Heterocyclic Letters
Vol. 5 | No.3 |459-466| May-July| 2015
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS AND CHARACTERIZATION OF PYRROLO[2,1-C][1,4]BENZODIAZEPINE-CIRCUMDATIN CONJUGATES

B.Srinivas[1], N. Saritha Devi[2], G.K Sreenivasulu[3], R.Parameshwar[4]

[1]*Department of Humanities & Sciences, GNITC, Ibrahimpatnam, Ranga Reddy, Telangana.*
[2]*Department of Pharmacy, Kakatiya University, Warangal, Telangana.*
[3]*Department of Humanities & Sciences, KMIT, Hyderabad, Telangana.*
[4]*School of Pharmacy, GNITC, Ibrahimpatnam, Ranga Reddy Distict, Telangana.*
Email:- srichemistry@gmail.com

Abstract:-We have accomplished an efficient, convenient, and inexpensive and diversity oriented method for the synthesis of C8-linked pyrrolo[2,l-c] [1,4] benzodiazepine-circumdatin conjugate **12**.The structures of all the newly synthesized molecules were assigned by elemental analysis and spectral data.

Keywords: Triphosgene, azide derivative, triethyl amine, L-proline methyl ester.

Introduction

Many natural products are heterocyclic compounds and a good number of them are quinazolinone alkaloids. [1]Due in parts to its wide range of useful pharmacological properties, the structure of quinazolinone has been extensively utilized as a valuable scaffold for drug discovery in medicinal chemistry. A large number of structurally interesting and biologically important natural and synthetic quinazolinones are known in the literature.

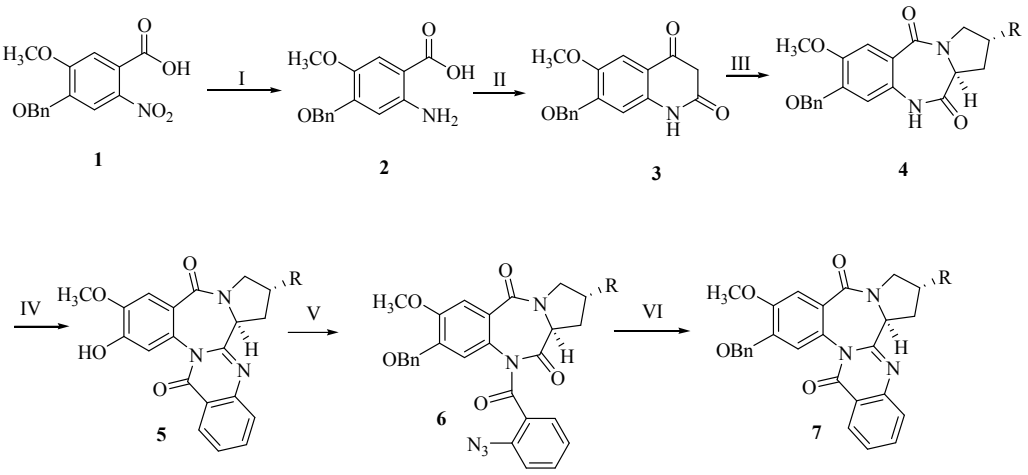
Despite major breakthroughs in diagnosis and treatment, cancer is still the second leading cause of death in the Western world. The discovery and development of new, more active, more selective, and less toxic compounds for the treatment of malignancy are one of the most important goals in medicinal chemistry. The understanding biology of the fundamental of cancer increased dramatically in recent years and has strongly impacted both experimental and clinical tumor therapy. Since the 1990s, various pharmacological investigations of newly synthesized benzothiazoles demonstrated interesting pharmacological activities and led to development of new medications for treating diseases,

Benzothiazole containing heterocycles are an important class of compounds in pharmaceuticals, biologically active molecules and materials. The versatile and synthetically

accessible 2-arylbenzothiazole scaffold has provided the inspiration for the discovery of a number of new antitumor agents with unusual mechanisms of action in recent years. The 2-(4-aminophenyl) benzothiazoles provide a case in point and illustrate the wider benefits of a "chemistry-led" approach to drug discovery.

