A facile synthesis of quinazolino[1,4]benzodiazepine alkaloids *via* reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)amides: Total synthesis of asperlicin C, circumdatin H, and analogues

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Abstract

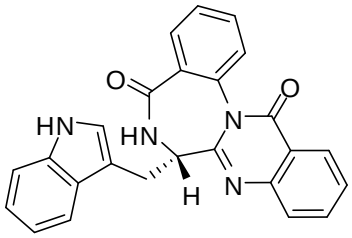
A facile and short synthesis of a series of quinazolino[1,4]benzodiazepine alkaloids, including asperlicin C, circumdatin H and some analogues, is reported utilizing coupling of readily available [1,4]benzodiazepine with 2-nitrobenzoyl chlorides, followed by a reductive *N*-heterocyclization.

Keywords: 1,4-benzodiazepine, *N*-heterocyclization, asperlicin C, circumdatin H

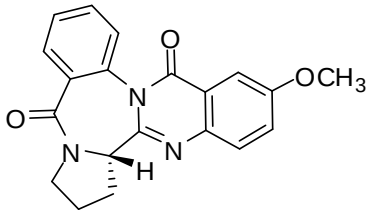
Introduction

The quinazoline-4-one moiety fused with benzodiazepine ring system is part of considerable number of naturally occurring alkaloids isolated from fungal species or their cultures.[1-6] These alkaloids, with diverse biological activities, include asperlicins,[7-9] circumdatins,[10-13] benzomalvins[14] and sclerotigenin.[15,16] Various methods for the synthesis of alkaloids encompassing a quinazolino[1,4]benzodiazepine moiety in their skeleton have been developed and numerous research papers and several reviews have recently appeared.[1,17-27] The implementations of 2-azidobenzoylamides in aza-Wittig methodology [6,28-33] and transition metal-induced reductive *N*-heterocyclization[34-39] have emerged as versatile strategies for the construction of a variety of heterocyclic compounds. Although the aza-wittig and metal-induced reductive cyclization procedures afford quinazolino[1,4]benzodiazepines, they have some disadvantages such as cost and availability of the reagents such as 2-azidobenzoyl chloride and transition metals, generation of phosphine oxide by-product, harsh reaction conditions, low atom economy and synthetic practicality. Thus, the development of novel, mild, simple, economical and high yielding procedure is required. As a part of our ongoing research activity,[23-26] we planned the preparation of some quinazolino[1,4]benzodiazepine natural products using cheap,

readily available and environmentally friendly reagents. Commercially available 2-nitrobenzoyl chloride is an attractive starting material for the preparation of *N*-(2-nitrobenzoyl)amides which then undergo *N*-heterocyclization after the reduction using catalytic hydrogenation conditions.[40-43] Although, the use of H_2-Pd/C system in organic synthesis has become common practice, only a few examples have been reported for the catalytic reductive cyclization of *N*-(2-nitrobenzoyl)amides to the corresponding quinazolino[1,4]benzodiazepine using this procedure.[23] Herein, we report the use of this strategy towards the synthesis of asperlicin C **1**, circumdatin H **2** (Figure 1) and its analogues and several other quinazolino[1,4]benzodiazepine-2,5-diones.



Asperlicin C **1**



Circumdatin H **2**

Figure 1

Results and discussions

The naturally occurring quinazolino[1,4]benzodiazepine-2,5-dione alkaloids vary in structural complexity. Nevertheless, they all seem to be retrosynthetically available from *N*-benzoylated [1,4]benzodiazepine-2,5-dione skeleton. Our aim was to achieve a simple and cost-effective methodology for the construction of these biologically important alkaloids utilization a cheap and commercially available isatoic anhydride **3** and 2-nitrobenzoyl chlorides according to the strategy shown in Figure 2.

