Synthesis of Novel 1,4-Benzodiazepine-3,5-dione Derivatives: Reaction of 2-Aminobenzamides under Bargellini Reaction Conditions

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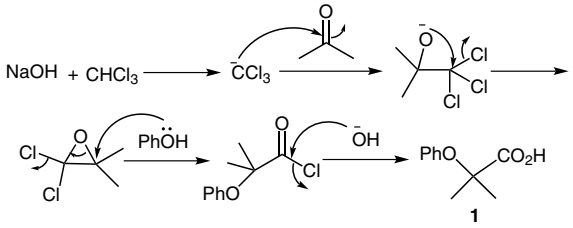
Abstract: In this paper, we report on a user-friendly synthesis of 1,4-benzodiazepine-3,5-dione derivatives via Bargellini-type reaction. The corresponding products were obtained using various 2-aminobenzamides under Bargellini reaction conditions, in good yields without unfavorable side reaction.

Key words: Bargellini-type reaction, 1,4-benzodiazepine-3,5-diones, 2-aminobenzamides, heterocycles, dichloro epoxide

The Bargellini reaction[1] in which phenol is condensed with acetone and chloroform in the presence of a strong base to produce a sterically hindered α-phenoxy-isobutric acid (**1**, Scheme 1), is a useful synthetic tool in organic synthesis and various nucleophiles and ketones have been employed in place of classic form.[2–6] In this manner, it has potentially been a constructive lead for the organic chemists. Preparation of griseofulvin analogues by Korger,[2] amino acids using sodium azide by Corey,[3] Butcher's report in the synthesis of druglike molecules utilizing diverse nucleophilic aromatic amines and cyclic ketones,[4] and Lai's synthesis of morpholine and morpholinone nitroxides[5] illustrate the importance of this reaction comprehensively.

Generally, in the Bargellini-type reaction dichloro epoxide intermediates are formed by the reaction of chloroform and ketones which are potentially active toward regioselective nucleophilic attacks (Scheme 1).



Scheme 1 Classic Bargellini reaction

However, studies of the Bargellini-type reactions are an important issue in the field of organic synthesis since this process provides an easy and diverse strategy for the synthesis of novel cyclic and acyclic compounds. Therefore, it presents practical and useful protocols in drug discovery processes and the total synthesis of natural products.

As a part of our current research on the development of novel synthetic routes toward new heterocycles particularly bioactive compounds,[7–11] we tried to outline an efficient approach to benzodiazepine derivatives. They were selected as our target compounds due to the effective biological properties and their use in wide range of medical applications.[12–14] Among various derivatives, 1,4-benzodiazepinediones have significant properties. They have been reported as potent antagonists of the HDM2-p53 interaction in vitro and in cell-based assays.[15]Also various reports proved that they possess anticonvulsant, anxiolytic, and antitumor properties, and are effective cholecystokinin receptor (CCK), opiate receptor, and also platelet glycoprotein IIb-IIIa antagonists.[16–18]

Despite the fact that frequent 1,4-benzodiazepine-2,5-dione derivatives have been synthesized and tested for the bioactivity properties,[15,19–21] only a few reports for the synthesis of 1,4-benzodiazepine-3,5-diones are found in the literature (**2**–**5**, Figure 1).[22–24] One of the earliest synthesis of 1,4-benzodiazepine-3,5-dione derivative was reported by Gärtner[22] through three steps from anthranilic acid using CCl_3CHO, $PhNHNH_2$, and Ac_2O (**3**, Figure 1).

