3H, s, $NOCH_3$), 3.08(3H, s, NCH_3), 1.40(9H, s, $OC(CH_3)_3$); HRMS (EI) calcd for $C_{20}H_{14}N_4O$ 505.5657, found. 505.5642. Anal. Calcd for $C_{27}H_{31}N_5O_5$: C, 64.14; H, 6.18; N, 13.85. Found: C, 64.35; H, 6.17; N, 13.77.

3,6-Bis(3'-indolyl)-2(1*H*)-pyrazinone (10):

Compound (**8**) (405 mg, 0.8 mmol) in THF (10 mL) was reduced with $LiAlH_4$ (46 mg, 1.2 mmol) at -10 ^oC for 1 h. The reaction was quenched with ethyl acetate (5 mL) and poured into water (5 mL). The mixture was extracted with ethyl acetate (3x10 mL). The extracts were washed with brine and dried over Na_2SO_4. After removal of solvent, the residue was dissolved in methanol (10 mL) and the whole was treated with acetyl chloride (0.6 mL) at 0 ^oC for 10 min. Then the mixture was stirred at rt for 4 h. After removal of solvent under reduced pressure, the residue (**9**) in acetonitrile (20 mL) was stirred at rt for 2 days. The solvent was removed. The crude product was subjected to flash chromatography (eluted solvent PE: EtOAc=5:10) to afford **10** (60 mg, 23%). Recrystallized from ethyl acetate/n-hexane. mp 283.5-284.3 ^oC. ν_{max}(KBr)/cm^{-1} 3560, 3412, 1645, 1620, 1500, 1455, 1420, 1334, 1235, 1160; δ_H (DMSO-d_6) 12.31(1H, br s, pyrazinone-NH), 11.86(1H, br s, NH), 11.63(br s, 1H, N'H), 8.85(1H, s, 2-H,), 8.80(1H, d, $J_{4,5}$ 7.8, 4-H), 8.22(1H, s, pyrazinone C=CH), 8.10(1H, d, J 7.7, 4'-H), 8.08(1H, d, J 8.1, 7-H), 7.62 (1H, d, J 8.1, 7'-H), 7.60(1H, s, 2'-H), 7.43(2H, m, 6-H and 6'-H), 7.09(2H, m, 5-H and 5'-H); HRMS (EI) Calcd for $C_{20}H_{14}N_4O$ 326.1167. Found 326.1169. Anal. Calcd for $C_{20}H_{14}N_4O$: C, 73.61; H, 4.32; N, 17.17. Found: C, 73.70; H, 4.35; N, 17.27.

2-(Indol-3-yl)-*N*-[2-(indol-3-yl)-2-oxoethyl]-2-oxoacetamide (14):

3-(α-Azidoacetyl)indole (**11**)[21] (400 mg, 2 mmol) in methanol (20 mL) containing 35% HCl (1 mL) was hydrogenated over 10% Pd/C (105 mg) for 3 h. The catalyst was filtered out. The filtrate was condensed under reduced pressure. The residue was recrystallized from methanol to afford 3-(aminoacetyl)indole hydrochloride (**12**) (390 mg).

To a solution of **12** (90 mg, 0.71 mmol) and triethylamine (0.4 mL, 2.85 mmol) in CH_2Cl_2 (20 mL) was added indolylglyoxylic chloride (**13**)[22] (190 mg, 0.91 mmol) at 0 ^oC. The mixture was stirred overnight. After work up as usual, the crude product was purified by chromatography on silica gel (eluted solvent CH_2Cl_2:CH_3OH=10:1) to afford **14** (165 mg, 67%). Recrystallized from ethanol. mp 264-265 °C. ν_{max} (KBr)/cm^{-1} 3386 and 3337(NH), 1675(CO), 1645(CONH), 1620($COCH_2$); δ_H (DMSO-d_6) 12.28(1H, s, NH), 12.09(1H, s, N'H), 8.94(1H, t, J, 5.75, CO*NH*CH), 8.84(1H, s, 2-H), 8.53(1H, s, 2'-H), 8.26(1H, d, $J_{4,5}$ 7.7, 4-H), 8.18(1H, $J_{4',5'}$ 7.7, 4'-H), 7.59 (1H, d, $J_{6,7}$ 8.1, 7-H), 7.50(1H, d, $J_{6',7'}$ 8.1, 7'-H), 7.32 (2H, dd, $J_{5,6(5',6')}$ 7.1, $J_{6,7(6',7')}$ 8.1, 6-H and 6'-H), 7.21(2H, dd, $J_{4,5(4',5')}$ 7.7, $J_{5,6(5',6')}$ 7.1, 5-H and 5'-H), 4.65(2H, d, J 5.7, $COCH_2N$); *m/z* (EI) 345(M^+, 3%), 316(16), 201(13), 144(100). Anal. Calcd For $C_{20}H_{14}N_4O$: C, 69.56; H, 4.38; N, 12.17. Found: C, 69.70; H, 4.40; N, 12.21.