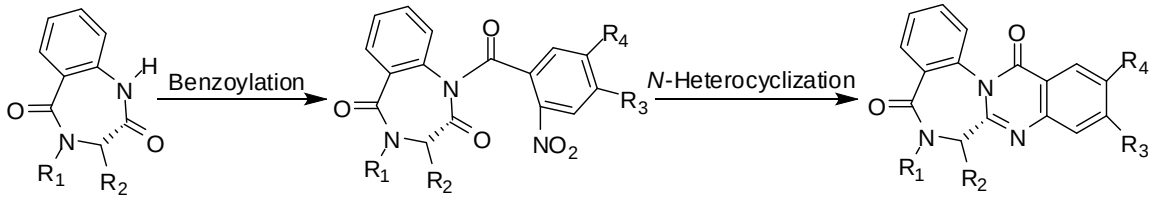
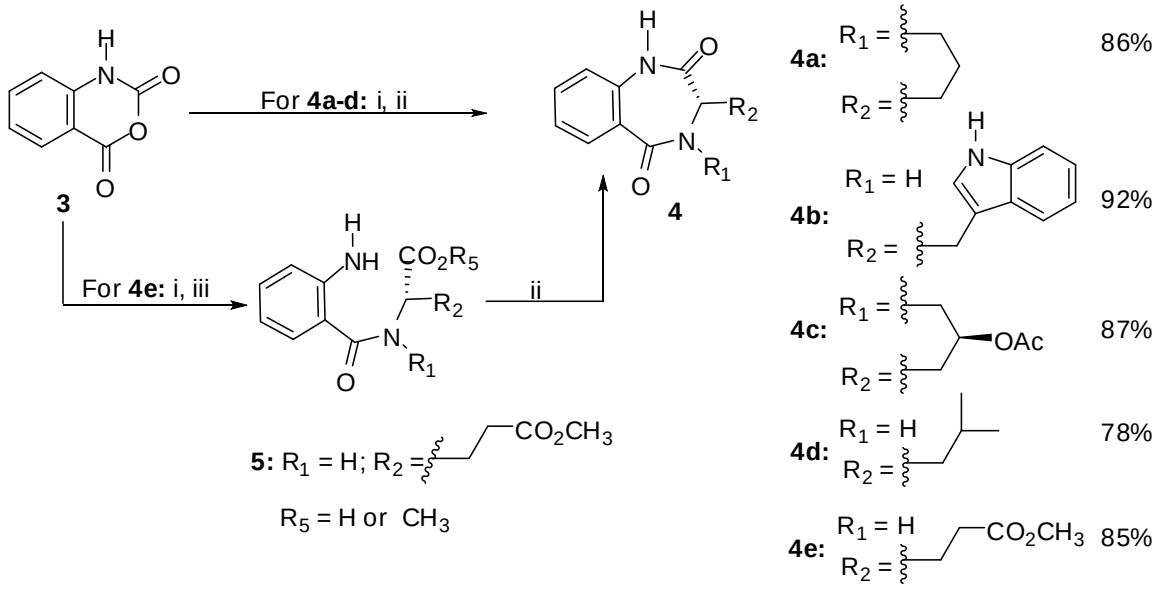


Figure 2

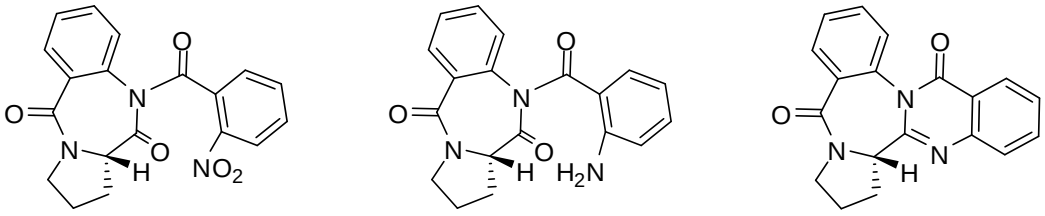
As shown in scheme 1, the preparation of five 1,4-benzodiazepine-2,5-diones **4a-e** was planned using the above-mentioned strategy. Benzodiazepines **4a-d** were readily prepared in excellent

yields through the condensation of isatoic anhydride **3** with the appropriate *L*-amino acids in aqueous solution in the presence of triethylamine followed by cyclization in refluxing glacial acetic acid.[44,45] Benzodiazepine **4e** was prepared in good overall yield by the coupling of glutamic acid with isatoic anhydride **3**[50] followed by esterfication and subsequent cyclization of **5**.



Scheme 1. Reagents and reaction conditions for the synthesis of benzodiazepines **4a-e**: (i) *L*-amino acid (1.0 eq), Et_3N (1.0 eq), H_2O, rt, 48 h; (ii) AcOH, reflux, 6 h; (iii) Me_2SiCl_2 / Methanol, rt, 24 h.

Benzoylation of proline-based 1,4-benzodiazepin-2,5-dione **4a**[46-49] with freshly prepared 2-nitrobenzoyl chloride in the presence of DMAP and Et_3N in dry CH_2Cl_2 was used for optimization study. Monitoring the crude reaction mixture by TLC indicated the clean and complete conversion of **4a** to the corresponding nitro derivative **6** within 3 hrs. However, aqueous work up resulted in partial hydrolyses of the product **6** to the starting materials 2-nitrobenzoic acid and **4a**. Compound **6** was isolated in acceptable yield after purification by column chromatography. The reduction of the nitro compound **6** to the corresponding amine **7** was conducted under mild conditions (H_2 /10% Pd/C). As planned in figure 2, this process was nicely accompanied by a simultaneous *N*-heterocyclization of the resulting amine **7** to give quinazolino[1,4]benzodiazepine **8a** in 65% yield. When the reaction was stopped before the completion, TLC showed only the starting nitro derivative **6** and the cyclized product **8a**.[32]