Results and Discussions

4-(benzyloxy)-5-methoxy-2-nitrobenzoic acid **1** was reduced in methanol with $SnCl_2.2H_2O$ which gave compound **2** in 60% yield and it was confirmed by ^{1}H NMR spectrum which showed two singlets for H-3 at δ 6.36 (s, 1H) and H-6 at δ 7.22 (s, 1H), 5.06 (s, 2H), peak for H-3 proton shifted in shielded . Anthranilic acid derivative was treated with triphosgene in dry THF at 0 °C to reflux temperature for 3 h to give isotopic anhydride **3** in 90% yield as a white solid. Compound **3** was condensed with L-proline and trans-4-hydroxy-L-proline in DMSO at 120 °C afforded corresponding dilactams85% yield respectively as a white solid**4**. Dilactams**4**was acylated with freshly prepared o-azido benzoyl chloride in dry THF by using triethyl amine and cat. DMAP at 20 °C for 2 h afforded corresponding azide intermediates **5** which was used in the next step without any further purification. Intermediate **5** was treated with n-*tri*-butylphosphine in dry benzene at 60 °C for 2 h which gave circumdatin analogues **7**in 70% yield as a white colored solid. Compound was confirmed from ^{1}H NMR which showed a peak of chiral proton H-19 at δ 4.56 (d, J = 7.55 Hz, 1H), benzylic two protons CH_2 showed two doublets at δ 5.06 (d, 1H, J = 12.08 Hz) and 5.25 (d, 1H, J = 12.08 Hz), OCH_3 protons showed one singlet at δ 3.98 integrated for three protons.

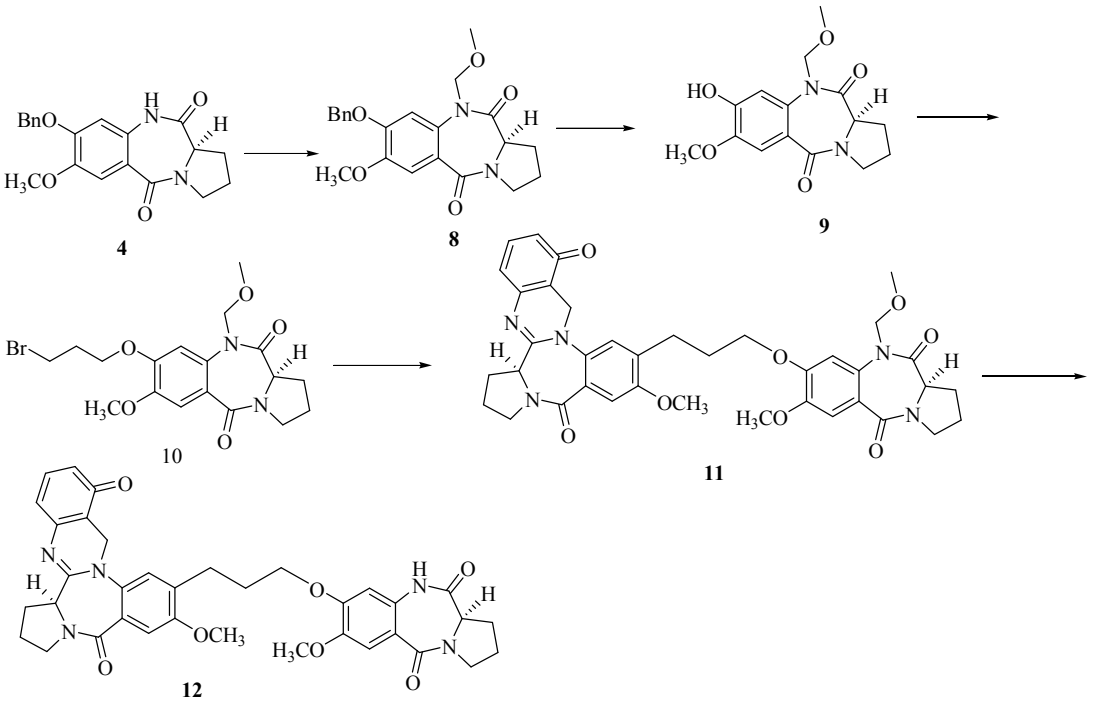


Reagents and conditions: (i) $SnCl_2.2H_2O$, MeOH, reflux, 4 h, (ii) Triphosgene, THF, 0 °C, r.t.
(iii) L-proline, DMSO, 110 °C, 4 h, (Iv) Et_3N, DMAP, THF, 20 °C, 2 h (v) n-Bu_3P, toluene, 60 °C, 2 h, 70%
(VI) Pd/C, H_2, EtOH,