3,5-Bis(3'-indolyl)-2(1*H*)pyrazinone (16):

Compound (**14**) (150 mg, 0.43 mmol) in methanol (5 mL) was added to liquid ammonia (10 mL) in autoclave. The mixture was heated at 80 ^oC for 3 days under 50 psi. After evaporation of ammonia, the crude product was purified by chromatography (elued solvent CH_2Cl_2:CH_3OH=25:1) on slica gel to afford **16** (65 mg, 63%). Recrystallized from ethanol. mp >300 °C. ν_{max}(KBr)/cm^{-1} 3555 and 3410(NH),

1640(CO); δ_H (DMSO-d_6) 12.27(1H, br s, pyrazinone-CONH), 11.64(1H, s, NH), 11.35(1H, s, N'H), 8.90(1H, s, 2-H), 8.79(1H, d, $J_{4,5}$ 7.7, 4-H), 8.04(1H, d, $J_{4'5'}$ 7.7, 4'-H), 7.85(1H, s, pyrazinone-CH), 7.53(1H, d, $J_{6,7}$ 8.1, 7-H), 7.52 (1H, s, 2'-H), 7.47(1H, d, $J_{6',7'}$ 8.1, 7'-H), 7.24(2H, dd, $J_{5,6(5',6')}$ 7.1, $J_{6,7(6',7')}$ 8.1, 6-H and 6'-H), 7.08(2H, dd, $J_{4,5(4',5')}$ 7.7, $J_{5,6(5',6')}$ 7.1, 5-H and 5'-H); δ_c (DMSO-d_6) 153.62, 150.31, 136.82, 136.67, 136.25, 131.31, 131.14, 129.97, 125.98, 124.50, 123.20, 122.56, 122.15, 121.40, 120.43, 119.89, 119.89, 119.33, 116.24, 113.33, 111.83. HRMS (EI) calcd for $C_{20}H_{14}N_4O$ 326.1167, found 326.1178. Anal. Calcd For $C_{20}H_{14}N_4O$: C, 73.61; H, 4.32; N, 17.17. Found: C, 73.68; H, 4.40; N, 17.07.

REFERENCES

1. D. J. Faulkner, *Nat. Prod. Rep*., 1999, **16**, 155.
2. A. E. Wright, S. A. Pomponi, S. S. Cross, and P. McCarthy, *J. Org. Chem*., 1992, **57**, 4772.
3. S. Sakemi and H. H. Sun, *J. Org. Chem.*, 1991, **56**, 4304.
4. S. P. Gunasekera, P. J. McCarthy, and M. Kelly-Borges, *J. Nat. Prod.*, 1994, **57**, 1437.
5. P. Wipf, *Chem. Rev.*, 1995, **95**, 2115.
6. X. H. Gu, X. Z.Wan, and B. Jiang, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 569.
7. Y. Okada, H. Taguchi, and T. Yokoi, *Tetrahedron Lett*., 1996, **37**, 2249.
8. Y. Okada, H. Taguchi, and T. Yokoi, *Chem. Pharm. Bull.*, 1996, **42**, 2259.
9. B. P. Clark and J. R. Harris, *Synth. Commun.*, 1997, **27**, 4223.
10. A. H. Kantz, A. Demerson, C. C. Shaw, A. A. Asselin, L. G. Humber, M. Conway, G. Gavin, C. Guinosso, N. P. Jensen, D. Mobilio, R. Noureldin, J. Schmid, U. Shah, D. E. Engen, T. Chau, and M. Weichman, *J. Med. Chem.*, 1988, **31**, 1244.
11. B. Jiang, J. M. Smallheer, C. Amaral-Ly, and M. A. Wuonola, *J. Org. Chem*., 1994, **59**, 6823.
12. K. N. F. Shaw, A. McMillan, A. G. Gudmundson, and M. D. Armstrong, *J. Org. Chem.*, 1958, **23,** 1171.
13. E. J. Corey, L. S. Melvin, and M. E. Haslanger, *Tetrahedron Lett*., 1975, 3117.
14. J. A. Fehrentz and B. Castro, *Synthesis*, 1982, 676.
15. D. L. Nguyen, R. Seyer, A. Heitz, and B. Castro, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1025.
16. C. J. Moody and M. C. Bagley, *J. Chem. Soc., Perkin Trans. 1*, 1998, 601.
17. J. R. Hwu, M. L. Jain, S. C. Tsay, and G. H. Hakimelahi, *Tetrahedron Lett.*, 1996, **37**, 2035.
18. A. M. Felix, E. P. Heimer, T. J. Cambros, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.*, 1978, **43**, 4194.
19. J. Coste, M. N. A. Dufour, Pantaloni, and B. Castro, *Tetrahedron Lett.*, 1990, **31**, 669.
20. J. Bergman, J. E. Backvall, and J. O. Lindstrom, *Tetrahedron*, 1973, **29**, 971.
21. C. J. Moody and J. G. Ward, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2903.

22. M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.,* 1954, **76**, 6208.
23. R. H. Bradbury, D. Griffiths, and J. E. Rivert, *Heterocycles*, 1990, **31**, 1647.
24. M. Chihiro, H. Nagamoto, I. Takemura, K. Kitano, H. Komatsu, K. Sekiguchi, F. Tabusa, T. Mori, M. Tominaga, and Y. Yabuuchi, *J. Med. Chem*., 1995, **38**, 353.