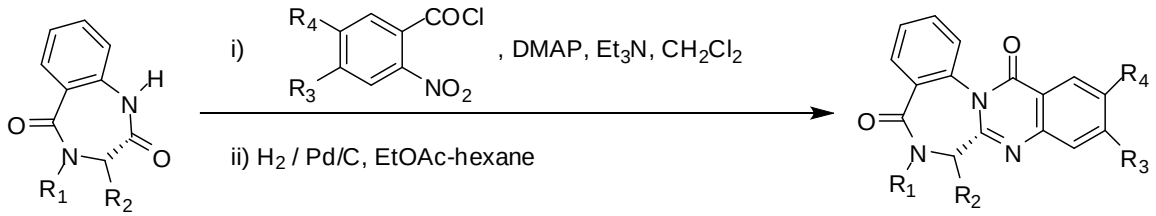


6 **7** **8a**

Figure 3.

We found the purification of **6** is not necessary for the reductive cyclization process. Therefore, the nitro intermediate **6** was not purified to avoid hydrolysis during the work-up. After concentration, the crude nitro derivative was dissolved in 40% ethyl acetate in hexanes and filtered through a short pad of silica gel. Next, the filtrate was subjected to reduction conditions (H_2, 10% Pd/C) to furnish the reductive *N*-heterocyclization product (**8a**, Entry 1) in good yield, no other product was isolated in significant amount. It is worthy to mention that passing the reaction mixture through a pad of silica gel was essential for the success of this reaction, otherwise, the filtrate did not yield **8a** even after long reaction time, probably due to the poisoning of the catalyst.

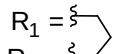
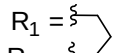
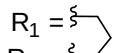
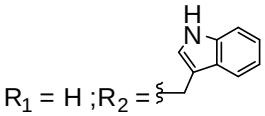
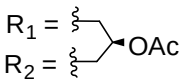
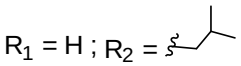
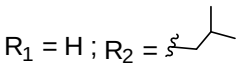
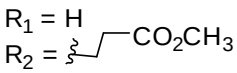
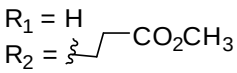
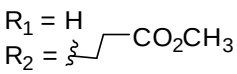
Encouraged by preliminary results, we then turned our attention towards the investigation and generalization of this strategy for the synthesis of quinazolino[1,4]benzodiazepine-2,5-diones including asperlicin C **1** as well as circumtadin H **2** and its analogues. Therefore, [1,4]benzodiazepines **4a-e** were subjected to this reaction sequence. These [1,4]benzodiazepines were first treated with the appropriate 2-nitrobenzoyl chlorides to afford the corresponding *N*-benzoyl derivatives, which, in turn, underwent reductive cyclization to cleanly afforded the corresponding quinazolino[1,4]benzodiazepine **1**, **2** and **8a-h** in good yields (Scheme 2, Table 1).



4a-e **1, 2 and 8a-h** (53-75%)

Scheme 2. Reagents and conditions for synthesis of quinazolinobenzodiazepine **1**, **2** and **8a-h**

Table 1. Synthesis of quinazolinobenzodiazepine **1**, **2** and **8a-h**

Entry	Benzodiazepinedione	R_1, R_2	R_3, R_4	Product, Yield (%)
1	**4a**		R_3=H R_4=H	**8a**, 61
2	**4a**		R_3=H R_4=OCH_3	**2**, 68
3	**4a**		R_3=Cl R_4=H	**8b**, 55
4	**4b**		R_3=H R_4=H	**1**, 60
5	**4c**		R_3=H R_4=OCH_3	**8c**, 67
6	**4d**		R_3=Cl R_4=H	**8d**, 53
7	**4d**		R_3=H R_4=Cl	**8e**, 56
8	**4e**		R_3=H R_4=H	**8f**, 65
9	**4e**		R_3=H R_4=OCH_3	**8g**, 75
10	**4e**		R_3=H R_4=Cl	**8h**, 60

In order to show the efficiency of our methodology, we coupled 5-methoxy-2-nitrobenzoyl chloride with proline-derived benzodiazepine 4**a** afforded the naturally occurring circumdatin H[32] (**2**, Entry 2) in 68% yield after the hydrogenation reaction. Furthermore, the naturally occurring asperlicin C[21,22,33,30] (**1**, Entry 4) was prepared from the reaction of 2-nitrobenzoyl chloride and tryptophan-derived benzodiazepine **4b**[21,22,33,31] followed by hydrogenation.

