

Synthesis of aromatic and heteroaromatic annelated [1,4]diazepines

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Dedicated to Professor R.A. Abramovitch on the occasion of his 70th birthday

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Abstract

4-Chlor-3-coumarincarbaldehyde **2** or 4-azido-3-coumarincarbaldehyde **3** are converted into 1,4-benzodiazepines **9–12** by nucleophilic substitution with diamines **4–7** and subsequent cyclization with good yields. Following the same methodologies, carbaldehydes **2** or **3** when treated with 2-aminophenol **8** afforded 4-(2'-hydroxyphenyl)-amino-3-coumarincarbaldehyde **13** in good yields.

Keywords: Annelated [1,4]diazepines 4-substituted-3-coumarincarbaldehyde, diamines, 2-aminophenol

Introduction

1,4-Benzodiazepines have been the object of intense studies since the early 1960s because of their value in psychotherapy. An impressive number of synthetic routes have thus been described.¹ Recently the attention has been concentrated on the synthesis of analogs having heterocycles in place of the benzene ring and on compounds having additional fused heterocyclic rings.

Our target was the synthesis of new compounds possessing 7-membered rings with two heteroatoms a 1,4-diazepines and 1,4-oxazepines having fused heterocyclic ring of coumarin such as **9–12** as depicted in figure 1 and 6-oxo-benzo[*b*]benzopyrano[3,4-*f*][1,4]oxazepine **15** (Figure 1, Scheme 2).

Two methods were used for the preparation **9–12**:

- a first one involving the transformation of 4-chloro compound **2** into 4-azido-3-coumarincarbaldehyde **3**, its reaction with *o*-arylenediamines **4–7** and subsequent cyclisation

(method A),

- an alternative one by reacting directly the 4-chloro-3-coumarincarbaldehyde **2** with the same *o*-arylenediamines **4–7**, followed by ring closure to get 1,4-diazepines **9–12** (method B).

Results and Discussion

The compound **2** was prepared from 4-hydroxycoumarin **1** under Vilsmeier conditions (POCl₃/DMF). We studied three procedures described in the literature: chloroformylation of **1** carried out with an equimolecular mixture of POCl₃ and DMF in trichlorethylene (yield = 97%)² or in chloroform (65%)³ or in a mixture of POCl₃ and excess of DMF (85%).⁴

Literature^{2,4} claims high yields of carbaldehyde **2** and 4-chlorocoumarin without any indication of their ratio. Steinführer and al.³ proved that the reaction mixture contained a mixture of 4-chloro-3-coumarincarbaldehyde **2** (65%) with 4-chlorocoumarin as a side product (20%). After further optimization, we could obtain up to 72% of the carbaldehyde **2**, the undesired chlorocoumarin having been easily separated inside Soxhlet apparatus.

We prepared 4-azido-3-coumarincarbaldehyde **3** from the 4-chloro-3-coumarincarbaldehyde **2** by reaction with NaN₃ in aqueous acetone. In comparable reaction times, we could at room temperature achieve better yields (up to 87%) than those described in the literature.³ The compounds **3** could be separated from the reaction mixture by simple filtration.

Steinführer and coll.³ presented 4-azido-3-coumarincarbaldehyde **3** as an useful starting material for synthesis of a variety heterocycle-fused coumarins, i. e. for the preparation of the product **9** (36%).

The reaction between azidocarbaldehyde **3** and diamines **4–7** was tested as possible route to the title 1,4-diazepines **9–12**. Under reaction conditions described in literature³ (DMF, 4 h, method A), followed by column chromatography and crystallization from acetonitrile, pure compounds **9–12** were obtained (Scheme 1).

We carried out the preparation of derivatives **9–12** starting from 4-chloro-3-coumarincarbaldehyde **2**, and treating it successively with diamines **4–7** under mild basic conditions (triethylamine in ethanol, method B). Method B (one step shorter than method A) leads to satisfactory yields of derivatives **9–12**. When diamine **4** reacted with carbaldehyde **2** an intermediate **16** could be isolated.

TLC was used to monitor the progress of the reaction, the structures of products were assessed by MS, IR and/or NMR method. The spectroscopic data MS, IR and ¹H-NMR are in agreement with the structure of 4-chlorocoumarin.⁵

The reaction with 2-aminophenol **8** is a possible route to get the 1,4-oxazepine ring. The reaction failed to deliver the desired product **15**, since the aminophenol **8** replaced the chlorine atom or azido group, giving access to **13** instead of the desired oxygen-bridged product **15** (Scheme 2).