Scheme-1

Amide NH of dilactam **4** was converted to N-MOM by reacting with methoxymethyl chloride in dry THF by using sodium hydride at 0 °C afforded (S)-8-(benzyloxy)-7-methoxy- 10-(methoxymethyl)-2,3-dihydro- l*H*-benzo[e]pyrrolo[1,2-a] [1,4]diazepine-5,11 l*H*,11) (10*H*, 11a H)-dione **8** in 80% yield as a sticky solid. Product was confirmed from ^{1}H NMR which showed a peak at δ 4.03-4.17 (m, 1H) for chiral proton and two doublets for methyleneprotons of N-MOM

at δ 4.44 (d, 1H, *J* = 9.63 Hz), 5.37 (d, 1H,*J* = 9.63 Hz), Then MoM-protected dilactam **8** was debenzylated by using hydrogenation with 5% Pd/C in ethyl acetate afforded dilactam **9** in 90% yield as a light yellow solid. Product was evident from ^{1}H NMR by the appearance of a peak for chiral proton H-11 at δ 4.10-4.18 (m, 1H), two doublets for methoxy methylene protons CH_2 at δ 4.68 (d, 1H, *J* = 9.82 Hz), 5.40 (d, 1H, *J* = 9.82 Hz) and two singlets for two OCH_3 protons at δ 3.43 and at δ 3.93. Formation of ether **10** was carried out at phenolic OH of dilactam **9** in dry acetone by using 1,3-dibromopropane and K_2CO_3 at 50 °C for 6 h. Product was confirmed from ^{1}H NMR by the appearance of peak at δ 4.10-4.25 (m, 3H, H-11+CH_2Br). Compound **10** was coupled with free OH of circumdatin analogue **8** in dry acetone by using K_2CO_3 as a base at 50 °C for 6 h, which gave C8-linked pyrrolo[2,l-c][l,4]benzodiazepine-circumdatin conjugate **11**. Compound **11**was evident by the appearance of two doublets for methoxy methylene protons CH_2 at δ 4. 66 (d, 1H, *J* = 10.61 Hz), 5.44 (d, 1H, *J* = 10.61 Hz) and three singlets for three OCH_3groups atδ 3.47, 3.83 and 3.96 ppm. Finally target compound **12** was prepared by deprotecting MOM protection of dilactam by using 10% HC1 in MeOH/THF in 85 % yield. Compound was confirmed from ^{1}H NMR by the disappearance of two doublets of methoxy methylene protons and disappearance of one singlet of methoxy group of MoM and also ESI-MS showed a peak at 666 (M+H).



Reagents and conditions : (i) methoxy methyl chloride (mom-Cl), NaH, THF
(ii) H2/Pd-C, ethyl acetate(iii) 1,3-dibromopropane, K2CO3, acetone, 55 °C, 6 h
(iv) 98a, K2CO3, acetone, 55 °C, 6 h, (v) 2N HC1, THFrMeOH, r.t., 2 h.

Scheme-2

Experimental Section

General Conditions: All the used reactants, reagents and solvents were obtained from commercial sources and were of analytical grade. Melting points were determined by open capillary method. ^{1}H NMR ($CDC1_3$ + DMSO- d_6, $_{300}$ MHz) and ^{13}C NMR ($CDC1_3$ + DMSO- d_6, 75 MHz) were recorded on spectrometer TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70H instrument. The purity of the compounds was checked by TLC on silica gel plates using a mixture of n-hexane and ethyl acetate.

General procedure for the synthesis 7-Amino-4-benzyloxy-5-methoxybenzoic acid (2)

A solution of substituted nitrobenzoicacid **1** (4.5 g, 14.85 mmol) and $SnCl_2.2\ H_2O$ (13.36 g, 59.40 mmol) in MeOH (80 mL) was stirred at 70^{o}C for 5 h. The mixture was concentrated under vacuum to thick syrup; then ethyl acetate (100 mL) was added. The organic phase was washed with water until it turned to a clear solution, brine and dried over Na_2SO_4. After removal of solvent, the crude material was recrystallized from ethyl acetate to afford a yellow solid **2** (3.04 g, 75%). m.p. 158-160 -C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.73 (s, 3H), 5.06 (s, 2H), 6.36 (s, 1H), 7.21 (s, 1H), 7.25-7.50 (m, 5H); ^{13}C-NMR (75 MHz, $CDC1_3$+DMSO-d_6): δ 55.96, 69.44, 100.24, 101.45, 113.70, 126.82, 127.35, 127.89, 135.84, 139.37, 147.27, 153.16, 168.93; ESI-MS: *m/z* 274 (M^{+}+H)