The results presented in Table 1 indicated that, in general, the reductive cyclization proceeds with both electron-donating and electron-withdrawing substitutions at the benzoylating agent. Moreover, electron-donating groups afforded quinazolino[1,4]benzodiazepine in a slightly higher yields than that of electron-withdrawing substitutions. We attribute this result to the enhancement of the cleavage rate of the 2-nitrobenzoyl group by electron-withdrawing substituent during the aqueous work-up and purification.

Conclusions

The present work provides an efficient and inexpensive procedure for the synthesis of quinazolino[1,4]benzodiazepine-2,5-dione scaffold found in several naturally occurring alkaloids. The [1,4]benzodiazepine-2,5-diones used in this methodology were very easily accessible from commercially available amino acids and isatoic anhydride. This experimentally simple and eco-friendly approach was in the synthesis of circumtadin H and analogous as well as asperlicin C.

Experimental Section

General. Melting points were measured using an electrothermal digital melting point apparatus and were uncorrected. IR spectra were recorded using a Nicolet-Impact 410 FT-IR spectrophotometer. Both ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance spectrometer (400 MHz, for ^{1}H; 100 MHz for ^{13}C). The chemical shifts are given in δ scale (ppm) relative to TMS as the internal standard. Mass spectra (MS) were obtained on API 3000 LC/MS/MS spectrometer manufactured by Applied Biosystems MDS Sciex with APCI/ESI ion source type in positive ion detection.

General method for the synthesis of Benzodiazepinediones (4a-d)

Trietylamine (1.00 g, 0.01 mol) was added to a mixture of isatoic anhydride (0.1 mol) and *L*-amino acid (0.01 mol) in water (40 mL). The mixture was stirred at rt for 12 h. The homogeneous solution was concentrated under vacuum to give oily material. The oily residue was then heated at reflux in glacial acetic acid (50 mL) for 6 h. The solution was concentrated and the resulting solid was recrystalized from ethyl acetate/hexane solution.

(2*R*)-2-Acetoxy-1,2,3-trihydropyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-dione (4c). mp 255-258 ºC. IR (KBr, cm^{-1}): 3238, 1743, 1701, 1618, 1044, 1480, 1452, 1418, 1244, 760. ^{1}H-NMR ($CDCl_3$): δ 8.16 (bs, 1H, NH), 8.03 (dd, *J* = 7.9, *J'* = 1.6 Hz, 1H, Ar-H), 7.51 (m, 1H, Ar-H), 7.31 (m, 1H, Ar-H), 7.01 (bt, *J*=8.1 Hz, 1H, Ar-H), 5.40 (m, 1H, C*H*OAc), 4.29 (t, *J* = 7.6 Hz, 1H, NC*H*), 4.15 (dt, *J* = 13.5, *J'* = 2.1 Hz, 1H, NCH*H*), 3.73 (dd, *J* = 13.5, *J'* = 4.6 Hz, 1H, NC*H*H), 3.09 (ddd, *J* = 14.3, *J'* = 6.9, *J*'' = 5.5 Hz, 1H, NCH-CH*H*-), 2.28 (m, 1H, NCH-C*H*H-), 2.04 (s, 3H, -O_2CCH_3). ESI-MS: m/z 297 $[M+Na]^+$, 275 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85% Found: C, 65.25; H, 5.53; N, 10.72%.

(3S)-3-Isobutyl-1,4-benzodiazepine-2,5-dione. (4d). mp 251-253 ºC. FTIR (KBr, cm^{-1}): 2940, 1674, 1489, 1406. ^{1}H-NMR (Acetone-d_6): δ 9.37 (1H, br s, N*H*), 7.87 (1H, d, *J* = 7 Hz, Ar*H*), 7.54 (1H, t, *J* = 7 Hz, Ar*H*), 7.50 (1H, br s, NH), 7.25 (1H, t, *J* = 8 Hz, Ar*H*), 7.21 (1H, d, *J* = 8 Hz, Ar*H*), 3.88 (1H, dt, *J* 9, *J* = 6 Hz, stereogenic CH), 1.84 (1H, m, C*H*), 1.72 (2H, m, CH_2), 0.92 (3H, d, *J* = 6 Hz, CH_3),0.86 (3H, d, *J* = 6 Hz, CH_3). ^{13}C-NMR (Acetone-D_6): 173.0, 168.8,

138.3, 133.4, 131.6, 125.1, 125.0, 121.5, 52.3, 37.3, 25.3, 23.5, 21.2. ESI-MS: m/z 232 [M+]. Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06% Found: C, 67.32; H, 7.18; N, 11.88%.