In conclusion, new practical and efficient synthetic methodology of preparation of 6-oxo-

13H-benzo[*b*]benzopyrano[3,4-*f*][1,4]diazepine **9**, 6-oxo-13H-10-methylbenzo[*b*]benzopyrano[3,4-*f*][1,4]diazepine **10**, 11-oxo-5H-benzopyrano[3,4-*f*]pyrido[3,2-*b*][1,4]diazepine **11**, 9-oxo-3H-benzopyrano[3,4-*f*]pyrido[3,4-*b*][1,4]diazepine **12** have been described. The products could be prepared in appreciable yields using method A and method B. Finally, this study has contributed to finding an efficient production of new compounds belonging to the family of substituted 1,4-diazepines.

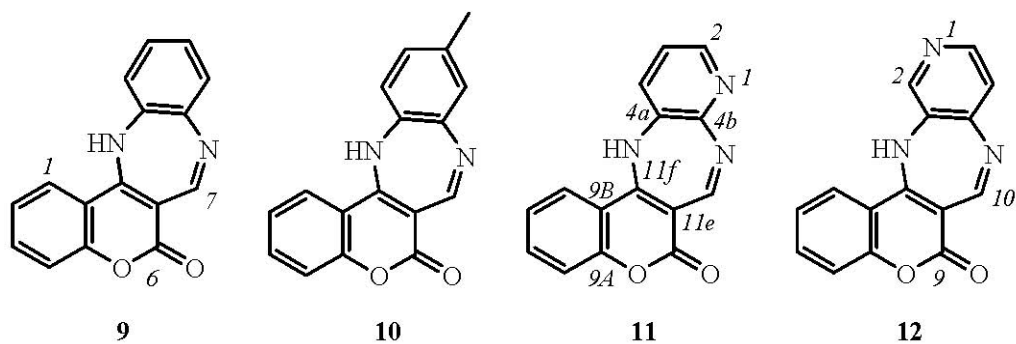
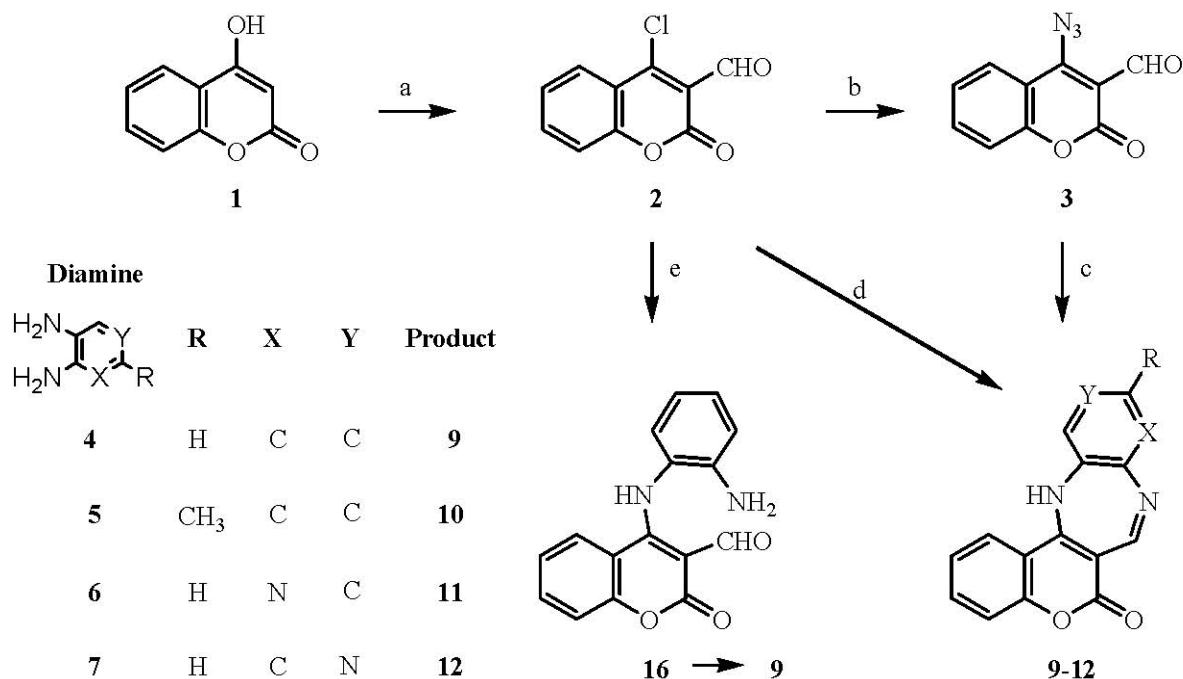
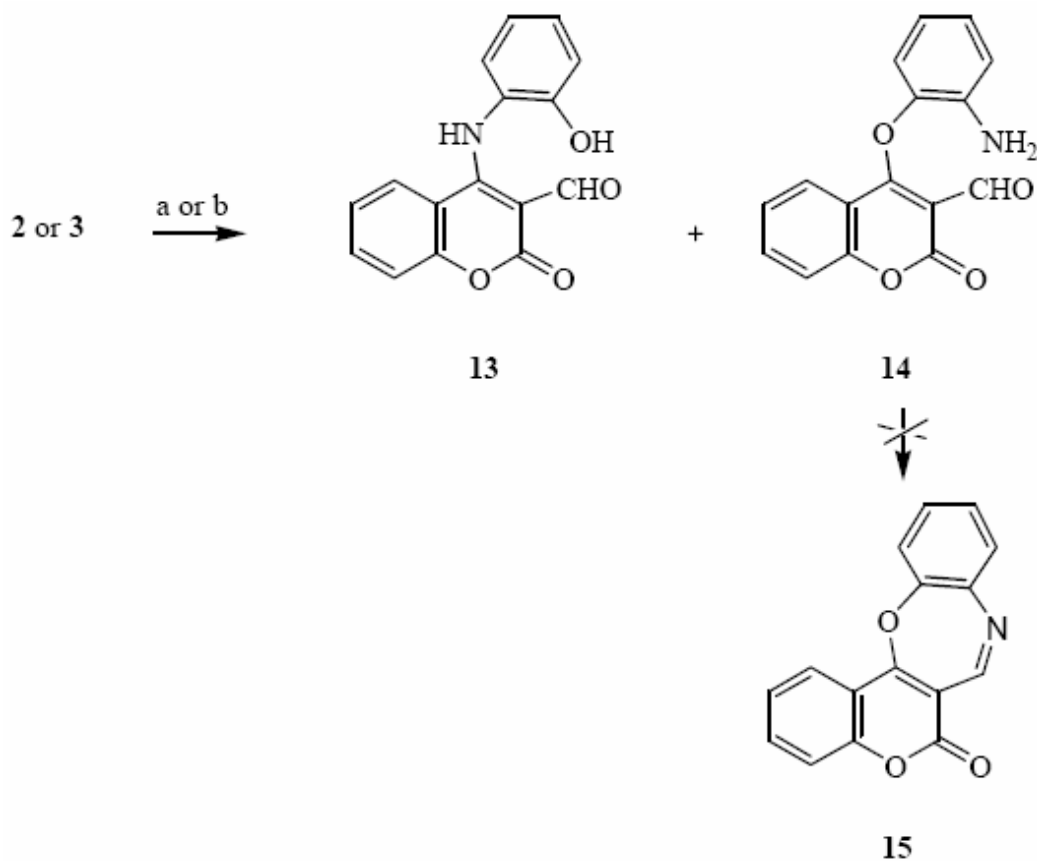