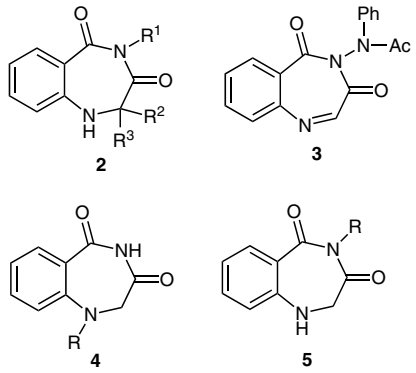


Figure 1 General structure of 1,4-benzo[*e*][1,4]diazepine-3,5-dione derivatives **2**; the first reported 1,4-benzodiazepine-3,5-dione **3**[22] and 1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-diones **4** and **5**[23]

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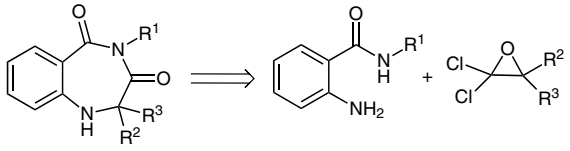
Recently, some 1*H*-1,4-benzodiazepine-3,5(2*H*,4*H*)-diones (**4** and **5**, Figure 1), were prepared from *N*-carbamoylmethylanthranilic acids by Wiklund et al.[23] It was discovered that for a successful synthesis, substituted starting materials with electron-withdrawing groups are required.



Scheme 2 Suggested retrosynthetic analysis of 1,4-benzodiazepine-3,5-diones

Therefore, there is a strong demand for the development of new syntheses of these scaffolds and investigation of their biological properties.

To obtain the 1,4-benzodiazepine-3,5-dione derivatives, a retrosynthetic analysis to title compound was outlined in Scheme 2. As can be seen in Scheme 2, a feasible strategy in which compounds can be prepared by the reaction of ambident nucleophiles and epoxides via the Bargellini reaction is suggested.

So we focused on this route and expanded the Bargellini reaction using 2-aminobenzamides **10** as efficient bident nucleophiles to report the successful synthesis of novel 1,4-benzodiazepine-3,5-dione derivatives **11** (Scheme 3). We realized that compounds **10** react easily with dichloro epoxide intermediates (generated by the reaction of chloroform and acetone–ethyl methyl ketone in the presence of NaOH) to produce the lead benzodiazepinediones **11**.

It is worthwhile to mention that all 2-aminobenzamide derivatives **10** were synthesized by a simple and green procedure. An equivalent amount of isatoic anhydride **9** and amines **8** were reacted in water at room temperature for two hours. After this time the precipitated products were filtered and dried. The obtained 2-aminobenzamides were completely pure and used for further reactions.

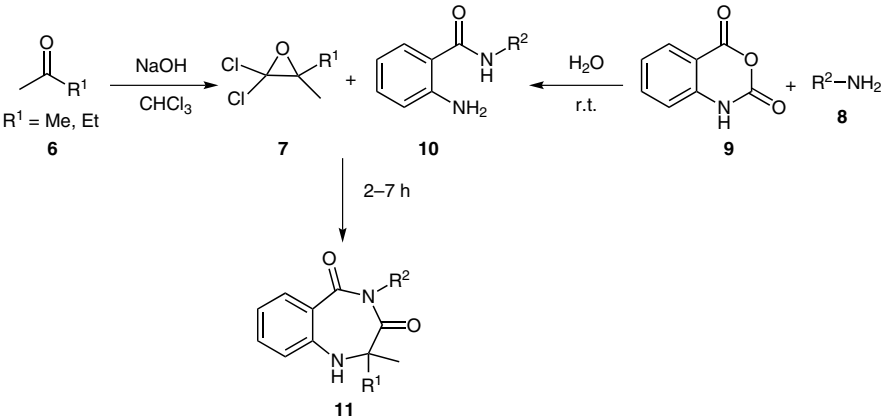
Our experiments initiated by the reaction of chloroform (60 mmol) and dried acetone (40 mmol) in the presence of sodium hydroxide (60 mmol) at room temperature. After a few minutes as we expected 2,2-dichloro-3,3-dimethyloxirane was formed when a white emulsion was appeared. At this step 2-amino-*N*-benzylbenzamide (2 mmol) was added to the resulting mixture and the reaction continued at the same temperature. After three hours the corresponding seven-membered heterocycle **11c** (Table 1, entry 1) was formed in a good yield (80%). The combination of all analytical information confirmed the given structure **11c**.[25]