7-Benzyloxy-6-methoxyisatoic anhydride (3)

To a solution of compound **2** (3 g, 10.98 mmo1) in THF (60 mL) was added triphosgene (3.57 g, 12.08 mmol) in one portion. The reaction mixture was refluxed for 3 h. After being cooled to room temperature, the solution was poured into ice/water. The resulting precipitate was filtered and recrystallized from MeOH to give a white solid **3** (3.11 g, 95%). m.p. 233-235 ^{o}C; ^{1}H-NMR ($CDC1_3$ + DMSO- d_6, 300-MHz): δ 3.87 (s, 3H), 5.22 (s, 2H), 6.78 (s, 1H), 7.49-7.36 (m, 6H), 11.48 (s, 1H, NH); ^{13}C-NMR ($CDC1_3$ + DMSO-d_6, 75 MHz): δ 56.23, 70.91, 99.45, 101.78, 109.32, 127.68, 128.35, 128.68, 135.31, 137.65, 146.45, 147.98, 156.04, 159.55; ESI-MS: *m/z* 300 (M^{+}+H).

8-Benzyloxy-7-methoxypyrrolo [2,l-c][l,4]benzodiazepine-5,11-dione (4)

The mixture of isatoic anhydride **3** (3 g, 10.03 mmol) and L-proline (1.26 g, 11.03 mmol) in DMSO (8 mL) was heated at 120 °C for 4 h. After being cooled to room temperature, the solution was poured onto ice (60 mL), the resulting precipitate was filtered and recrystallized from MeOH to give a white solid. **4** (3.35 g, 65%). m.p. 191-193 °C; ^{1}H- NMR (300 MHz, DMSO-d_6): δ 1.90-2.05 (m, 3H), 2.60-2.72 (m, 1H), 3.42-3.73 (m, 2H), 3.87 (s, 3H), 3.97 (d, 1H, J = 6.04 Hz), 5.01-5.15 (m, 2H), 6.73 (s, 1H), 7.25-7.5 (m, 6H), 10. l9 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 23.1, 25.6, 46.8, 55.5, 56.3, 69.9, 111.8, 118.6, 128.0, 128.1, 128.4, 130.6, 136.1, 145.3, 150.5, 164.3, 170.3; ESI-MS: *m/z* 375 (M^{+}+Na), 353 (M^{+}+H), 323, 220.

(S)-10-(2-azidobenzoyl)-8-(benzyloxy)-7-methoxy-2,3-dihydro-1*H*-benzo[e]pyrrolo[l,2 *a*] [l,4]diazepine-5,11(10*H*,11a*H*)-dione (5)

To a stirred solution of (S)-8-(benzyloxy)-7-methoxy-2,3-dihydro-1*H*-benzo[*e*]pyrrolo[l,2-*a*][l,4]diazepine-5,l1(10*H*,11*H*)-dione **4** (3 g, 8.52 mmol) in dry THF (30 mL) was added triethylamine (1.29 g, 12.78 mmol) under nitrogen atmosphere at 20°C and stirred for 20 min. To this 4-dimethylaminopyridine (0.727 g. 5.96 mmol) was added in one portion and allowed to stirr at same temperature for 20 min. Then freshly prepared 2-azidobenzoyl chloride **5** (1.85 g, 10.22 mmol) in dry THF (5 mL) wad added dropwise over 10 min and stirred at 20°C for 2 h. The solvent was evaporated under reduced pressure and the resulting residue was dissolved in dichloromethane (100 mL) and the organic layer was washed with water (2 x 30 mL), dried over anhydrous sodium sulphate and evaporated to give the compound **5** (3.20 g) as thick liquid and used immediately in the next step without any further purification.