Figure 1



Scheme 1. (a) POCl₃/DMF; (b) NaN₃, acetone–water; (c) 4–7, DMF; (d) 4–7, Et₃N, EtOH, reflux, 3.5 h; (e) 4–7, Et₃N, EtOH, reflux, 1 h.



Scheme 2. (a) aminophenol **8**, DMF; (b) aminophenol **8**, Et₃N, EtOH, reflux, 3.5 h.

Table 1. Synthesis of substituted 1,4-diazepines **9–12** and 4-(2'-hydroxyphenyl)amino-3-coumarincarbaldehyde **13**

Diamine 4–7 / Hydroxyamine 8	Product	Yield (%)	Method	mp (°C)
4	9	68	A	239–243
		64	B	(lit. ³ 238–240)
5	10	81	A	243–246
		80	B	
6	11	57	A	235–238
		53	B	
7	12	52	A	239–243
		48	B	
8	13	81	A	190–192
		78	B	

Experimental Section

General Procedures. Flash chromatography was carried out on 0.04–0.063 mm (Merck) silica gel, thin layer chromatography was carried out on aluminium backed silica plates by Merck and plates were revealed using a UV 254 light. $^1\text{H-NMR}$ (300 MHz) and $^{13}\text{C-NMR}$ (75 MHz) spectra were recorded on a Varian VXR 300 instrument at 293 °K in CDCl_3 or DMSO *d*-6. Spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), some combinations of these were made by DEPT editing of the spectra. The IR-spectra were recorded on a Philips Analytical PU 9800 spectrometer. The MS-spectra were recorded on a AEI MS 902 S electron ionization spectrometer (EI = 70 eV). The elemental analyses were recorded on a Perkin–Elmer 2400 spectrometer.

Materials. The 4-hydroxycoumarin **1**, aromatic and heteroaromatic diamines **4–7** and 2-aminophenol **8** were purchased from Fluka, DMF were purified, dried and distilled over CaH₂ prior to use.

4-Chloro-3-coumarincarbalddehyde (2). To a stirred mixture of 4-hydroxycoumarin **1** (9.72 g, 0.06 mol) in anhydrous DMF (46.2 mL, 0.6 mol) were added dropwise POCl_3 (27.6 g, 0.18 mol) at -10° to -5°C . The reaction mixture was then stirred for 1 h at room temperature and heated and stirred for 2 h at 60°C . After the reaction completed, the mixture was poured onto crushed ice (200 g) under vigorous stirring. After storing the mixture overnight at 0°C the pale yellow solid was collected by filtration and washed successively with Na_2CO_3 (5%) and water, and then was air-dried. 4-chlorocoumarin **2a** (2.50 g, 20%) was separated by Soxhlet extraction as the second product. Recrystallization from acetone gave 8.99 g (72%) of **2** as a pale yellow powder with mp $115\text{--}120^\circ\text{C}$ (lit. 130°C ,² $125\text{--}127^\circ\text{C}$,³ $120\text{--}122^\circ\text{C}$); $^1\text{H-NMR}$ δ 10.39 (1H, s, CH=O), 8.19–7.40 (4H, m, ar-H); $^{13}\text{C-NMR}$ δ 186.81 (11-C), 158.44 (2-C), 153.28 (4-C), 153.27 (9-C), 135.68 (7-C), 127.65 (5-C), 125.56 (6-C), 118.39 (10-C), 118.22 (3-C), 117.20 (8-C); IR ν 2920, 2874, 1720, 1702, 1603, 1587, 1541 cm^{-1} ; MS *m/z*: 208 (MH^+ , 11), 182 (31), 180 (100), 154 (31), 152 (91), 124 (20), 101 (11), 89 (80), 63 (37), 62 (31), 61 (14), 39 (17), 36 (31), 32 (14), 28 (80).

4-Chlorocoumarin.⁵ $^1\text{H-NMR}$ δ 7.88–7.30 (4H, m, ar-H), 6.62 (1H, s, 3-H); IR ν 3098, 3069, 3040, 1754, 1721, 1611, 1603, 1449, 1348, 1273, 1177 cm^{-1} ; MS *m/z*: 182 (12), 180 (MH^+ , 40), 154 (16), 152 (52), 89 (44), 63 (24), 62 (16), 39 (10), 32 (20), 28 (100).

4-Azido-3-coumarincarbalddehyde (3). A solution of 4-chloro-3-coumarincarbalddehyde **2** (0.2 g, 1 mmol) in acetone (5 mL) was stirred and ice-cooled. The solution of NaN_3 (0.13 g, 2 mmol) in water (1 mL) was added dropwise in the solution and this mixture was stirred for 0.75 h at room temperature. After evaporation of acetone, the crude product was separated by filtration and recrystallized from dichloromethane. We have obtained 0.18 g (87%) of **3** as white solid with mp $122\text{--}130^\circ\text{C}$ (lit. ³ $120\text{--}130^\circ\text{C}$); $^1\text{H-NMR}$ δ 10.13 (1H, s, CH=O), 8.05–7.46 (4H, m, ar-H); $^{13}\text{C-NMR}$ δ 189.27 (11-C), 160.60 (2-C), 153.70 (4-C), 153.33 (9-C), 135.61 (7-C), 125.83 (5-C),

125.21 (6-C), 116.94 (8-C), 115.84 (10-C), 109.80 (3-C); IR ν 3071, 3047, 2170, 1716, 1674, 1525, 1485, 1359 cm^{-1} ; MS m/z : 215 (MH^+ , 7), 187 (78), 159 (12), 143 (39), 130 (12), 115 (39), 104 (22), 103 (100), 91 (12), 76 (56), 63 (24), 50 (17), 39 (17), 28 (22).