The six protons of two methyl groups show a chemical shift of δ = 1.35 ppm. The existence of NCH_2 protons is elucidated by the signal at lower field (δ = 5.03 ppm). Nine aromatic protons are found at δ = 7.03–7.99 ppm. The presence of a signal related to the NH group at δ = 6.80 ppm provides further evidence for the formation of a benzodiazepine. Fifteen distinct resonances were observed in ^{13}C NMR spectroscopy. Signals at δ = 23.3, 48.5 and 56.5 confirmed the presence of methyl, methylene, and quaternary aliphatic carbon, respectively. Ten aromatic carbons were observed between δ = 116.4 and 145.8 ppm. Two signals at δ = 167.6 and 176.4 ppm belong to two amide carbonyl groups.

As shown in Table 1, we then investigated reaction of various 2-aminobenzamides under the same condition as described above.[25] All the reactions were achieved efficiently and no other side products were observed.

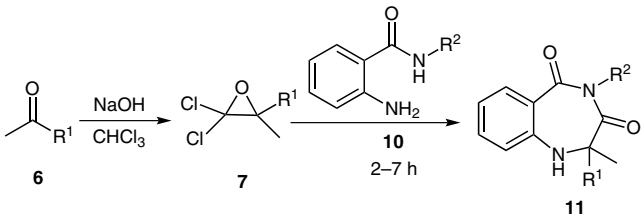
In the next step we continued our investigation using ethyl methyl ketone instead of acetone and followed the similar reactions (Table 1, entries 2, 4, 6, 8, and 10). As reported in Table 1, good results were obtained, and no remarkable difference was observed in the yield, reaction time, and reactivity. All products were stable and characterized by IR, ^1H NMR, and ^{13}C NMR spectroscopy and mass spectrometry.[22]

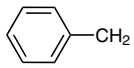
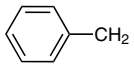
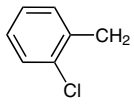
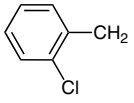
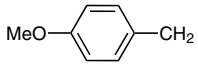
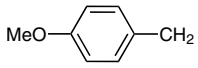
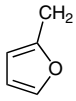
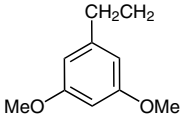
In summary, we have found that 2-aminobenzamides can react as efficient nucleophiles in the Bargellini reaction to prepare potentially bioactive 1,4-benzodiazepine-3,5-dione derivatives. This procedure, in which products are obtained in good yields, can be an important alternative for the synthesis of 1,4-benzodiazepine-3,5-diones.



Scheme 3 Synthesis of 1,4-benzodiazepine-3,5-diones via Bargellini-type reaction

Table 1 Synthesis of 1,4-Benzodiazepine-3,5-dione Derivatives **11**



Entry	R^1	R^2	Product	Time (h)	Yield (%)[a]
1	Me	H	**11a**	2	85
2	Et	H	**11b**	2	85
3	Me		**11c**	3	80
4	Et		**11d**	3	75
5	Me		**11e**	3	82
6	Et		**11f**	3	75
7	Me		**11g**	4	75
8	Et		**11h**	4	70
9	Me		**11i**	6	65
10	Et		**11j**	7	60
11	Me		**11k**	4	70

[a] Isolated yields.