Methyl-3-((3S)-2,3,4,5-tetrahydro-2,5-dioxo-1H-benzo [f][1,4] diazepin-3-yl)propanoate (4e). Triethylamine (2.00 g, 0.02 mol) was added to a mixture of isatoic anhydride and glutamic acid (1.47g, 0.01 mol) in water (30 mL). The mixture was stirred at rt for 24 h. The solution was concentrated at reduced pressure to obtain dark oil which was dissolved in methanol and cooled to -5 ^oC. This solution was added to a solution of dichlorodimethylsilane (4 mL) in methanol at -5 ^oC. The reaction mixture was sealed and stirred at room temperature for 24h. Methanol was evaporated under reduced pressure. The crude product was dissolved in ethyl acetate then washed by 5% aqueous $NaHCO_3$ solution. The aqueous layer extracted twice with ethyl acetate and the combined organic layer was evaporated to afford diester **5**. The diester was dissolved in glacial acetic acid (40 mL) and refluxed for 7 h. Acetic acid was evaporated at reduced pressure. The crued product was recrystalized from ethyl acetate/ hexane to produce **4e** as a white crystals (2.25 g, 85%), mp 179-180 ^oC. FTIR (KBr, cm^{-1}): 3178, 3066, 2932, 1735, 1670. ^{1}H-NMR ($CDCl_3$): δ: 9.3 (1H, bs, N*H*); 7.93 (1H, dd, *J* = 8, 1.2 Hz, ArH), 7.81 (1H, bs, N*H*), 7.48 (1H, t, *J* = 8 Hz, Ar*H*), 7,26 (1H, t, *J* = 8 Hz, Ar*H*), 7.07 (1H, d, *J* = 8 Hz, Ar*H*), 3.78 (1H, dt, *J* = 8, *J'* = 6 Hz, stereogenic C*H*), 3.66 (3H, s, OCH_3), 2.57 (2H, m, CH_2), 2.32 (1H, m, CH_2), 2.13 (1H, m, CH_2). ^{13}C-NMR (CD_3CN) δ:173.5, 171.4, 168.3, 136.5, 132.6, 130.9, 126.2, 124.7, 121.5, 51.5, 51.2, 29.7, 23.3. . ESI-MS: m/z 263 $[M+H]^+$.

(S)-10-(2-Nitrobenzoyl)-1,2,3-trihydropyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-dione (6). Freshly prepared *o*-nitro benzoyl chloride (0.38 g, 2.0 mmol) in dry CH_2Cl_2 (3.0 mL) was added drop-wise, while stirring, to a solution containing benzodiazepine **1a** (0.44 g, 2.0 mmol), triethylamine (0.26 g, 2.6 mmol) and catalytic DMAP in dry CH_2Cl_2 (50 mL) at rt. After the addition was complete, the reaction mixture was further stirred for 3 h. The reaction mixture was then concentrated and the crude product was purified by column chromatography on silica gel (40% EtOAc/hexanes) to furnish **6** in moderate yield (0.44 g, 60%); ^{1}H-NMR ($CDCl_3$): δ 8.25 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.94 (dd, *J* = 7.7, *J'* = 1.4 Hz, 1H, Ar-*H*), 7.58-7.75 (m, 4H, Ar-*H*), 7.52 (bt, *J* = 7.5 Hz, 1H, Ar-*H*), 7.32 (bd, *J* = 7.5 Hz, 1H, Ar-*H*), 4.21 (bd, *J* = 7.4 Hz, 1H, NC*H*), 3.79 (m, 1H, NC*H*H), 3.53 (m, 1H, NCH*H*), 2.41 (m, 1H, NCHC*H*H-), 1.91 (m, 2H, CH*H*), 1.73 (m, 1H, C*H*H); ^{13}C NMR ($CDCl_3$): δ 171.8, 167.4, 165.1, 144.9, 134.7, 134.22, 133.3, 132.1, 131.46, 129.9, 129.6, 1299, 128.9, 126.4, 124.2, 59.9, 46.5, 26.1, 23.5.

General Procedure for the Synthesis of Quinazolinobenzodiazepines 1, 2, and 8a-h

Freshly prepared *o*-nitrobenzoyl chloride (1.0 eq., 2 mmol) in CH_2Cl_2 (3.0 mL) was added drop-wise to a solution of benzodiazepindione **4** (1.0 eq., 2 mmol) in dry CH_2Cl_2 (50 mL) containing triethylamine (1.3 eq., 2.6 mmol) and catalytic of DMAP. The mixture was stirred at rt for 3 h, and then the reaction mixture was concentrated, passed through a short pad of silica gel and directly used in the next step without further purification. The reduction was carried out using hydrogen gas in the presence of 10% Pd/C as catalyst (25% wt/sample wt) for 3 h. After reduction was complete, as observed TLC monitoring, the reaction mixture was filtered through

celite, concentrated and purified by column chromatography on silica gel (25-45% EtOAc/hexanes) to furnish target compounds **1**, **2** and **8a-h** with 53-75% yields over the two steps.