[1,4]Diazepines 9–12. General procedure A

4-azido-3-coumarincarbaldehyde **3** (0.2 g, 1 mmol) was suspended in 4 mL of DMF, then aromatic or heteroaromatic diamine **4–7** (1 mmol) was added. The mixture was stirred for 4 h at room temperature, then heated at 70 °C for 25 min and 110 °C for 10 min. After cooling the mixture was poured onto crushed ice, the precipitated [1,4]diazepines were filtered off, washed with water and dried. **General procedure B.** A mixture of 4-chlor-3-coumarincarbaldehyde **2** (0.2 g, 1 mmol), aromatic or heteroaromatic diamine **4–7** (1.1 mmol) and Et_3N (2 mmol) in 98 % EtOH (10 mL) was heated under reflux for 3.5 h. The reaction mixture was cooled and the formed solid was collected by filtration and dried.

6-Oxo-13H-benzo[*b*]benzopyrano[3,4-*f*][1,4]diazepine (9). Purification by column chromatography (SiO_2 , chloroform/acetonitrile 10:1) and recrystallization from acetonitrile gave the product **9** with mp 239–243 °C (lit.³ 238–240 °C) in the yield indicated in the Table 1; $^1\text{H-NMR}$ δ 9.28 (1H, s_{br} , 7-H), 8.34–6.09 (8H, m, ar-H); IR ν 3448, 3267, 3067, 1686, 1640, 1609, 1583, 1488, 1481, 1459, 1382 cm^{-1} ; MS m/z : 263 (23), 262 (MH^+ , 100), 261 (20), 234 (15), 233 (9), 206 (9), 205 (15), 179 (9), 39 (9), 28 (16). Anal. Calcd for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_2$: C, 73.28; H, 3.82; N, 10.69; O, 12.21. Found: C, 72.79; H, 3.91; N, 10.63; O, 12.01.

6-Oxo-13H-10-methylbenzo[*b*]benzopyrano[3,4-*f*][1,4]diazepine (10). Purification by column chromatography (SiO_2 , chloroform/acetonitrile 10:1) and recrystallization from acetonitrile gave the product **10** with mp 243–246 °C in the yield indicated in the Table 1; $^1\text{H-NMR}$ δ 9.32 (1H, s_{br} , 7-H), 8.04–6.87 (8H, m, ar-H), 2.25 (3H, s, CH_3); IR ν 3287, 3113, 1685, 1638, 1605, 1576, 1480, 1364 cm^{-1} ; MS m/z : 277 (18), 276 (MH^+ , 100), 275 (16), 247 (9), 44 (9). Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_2$: C, 73.91; H, 4.35; N, 10.14; O, 11.59. Found: C, 73.84; H, 4.46; N, 10.39; O, 11.78.

11-Oxo-5H-benzopyrano[3,4-*f*]pyrido[3,2-*b*][1,4]diazepine (11). Purification by column chromatography (SiO_2 , chloroform/acetonitrile 5:2) and recrystallization from acetonitrile gave the product **11** with mp 235–238 °C in the yield indicated in the Table 1; $^1\text{H-NMR}$ δ 9.43 (1H, s_{br} , NH), 7.89–6.73 (7H, m, ar-H), 6.75 (1H, s, 12-H); $^{13}\text{C-NMR}$ δ 162.10 (12-C), 161.47 (11-C), 159.74 (11f-C), 153.32 (9A-C), 149.55 (4b-C), 145.26 (2-C), 139.46 (8-C), 138.17 (4a-C), 133.66 (6-C), 125.55 (4-C), 124.04 (3-C), 123.98 (7-C), 120.19 (9B-C), 116.70 (9-C), 101.02 (11e-C); IR ν 3440, 3285, 3160, 3110, 1680, 1620, 1595, 1550, 1400, 1340 cm^{-1} ; MS m/z : 265 (12), 264 (35), 263 (MH^+ , 100), 262 (17), 236 (33), 235 (76), 234 (17), 208 (11), 206 (28), 179 (13), 117 (23), 104 (12), 89 (9). Anal. Calcd for $\text{C}_{15}\text{H}_9\text{N}_3\text{O}_2$: C, 68.44; H, 3.42; N, 15.96. Found: C, 68.21; H, 3.28; N, 15.99.