(S)-13-(benzyloxy)-12-methoxy-5b,6,7,8-tetrahydrobenzo[6,7]pyrrolo[2',l':3,4][l,4]diazepino[2,l-*b*]quinazoline-10,16-dione (6)

To a stirred solution of azide derivative **5**(3.20 g) in anhydrous benzene (30 mL) was added Bu_3P (1.89 g, 9.375 mmol) in one portion under nitrogen atmosphere at room temparature. The mixture was refluxed at 60 °C for 1 h and then left at room temparature overnight. After completion of the reaction, the solvent was evaporated and the resulting residue was dissolved in CH_2C1_2 (100 mL). The organic layer was washed with 0.5 N aq HC1 :(3 x 60 mL) followed by brine (2 x 30 mL), and then dried (Na_2SO_4) and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography to give circumdatin analogue **6** as a white solid (2.50 g, 65%). m.p. 105-108 °C. IR (KBr): *V*max 2922, 2852, 1688, 1639, 1606, 1514, 1454, 1429, 1361, 1268, 1243, 1218, 1185, 1132, 1110, 1079, 1058, 1021, 973, 926 cm^{-1}; ^{1}H-(300 MHz, $CDC1_3$): δ 1.96-2.43 (m, 1H), 3.08-3.28 (m, 1H), 3.52-3.68 (m, 1H), 3.69-3.84 (m, 1H), 3.98 (s, 1H), 4.53-4.60 (m, 1H), 5.06 (d, 1H, *J* = 12.08 Hz), 5.25 (d, 1H, *J* = 12. 08 Hz), 7.09 (s, 1H), 7.29-7.59 (m, 7H), 7.66-7.86 (m, 2H), 8.28-8.36 (m, 1H); ^{13}C-NMR (75 MHz, $CDC1_3$): δ 23.6, 26.9, 46.5, 56.2, 58.9, 71.1, 111.1, 111.3, 112.7, 121.3, 125.2, 126.5, 126.6, 127.3, 127.5, 128.1, 128.5, 134.6, 135.8, 146.0, 149.2, 149.5, 153.8, 161.6, 164.4; ESI-MS: *m/z* 476 (M^++Na), 454 (M^++H), 371.

(S)-13-hydroxy-12-methoxy-5b,6,7,8-tetrahydrobenzo[6,7]pyrrolo[2',l':3,4] [l,4]diazepino[2,l-*b*]quinazoline-10,16-dione (7)

To a solution of compound **6** (2.4 g, 5.29 mmol) in absolute EtOH (60 mL) was added 10% Pd/C (8.8 g) and hydrogenated by usingby hydrogen balloon. The reaction mixture was stirred at room temperature for 12 h until TLC indicated that the reaction was complete. The reaction mixture was filtered through Celite. concentrated under vacuum, Purification of the residue by flash chromatography to give whitesolid product **7** (1.69 g, 88%). m.p. 250 °C IR (KBr): *V*max 2957, 2924, 2853, 1688, 1605, 1516, 1461, 1436, 1407, 1374, 1282, 1248, 1217, 1130, 1081, 1057, 1023, 974, 926, 878, 772, 697, 664 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.95-2.39 (m, 3H), 3.1-3.24 (m, 1H), 3.48-3.66 (m, 1H), 3.68-3.82 (m, 1H), 3.98 (s, 1H), 4.57 (d, 1H, *J* = 7.40 Hz), 7.05

(s, 1H), 7.40 (s, 1H), 7.5 (t, 1H, *J* = 7.40 Hz), 7.67 (d, 1h, *J* = 8.32 Hz), 7.76 (t, 1H, *J* = 7.40 Hz), 8.30 (d, 1H, *J* - 7.40 Hz); ESI- MS: *m/z* 386 (M^++Na), 364 (M^++H), 235, 179.

(S)-8-(benzyloxy)-7-methoxy-10-(methoxymethyl)-2,3-dihydro-lflr-benzo[e]pyrrolo[l,2a] [l,4]diazepine-5,11(10*H*,11a*H*)-dione (8)