Asperlicin C (1). mp 273-275 ºC. IR (KBr, cm^{-1}): 3370, 3155, 3051, 2913, 1674, 1618, 1452. ^{1}H-NMR ($CDCl_3$): δ 8.34 (bd, *J* = 7.7 Hz, 1H, Ar-*H*), 8.10 (bs, 1H, indole N*H*), 7.81-7.91 (m, 3H, Ar-*H*), 7.49-7.64 (m, 5H, Ar-*H*), 7.37 (bd, *J* = 8.0 Hz, 1H, Ar-***H***), 7.23 (bd, *J* = 2.4 Hz, 1H, Ar-*H*), 7.20 (m, 1H, Ar-*H*), 7.10 (m, 1H, Ar-*H*), 6.38 (bd, *J* = 6.0 Hz, 1H, N*H*), 4.56 (dt, *J* = 8.3, *J*' = 6.0 Hz, 1H, HNC*H*CON), 3.84 (dd, *J* = 15.3, *J*' = 6.0 Hz, 1H, -C*H*H-indole), 3.53 (dd, *J* = 15.3, *J*' = 6.0 Hz, 1H, -CH*H*-indole). ESI-MS: m/z 407 $[M+H]^+$. [21,22,30,32]

Circumdatin H (2). mp. 198-201 ºC. IR (KBr, cm^{-1}): 3065, 2975, 1680, 1653, 1611, 1597, 1493, 1459, 1417, 1362, 1272, 1244, 1078, 1023, 836. ^{1}H-NMR ($CDCl_3$): δ 8.00 (dd, *J* = 7.2, *J*' = 1.1 Hz, 1H, Ar-*H*), 7.68 (d, *J* = 2.9 Hz, 1H, Ar-*H*), 7.65 (d, *J* = 8.9 Hz, 1H, Ar-*H*), 7.50-7.60 (m, 3H, Ar-*H*), 7.38 (dd, *J* = 8.9, *J*' = 2.9 Hz, 1H, Ar-*H*), 4.54 (dd, *J* = 7.9, *J*' = 1.5 Hz, 1H, NC*H*-), 3.93 (s, 3H, -OC***H₃***), 3.79 (m, 1H, NC*H*H-), 3.62 (ddd, *J* = 12.1, *J*' = 9.7, *J*'' = 7.2 Hz, 1H, NCH*H*-), 3.16 (m, 1H, NCH-C*H*H-), 2.32 (m, CH*H*, 1H), 2.17 (m, CH*H*), 2.08 (m, 1H, C*H*H). ^{13}C NMR ($CDCl_3$): δ 164.9, 162.1, 159.4, 151.9, 141.0, 133.8, 132.8, 131.1, 130.3, 129.6, 129.1, 128.8, 125.3, 122.7, 107.3, 59.2, 56.3, 46.9, 27.4, 24.1. ESI MS: m/z 348 $[M+H]^+$.[31]

Circumdatin E Analogue (8a). mp 228-230 ºC. IR (KBr, cm^{-1}): 2975, 1687, 1639, 1611, 1466, 1403, 767. ^{1}H-NMR ($CDCl_3$): δ 8.30 (dd, *J* = 7.8, *J*' = 1.5 Hz, 1H, Ar-*H*), 7.99 (m, 1H, Ar-*H*), 7.78 (m, 1H, Ar-*H*), 7.70 (bd, *J* = 8.1 Hz, 1H, Ar-*H*), 7.48-7.60 (m, 4H, Ar-*H*), 4.54 (dd, *J* = 7.9, *J*' = 1.4 Hz, 1H, NC*H*CO), 3.79 (m, 1H, NC*H*H-), 3.60 (ddd, *J* = 12.1, *J*' = 9.7, *J*'' = 7.2 Hz, 1H, NCH*H*-), 3.17 (m, 1H, NCH-CH*H*), 2.31 (m, 1H, NCH-C*H*H), 2.02-2.20 (m, CH_2, 2H). ^{13}C NMR ($CDCl_3$): δ 164.6, 161.8, 153.8, 146.3, 134.9, 133.4, 132.5, 130.9, 130.1, 128.8, 128.5, 127.6, 127.7, 127.6, 121.7, 59.0, 46.7, 27.2, 23.8. ESI-MS: m/z 318 $[M+H]^+$.[31]