9-Oxo-3H-benzopyrano[3,4-*f*]pyrido[3,4-*b*][1,4]diazepine (12). Purification by column chromatography (SiO_2 , chloroform/acetonitrile 10:1) and recrystallization from acetonitrile gave

the product **12** with mp 239–243 °C in the yield indicated in the Table 1; $^1\text{H-NMR}$ δ 9.10 (1H, s_{br} , NH), 7.90–6.70 (8H, m, ar-H, 10-H); IR ν 3448, 3089, 1689, 1635, 1607, 1555, 1480 cm^{-1} ; MS m/z : 264 (21), 263 (MH^+ , 100), 262 (24), 236 (26), 235 (9), 234 (12), 206 (11), 89 (8), 76 (11), 63 (17), 51 (13), 50 (13), 41 (13), 39 (16), 28 (39). Anal. Calcd for $\text{C}_{15}\text{H}_9\text{N}_3\text{O}_2$: C, 68.44; H, 3.42; N, 15.96; O, 12.16. Found: C, 68.07; H, 3.59; N, 16.04; O 12.31.

4-(2'-Hydroxyphenyl)amino-3-coumarincarbaldehyde (13). The reaction of **2** or **3** with 2-aminophenol **8** in similar conditions to the general procedures A and B. Purification by column chromatography (SiO_2 , chloroform/acetonitrile 20:1) and recrystallization from acetonitrile gave the product **13** with mp 190–192 °C in the yield indicated in the Table 1; $^1\text{H-NMR}$ δ 12.76 (1H, s_{br} , OH), 10.30 (1H, s_{br} , N-H), 10.05 (1H, s, CH=O), 7.65-6.91 (8H, m, ar-H); $^{13}\text{C-NMR}$ δ 191.32 (11-C), 161.68 (2-C), 157.98 (4-C), 154.43 (9-C), 151.67 (2'-C), 135.00 (7-C), 129.58 (5-C), 126.78 (6-C), 126.38 (8-C), 125.38 (1'-C), 123.55 (6'-C), 119.96 (4'-C), 118.03 (3'-C), 116.85 (5'-C), 113.63 (10-C), 97.21 (3-C); IR ν 3485, 3400, 1720, 1686, 1657, 1630, 1613, 1563, 1501, 1450 cm^{-1} ; MS m/z : 281 (MH^+ , 62), 280 (100), 265 (12), 264 (55), 252 (43), 236 (10), 211 (14), 181 (14), 165 (8), 120 (10), 89 (12), 77 (10), 65 (14), 63 (14), 51 (10), 39 (17), 32 (14), 28 (64). Anal. Calcd for $\text{C}_{16}\text{H}_{11}\text{NO}_4$: C, 68.33; H, 3.94; N, 4.98. Found: C, 68.58; H, 3.99; N, 4.98.

4-(2'-Aminophenyl)amino-3-coumarincarbaldehyde (16). The product **16** was prepared according to a general procedure B in refluxing EtOH for 1 h. Recrystallization from chloroform–diethyl ether gave 0.22 g (84%) of the solid with mp 192–195 °C; $^1\text{H NMR}$ δ 10.28 (1H, s, NH), 10.05 (1H, s, CH=O), 7.70-6.91 (8H, m, ar-H); $^{13}\text{C NMR}$ δ 191.40 (11-C), 161.70 (2-C), 158.00 (4-C), 154.60 (9-C), 151.80 (2'-C), 135.20 (7-C), 129.80 (5-C), 127.00 (6-C), 126.50 (8-C), 125.60 (1'-C), 123.60 (6'-C), 120.10 (4'-C), 118.10 (3'-C), 117.00 (5'-C), 113.80 (10-C), 97.30 (3-C); IR ν 3421, 3234, 1728, 1707, 1619, 1565 cm^{-1} ; MS m/z : 281 (68), 280 (MH^+ , 100), 264 (56), 252 (44), 236 (9), 211 (16), 183 (9), 181 (15), 165 (9), 120 (9), 89 (12), 65 (15), 63 (12), 51 (9), 39 (15), 28 (62).

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