To a stirred solution of dilactam**4** (2 g, 5.68 mmol) in THF (80 mL) was added NaH (0.30 g, 12.5 mmol) under nitrogen atmosphere at 0 °C, and the reaction mixture was stirred at the same temperature for 30 min. MOMC1 (6.4 mL, 11.92 mmol) was added drop wise into the reaction mixture. The resulting solution was stirred at room temperature for 24 h. The reaction mixture was poured onto ice and exracted with ethyl acetate (3 x 60 mL). The collected organic layers were washed with |saturated $NaHCO_3$, water, and brine, and dried over anhydrous sodium sulphate. Solvent was evaporated under reduced pressure and resulting residue was purified by column chromatography to give a yellow sticky product **8** (2.00 g, 89%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.84-2.26 (m, 3H), 2.59-2.79 (m, 1H), 3.40 (s, 3H), 3.47-3.63 (m, 1H), 3.66-3.83 (m, 1H), 3.95 (s, 3H), 4.03-4.17 (m, 1H), 4.44 (d, 1H, *J*= 9.63 Hz), 5.21 (s, 2H), 5.37 (d, 1H, *J* = 9.63 Hz), 7.17 (s, 1H), 7.24-7.51 (m, 6H); ^{13}C-NMR (125 MHz, $CDC1_3$): δ 23.70, 26.50, 46.67, 56.15, 56.81, 57.50, 70.93, 79.67, 107.61, 111.39, 122.20, 127.38, 128.15, 128.59, 133.63, 135.94, 147.47, 150.64, 165.08, 170.30.

(S)-8-hydroxy-7-methoxy-10-(methoxymethyl)-2,3-dihydro-l*H*-benzo[e]pyrrolo[l,2-*a*] Diazepine-5, 11(10*H*, 11aH)-dione (9)

To a solution of compound **8** (1.8 g, 4.54 mmol) in ethyl acetate (40 mL) was added 10% Pd/C (8.8 g) and hydrogenated by using hydrogen balloon. The reaction mixture was stirred at room temperature for 6 h until TLC indicated that the reaction was complete. The reaction mixture was filtered through celite, concentrated under vacuum, Purification of the residue by flash chromatography to give white solid product **9** (1.18 g, 85%). m.p. 175-178 °C; IR (KBr): *V*max 2924, 2853, 1685, 1603, 1517, 1467, 1439, 1411, 1340, 1280, 1216, 1198, 1107, 1072, 1025, 966, 937, 913 crn^{-1}, ^{1}H-NMR (300 MHz, $CDC1_3$): δ 1.91-2.20 (m, 3H), 2.63-2.80 (m, 1H), 3.43 (s, 3H), 3.49-3.64(m, 1H), 3.70-3.84 (m, 1H), 3.93 (s, 3H), 4.10-4.18 (m, 1H), 4.68 (d, 1H, *J* = 9.82 Hz),5.40 (d, 1H, *J* = 9.82 Hz), 7.21 (s, 1H), 7.37 (s, 1H); ^{13}C-NMR (75 MHz, CDC13): δ 23.62, 26.40, 46.59, 56.06, 56.67, 57.48, 79.49, 108.89, 111.03, 121.48, 134.14, 144.96, 149.18, 165.23,170.21.

(S)-8-(3-bromopropoxy)-7-methoxy-10-(methoxymethyl)-2,3-dihydro-l*H*-benzo[e] pyrrolo [l,2-*a*][l,4]diazepine-5,11(10*H*,11a*H*)-dione (10)

To a solution of dione**9** (1 g, 3.26 mmol) in acetone (30 mL) was added anhydrous K_2CO_3 (1.35 g, 9.80 mmol) and 1,3-dibromopropane (3.90 g, 19.60 mmol), the mixture was heated at 50 °C for 6 h. After completion of the reaction, K_2CO_3 was removed by filtration and the filtrate was evaporated undercreduced pressure. The crude product was purified by silica gel and resulting crude was purified by column chromatography to afford compound **10** (1.18 g, 85%). ^{1}H-NMR (300 MHz, $CDC1_3$): δ 1.94-2.15 (m, 3H), 2.33-2.46 (m, 2H), 2.66-2.78 (m, 1H), 3.50 (s, 3H), 3.54-3.69 (m, 3H), 3.71-3.83 (m, 1H), 3.92 (s, 3H), 4.10-4.25 (m, 3H), 4.65 (d, 1H, *J* = 9.82 Hz),

5.47 (d, 1H, *J* = 9.82 Hz), 7.19 (s, 1H), 7.36 (s, 1H); ^{13}C-NMR (75,MHz, $CDC1_3$): δ 23.68, 26.47, 29.69, 31.90, 46.62, 56.02, 57.07, 57.48, 66.47, 79.73, 106.82, 111.41, 122.35, 133.70, 147.28, 150.90, 165.03, 170.32; ESI-MS: *m/z* 427 (M^++H).