Circumdatin E Analogue (8b). mp.240-241 ºC. IR (KBr, cm^{-1}): 3086, 2954, 1687, 1646, 1611, 1590, 1556, 1459, 1417; ^{1}H-NMR ($CDCl_3$): δ 8.24 (d, *J* = 8.5 Hz, 1H, Ar-H), 8.00 (bd, *J* = 7.7 Hz, 1H, Ar-H), 7.73 (d, *J* = 1.9 Hz, 1H, Ar-H), 7.51-7.62 (m, 4H, Ar-H), 7.48 (dd, *J* = 8.5, *J*' = 1.9 Hz, 1H, Ar-H), 4.54 (bd, *J* = 7.7 Hz, 1H, NC*H*CO), 3.80 (m, 1H, NC*H*H-), 3.61 (m, 1H, NCH*H*-), 3.14 (m, 1H, NCH-C*H*H-), 2.31 (m, 1H), 2.04-2.20 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 164.6, 161.3, 155.2, 147.3, 141.3, 133.1, 132.5, 131.1, 130.2, 129.2, 129.1, 128.4, 128.4, 127.4, 120.2, 59.1, 46.8, 27.2, 23.9. EIS-MS: m/z 352 $[M+H]^+$.

Circumdatin Analogue (8c). mp 234-235 ºC. IR (KBr, cm^{-1}): 3079, 2933, 1736, 1687, 1646, 1597, 1493, 1452, 1369, 1244, 1057, 1023, 725. ^{1}H-NMR ($CDCl_3$): δ 8.02 (d, *J* = 7.3 Hz, 1H, Ar-*H*), 7.53-7.69 (m, 5H, Ar-*H*), 7.39 (dd, *J* = 8.8, *J*' = 2.9 Hz, 1H, Ar-*H*), 5.55 (m, 1H, C*H*O_2CMe), 4.72 (dd, *J* = 8.2, *J*' = 5.4 Hz, 1H, NC*H*CO), 3.98 (bd, *J* = 13.3 Hz, 1H, NC*H*H-), 3.93 (s, 3H, -OC***H₃***), 3.77 (dd, *J* = 13.3, *J*' = 5.2 Hz, 1H, NCH*H*-), 3.69 (dt, *J* = 14.1, *J*' = 5.6 Hz, 1H, -NCH-CH*H*-), 2.33 (m, 1H), 2.07 (s, 3H, -O_2CC***H₃***). ^{13}C NMR ($CDCl_3$): δ 170.4, 164.8, 161.5, 159.2, 150.5, 140.3, 133.3, 131.5, 131.0, 130.1, 129.3, 128.9, 128.5, 125.00, 122.4, 107.0, 71.8, 57.4, 55.9, 51.0, 32.4, 21.1. ESI-MS: m/z: 406 $[M+H]^+$, 428 $[M+Na]^+$.

10-Chloro[7S-(isobutyl)-6,7-dihydroquinazolino[3,2-a][1,4]benzodiazepine-5,13-dione] (5d). mp 227-229 ºC, FTIR (KBr, cm^{-1}). 2940, 1700, 1666, 1597, 1459, 1385. ^{1}H-NMR ($CDCl_3$): δ 8.14 (1H, d, *J* = 8 Hz, Ar-*H*), 7.89 (1H, d, *J* = 8 Hz, Ar-*H*), 7.64 (1H, d, *J* = 2 Hz, Ar-*H*), 7.48-7.60 (3H, m Ar-*H*), 7.38, (1H, dd, *J* = 9, *J*' = 2 Hz, Ar-*H*), 6.07 (1H, d, *J* = 6 Hz, N*H*), 4.12 (1H, dt, *J* = 8, *J*' = 6 Hz, C*H*), 2.06 (1H, m, C*H*), 1.85 (2H, m, CH_2), 0.91 (3H, d, *J* = 6 Hz, CH_3), 0.82 (3H, d, *J* = 6 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 168.0, 161.2, 156.1, 147.4, 141.3, 133.3, 131.6, 130.6, 130.0, 129.0, 128.4, 128.3, 127.5, 120.1, 52.7, 38.20, 24.6, 23.2, 22.2. EI-MS: m/z 368.3 $[M+H]^+$.

11-Chloro[7S-(isobutyl)-6,7-dihydroquinazolino[3,2-a][1,4]benzodiazepine-5,13-dione] (8e). mp 268-269 ºC. FTIR (KBr, cm^{-1}), 3079, 2968, 1701, 1666, 1618, 1466, 1390. ^{1}H-NMR ($CDCl_3$): δ 8.12 (1H, d, *J* = 2, Ar-*H*), 7.88 (1H, dd, *J* = 8.2, Ar-*H*), 7.46-7.63 (5H, m, Ar-*H*), 7.03 (1H, d, *J* = 7Hz, Ar-*H*), 4.11 (1H, dt, *J* = 9, *J*' = 6 Hz, C*H*), 2.03 (1H, m, C*H*), 1.87 (2H, m, CH_2), 0.92 (3H, d, *J* = 7 Hz, CH_3), 0.80 (3H, d, *J* = 7 Hz,CH_3). ^{13}C NMR ($CDCl_3$): δ 168.3, 160.8, 155.2, 144.8, 135.3, 133.6, 133.4, 131.6, 130.7, 130.0, 129.5, 129.3, 128.4, 126.8, 122.6, 52.5, 38.1, 24.5, 23.2, 22.1.