Acknowledgment

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(25) **Synthesis of 1,2-Dihydro-4*H*-benzo[*e*][1,4]diazepine-3,5-dione Derivatives – General Procedure**
A mixture of anhydrous acetone–ethyl methyl ketone (40 mmol, 3 mL) and $CHCl_3$ (60 mmol, 4.6 mL) in the presence of NaOH powder (60 mmol, 2.3 g) was stirred at r.t. for 10 min (in the case of ethylmethyl ketone it should be stirred for 15 min). After this time, 2-aminobenzamide derivatives (2 mmol) were added to the reaction mixture and it continued for the corresponding time, as indicated in Table 1, at the same temperature. Upon completion of reaction the solution was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to yield the crude product which was purified by column chromatography eluting with PE–EtOAc (6:1).
1,2-Dihydro-2,2-dimethyl-4*H*-benzo[*e*][1,4]diazepine-3,5-dione (11a)
Yield 0.17 g (85%); white crystals; mp 228–230 °C. IR

(KBr): 3337 (NH), 1698 (C=O), 1636 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.48 (s, 6 H, CH_3), 4.11 (s, 1 H, NH), 6.78 (d, *J* = 7.6 Hz, 1 H, H_9), 7.02 (t, *J* = 7.6 Hz, 1 H, H_7), 7.40 (td, *J* = 7.6, 1.4 Hz, 1 H, H_8), 8.20 (dd, *J* = 7.6, 1.4 Hz, 1 H, H_6), 8.11 (s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.5, 56.5, 116.8, 118.6, 120.0, 131.8, 134.0, 146.8, 165.0, 173.6. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.80; H, 6.10; N, 13.55.

2-Ethyl-1,2-dihydro-2-methyl-4*H*-benzo[*e*][1,4]diazepine-3,5-dione (11b)

Yield 0.18 g (85%); white crystals; mp 160–162 °C. IR (KBr): 3359 (NH), 1698 (C=O), 1645 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.48 (s, 3 H, CH_3), 1.75 (dq, *J* = 14.8, 7.4 Hz, 1 H, CH_2CH_3), 1.80 (dq, *J* = 14.8, 7.4 Hz, 1 H, CH_2CH_3), 4.16 (s, 1 H, NH), 6.79 (d, *J* = 7.5 Hz, 1 H, H_9), 7.00 (t, *J* = 7.5 Hz, 1 H, H_7), 7.40 (dt, *J* = 7.5, 1.3 Hz, 1 H, H_8), 8.19 (dd, *J* = 7.5, 1.3 Hz, 1 H, H_6), 8.21 (s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.5, 22.7, 27.9, 60.8, 120.3, 120.6, 133.1, 134.8, 145.5, 164.3, 173.8. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.90; H, 6.55; N, 12.99.

4-Benzyl-1,2-dihydro-2,2-dimethyl-4*H*-benzo[*e*][1,4]-diazepine-3,5-dione (11c)

Yield 0.23 g (80%); white crystals; mp 100–102 °C. IR (KBr): 3335 (NH), 1698 (C=O), 1650 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.35 (s, 6 H, CH_3), 5.03 (s, 2 H, NCH_2), 6.80 (s, 1 H, NH), 6.99–7.05 (m, 2 H, H_9, $H_{4'}$), 7.17–7.19 (m, 3 H, H_7, $H_{2'}$, $H_{6'}$), 7.27–7.37 (m, 3 H, H_8, $H_{3'}$, $H_{5'}$), 7.98 (d, *J* = 7.2 Hz, 1 H, H_6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.3, 48.5, 56.5, 116.4, 117.9, 119.1, 126.7, 126.9, 128.2, 132.2, 133.9, 138.2, 145.8, 167.6, 176.4. Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.30; H, 6.40; N, 10.21.

4-Benzyl-2-ethyl-1,2-dihydro-2-methyl-4*H*-benzo[*e*]-[1,4]diazepine-3,5-dione (11d)