(S)-12-methoxy-13-(3-(((S)-7-methoxy-10-(methoxymethyl)-5,11-dioxo-2,3,5,10,11,11ahexahydro-l*H*-benzo[e]pyrrolo[l,2-*a*][l,4]diazepin-8-yl)oxy)propoxy)-5b,6,7,8-tetrahydrobenzo[6,7]pyrrolo[2',l':3,4][l,4]diazepino[2,l-b]quinazoline-10,16-dione,(11)

To a well stirred mixture of compound **8** (1 g, 2.75 mmol) and anhydrous K_2CO_3 (1.14 g, 8.26 mmol) in acetone (30 mL) was added compound **11** (1.17 g, 2.75 mmol) and the reaction mixture was heated at 50 °C for 6 h. After completion of the reaction, K_2CO_3 was removed by filtration and the filtrate was evaporated under reduced pressure and resulting crude was purified by column chromatography to afford compound **11** (1.46 g, 75%). m.p. 183-185°C; IR (KBr): *V*max 2925, 2311, 1688, 1607, 1515, 1464, 1432, 1362, 1271, 1244, 1219, '1196, 1163, 1133, 1107, 1058, 1024, 968, 875, 772, 699, 665 cm^{-1}; ^{1}H-NMR (500 MHz, $CDC1_3$): δ 1.94-2.22 (m, 4H), 2.23-2.36 (m, 1H), 2.36-2.47(m, 2H), 2.67-2.76 (m, 1H), 3.12-3.21 (m, 1H), 3.47 (s, 3H), 3.51-3.68 (m, 2H), 3.69-3.80,(m, 2H), 3.83 (s, 3H), 3.96 (s, 3H), 4.07-4.16 (m, 2H), 4.19-4.29 (m, 3H), 4.29-4.37 (m, 1H)4.55 (d, 1H, *J* = 7.43 Hz), 4.66 (d, 1H, *J* = 10.61 Hz), 5.44 (d, 1H, J = 10.61 Hz), 7.07 (s, 1H) 7.17 (s, 1H), 7.31 (s, 1H), 7.44 (s, 1H), 7.52 (t, 1H, *J* = 7.43 Hz), 7.71 (d, 1H, *J* = 8.49 Hz), 7.79 (t, 1H, *J* = 7.43 Hz), 8.27 (d, 1H, *J* = 7.43 Hz); ^{13}C-NMR (75 MHz, $CDC1_3$): δ 23.61, 26.44, 26.87, 28.65, 29.55, 46.48, 46.62, 55.94, 56.11, 57.02, 57.45, 58.87, 65.34, 65.60, 79.70, 106.59, 111.20, 111.32, 112.29, 113.95, 121.28, 122.09, 125.06, 126.72, 127.26, 127.41, 133.67, 134.63, 145.95, 147.17, 149.03, 149.41, 151.01, 153.72, 161.66, 164.39, 165.03, 170.24; ESI-MS: *m/z* 710 (M^++H), 732 (M^++Na).

(S)-2-methoxy-13-(3-(((S)-7-methoxy-5,ll-dioxo-2,3,5,10,ll,lla-hexahydro-l*H*-benzo [e] pyrrolo[l,2-a][l,4]diazepin-8-yI)oxy)propoxy)-5b,6,7,8-tetrahydrobenzo [6,7] pyrrolo[2',l':3,4][l,4]diazepino[2,l-b]quinazoline-10,16-dione (12)

To a solution of N-MOM **11** (0.2 g, 0.02 mmol) in MeOH:THF (10 ml) was added 10% HC1 and heated for a period of 10 h. After completion of reaction (monitored by TLC), reaction mixture was concentrated, diluted with water and extracted with ethyl acetate (3 x 20 ml). Combined oranic layer was washed with sat. $NaHCO_3$, brine and dried over sodium sulphate concentrated under reduced pressure to obtain crude solid. Product was purified by silica gel chromatography to give white solid **12** (0.159 g, 85%). ^{1}H-NMR (500 MHz, $CDC1_3$): δ 1.94-2.21 (m, 5H), 2.23-2.29 (m, 2H), 2.38-2.50 (m, 1H), 2.67-2.77 (m, 1H), 3.13-3.22 (m, 1H), 3.54-3.66 (m, 2H), 3.70-3.80 (m, 2H), 3.85 (s, 3H), 3.96 (s, 3H), 4.02 (d, 1H, *J* = 6.10 Hz), 4.13-4.21 (m, 1H), 4.21-4.35 (m, 3H), 4.56 (d, 1H, *J*= 7.01 Hz), 6.58 (s, 1H), 7.08 (s, 1H), 7.40 (s, 1H), 7.45 (s, 1H), 7.50 (t, 1H, *J* = 7.01 Hz), 7.70 (d, 1H, *J* = 8.08 Hz), 7.78 (t, 1H, *J* = 7.01 Hz), 8.16 (s, 1H), 8.24 (d, 1H, *J*= 7.01 Hz); ESI-MS: *m/z* 666 (M^++H), 688 (M^++Na).