Methyl [(7S)-6,7-dihydroquinazolino[3,2-a][1,4]benzodiazepine-5,13-dione]-7-yl-propanoate (8f). mp 213-215 ºC. FTIR (KBr, cm^{-1}): 2920, 1735, 1700, 1657, 1454, 1381. ^{1}H-NMR ($CDCl_3$)**:** δ 8.32 (1H, d, *J* = 8 Hz, Ar*H*), 7.52-7.8 (6H, Ar*H*), 7.98 (1H,d, *J* = 7 Hz, Ar*H*), 7.1 (1H, d, *J* = 6 Hz, N*H*), 4.30 (1H, dd, *J* = 13, *J*' = 6 Hz, C*H*), 3.68 (3H, s, OCH_3), 2.40 (1H, m, CH_2)**,** 2.66 (3H, m, CH_2). ^{13}C NMR ($CDCl_3$): δ 173.5, 168.1, 161.7, 154.2, 146.3, 134.9, 133.3, 131.4, 130.4, 130.0, 129.0, 128.4, 127.8, 127.7, 127.5, 121.9, 53.6, 51.9, 30.1, 24.9. ESI-MS: m/z 364 $[M^+]$. Anal. Calcd. for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.56% Found: C, 65.77; H, 5.21; N, 10.75%.

11-Methoxy[methyl [(7S)-6,7-dihydroquinazolino[3,2-a][1,4] benzodiazepine-5,13-dione]-7-yl-Propanoate] (8g). M.p.214-215 ºC. FTIR (KBr, cm^{-1}): 2928, 1735, 1692, 1666, 1493, 1381, ^{1}H-NMR ($CDCl_3$): 7.95 (1H, d, *J* = 7 Hz, Ar-*H*), 7.53-7.68 (5H, Ar-*H*), 7.38 (1H, dd, *J* = 9, *J*' = 3 Hz, Ar-*H*), 6.79 (1H, dd, *J* = 6, *J*' = 3 Hz), 4.29 (1H, dt, *J* = 13, *J*' = 6 Hz, C*H*), 3.91 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 2.56 (3H, m, CH_2), δ 2.39 (1H, m, CH_2). ^{13}C NMR ($CDCl_3$): δ 173.6, 168.2, 161.6, 159.4, 152.1, 140.7, 133.6, 131.5, 130.6, 130.1, 129.5, 129.1, 125.2, 122.7, 107.1, 56.1, 53.3, 52.3, 30.2, 24.7. ESI-MS: m/z 426 [M+Na]. Anal. Calcd. for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68% Found: C, 64.67; H, 5.21; N, 10.12%.

11-Chloro [methyl [(7S)-6,7-dihydroquinazolino[3,2-a][1,4] benzodiazepine-5,13-dione]-7-yl-propanoate] (8h). mp 206-207 ºC. FTIR (KBr, cm^{-1}), 2933, 1729, 1666, 1625, 1466, 1383. ^{1}H-NMR ($CDCl_3$): δ 8.28 (1H, d, *J* = 2 Hz, Ar-*H*), 7.97 (1H, d, *J* = 8 Hz, Ar-*H*), 7.74 (1H, dd, *J* = 9, *J*' = 2 Hz), 7.55-7.69 (4H, Ar-*H*), 6.43 (1H, d, *J* = 6 Hz, Ar-*H*), 4.32 (1H, dd, *J* = 13, *J*'=6 Hz, C*H*), 3.69 (3H, s, OCH_3), 2.53-2.74 (3H, m, CH_2), 2.40 (1H, m, CH_2). ^{13}C NMR ($CDCl_3$): δ 173.6, 167.6, 160.7, 154.4, 144.7, 135.5, 133.8, 133.1, 131.7, 130.5, 130.2, 129.6, 129.5, 128.4, 127.1, 122.8, 53,6, 52.1, 30.3, 24.6. ESI-MS: m/z 398 $[M+H]^+$. Anal. Calcd. for $C_{20}H_{16}N_3O_4Cl$: C, 60.38; H, 4.05; N, 10.56% Found: C, 61.81; H, 4.38; N, 10.88%.

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