References

I Rahbak, L.; Breinholt, J. J. Nat. Prod., **1999**, 62, 904-905.

II Jin-Rui Dai,; Brad K. Carte',Philip J. Sidebottom,; Alex Lee Sek Yew,; Siew-Bee Ng,;Yicum Huang,; Mark S. Butler. *J. Nat. Prod.*, **2001**, 64, 125-126

II) (a) Krohn, K.; Bahramsari, R.; Fkfrke, U.; Ludewig, K.; Kliche-Spory, C.; Michel, A.; Aust, H.-J.; Draeger, S.; Schulz, B.; Antus, *S. Phytochemistry*, **1997**, 45, 313-320, and references therein, (b) Cole, R. J.; Cox, R. H. *Handbook of Toxic Fungal Metabolites*; Academic Press: New York, **1981**; 129-132.

IV M. Pilar Lopez-Gresa,; M. Carmen Gonzalez,; Jaime Primo,;'Pilar Moya,; Vanessa Romero,; Ernesto Estornell. *J. Antibiot.*, **2005**, 58, 6, 416-419.

V Rahbak, L.; Breinholt, J. *J. Nat. Prod.*, **1999**, 62, 904-905.

VI (a) Yamazaki M,; Maebayashi Y,; Miyaki K. *Chem Pharm Bull*, **1972**,20, 2274-2276.

(b)MacDonald JC,; Bishop GG,; Mazurek M. *Tetrahedron*, **1976**, 32, 655-660.

VII Cutrone JQ, Krampitz KD, Shu YZ, Chang LP, Lowe SE. Stephacidin antitumor antibiotics. U.S. 6,291,461,September 18 **2001**.

VIII Fang N,;Casida JE. *J Agric Food Chem***1999**, 47: 2130-2136.

IX Nguyen HP,; Zhang D,; Lee U,; Kang JS,; Choi HD,; Son BW. *J Nat Prod.*, **2007**, 70, 1188-1190.

X Dahai Zhang, Xiudong Yang, Jung Sook Kang, Hong Dae Choi, ByengWha Son J. Antibiot., **2008**, 61, 1,4042,.

XI Bungni, T. S.; Ireland, C. M. *Nat. Prod. Rep.*, **2004**, *21*, 143.

XII RyuheiOokura,; KeijiroKito,; Takashi Ooi,; MichioNamikoshi,; TakenoriKusumi. *J.Org.Chem.*,**2008**, 73, 4245-1247

XIII Jiang Peng, Xiao-Yong Zhang, Zheng-Chao Tu,§ Xin-Ya Xu, and Shu-Hua Qi *J. Nat.Prod.*, **2013**, 76, 983-987

XIV Harrison, D. R.; Kennewell, P. D.; Taylor, J. B. *J. Heterocycl. Chem.,***1977**, 14, 1191.

XV Witt, A.; Bergmann, J. *J. Heterocycl. Chem.,***2002**, 39, 351.

XVI Snider, B. B.; Busuyek, M. V. *Tetrahedron*, **2001**, 57, 3301.

XVII Anette Witt,; Jan Bergman. *J. Org. Chem.*, **2001**, 66, 2784-2788

XVIII Ji-Feng Liu,; Mira Kaselj,; Yuko Isome,; Jennifer Chapnick,; Bailin Zhang,; Grace Bi,; Daniel Yohannes,; Libing Yu,; Carmen M. Baldino. *J. Org. Chem.,***2005**, 70, 10488-10493

XIX Umesh A. Kshirsagar,; Santosh B. Mhaske,; Narshinha P. Argade. *Tetrahedron Letters***2007**,48, 3243-3246

XX Ming-Chung Tseng,;Huei-Yun Yang,; Yen-Ho Chu. *Org. Biomol Chem.*, **2010**, 8,419-427.

Received on May 7, 2015