Yield 0.23 g (75%); white crystals; mp 134–136 °C. IR (KBr): 3467 (NH), 1695 (C=O), 1641 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.46 (s, 3 H, CH_3), 1.77–1.83 (m, 2 H, CH_2CH_3), 4.53 (s, 1 H, NH), 5.13 (d, *J* = 15.7 Hz, 1 H, NCH_2), 5.31 (d, *J* = 15.7 Hz, 1 H, NCH_2), 6.77 (d, *J* = 8.1 Hz, 1 H, H_9), 6.89 (t, *J* = 7.5 Hz, 1 H, H_7), 6.98–7.00 (m, 1 H, $H_{4'}$), 7.06–7.11 (m, 2 H, $H_{2'}$, $H_{6'}$), 7.29–7.39 (m, 3 H, H_8, $H_{3'}$, $H_{5'}$), 8.11 (d, *J* = 7.5 Hz, 1 H, H_6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.4, 20.3, 28.3, 47.1, 61.2, 118.1, 119.0, 119.6, 126.5, 126.8, 127.7, 129.2, 132.6, 133.2, 134.2, 134.9, 144.7, 167.5, 173.7. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.80; H, 6.35; N, 9.30.

4-(2-Chlorobenzyl)-1,2-dihydro-2,2-dimethyl-4*H*-benzo[*e*][1,4]diazepine-3,5-dione (11e)

Yield 0.27 g (82%); yellow crystals; mp 130–132 °C. IR (KBr): 3338 (NH), 1697 (C=O), 1622 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.51 (s, 6 H, CH_3), 4.37 (s, 1 H, NH), 5.26 (s, 2 H, NCH_2), 6.76 (dd, *J* = 8.2, 1.0 Hz, 1 H, H_9), 6.95 (ddd, *J* = 8.2, 6.5, 1.1 Hz, 1 H, $H_{4'}$), 7.05 (t, *J* = 7.0 Hz, 1 H, H_7), 7.14–7.17 (m, 2 H, $H_{5'}$, $H_{6'}$), 7.34 (dd, *J* = 6.5, 3.0 Hz, 1 H, $H_{3'}$), 7.38 (ddd, *J* = 8.2, 7.0, 1.5 Hz, 1 H, H_8), 8.20 (dd, *J* = 7.0, 1.5 Hz, 1 H, H_6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.7, 47.3, 58.0, 118.4, 119.1, 119.9, 126.6, 127.0, 127.9, 129.4, 132.9, 133.5, 134.3, 135.1, 144.8, 167.6, 173.5. MS: *m/z* (%) = 330 (17) $[M + 2]^+$, 328 (51) $[M^+]$, 300 (20), 203 (25), 160 (100). 132 (85), 92 (28), 65 (20). Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52. Found: C, 65.90; H, 5.45; N, 8.40.

4-(2-Chlorobenzyl)-2-ethyl-1,2-dihydro-2-methyl-4*H*-benzo[*e*][1,4]diazepine-3,5-dione (11f)

Yield 0.26 g (75%); yellow crystals; mp 134–136 °C. IR (KBr): 3350 (NH) 1697 (C=O), 1623 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.49 (s, 3 H, CH_3), 1.80 (dq, *J* = 14.8, 7.4 Hz, 1 H, CH_2CH_3), 1.87 (dq, *J* = 14.8, 7.4 Hz, 1 H, CH_2CH_3), 4.50 (s, 1 H, NH), 5.19 (d, *J* = 15.7 Hz, 1 H, NCH_2), 5.36 (d, *J* = 15.7 Hz, 1 H, NCH_2), 6.77 (d, *J* = 8.0 Hz, 1 H, H_9), 6.92 (t, *J* = 7.5 Hz, 1 H, $H_{4'}$), 7.05 (t, *J* = 8.2 Hz, 1 H, H_7), 7.12–7.18 (m, 2 H, $H_{5'}$, $H_{6'}$), 7.32–7.39 (m, 2 H, H_8, $H_{3'}$), 8.16 (d, *J* = 8.2 Hz, 1 H, H_6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.5, 27.2, 47.2, 61.3, 119.1, 119.7, 126.6, 127.1, 127.8, 128.6, 129.0, 129.3, 132.8, 133.3, 134.2, 144.7, 167.5, 173.7. Anal. Calcd for $C_{19}H_{19}ClN_2O_2$: C, 66.57; H, 5.59; N, 8.17. Found: C, 66.80; H, 5.40; N, 7.95.

4-(4-Methoxybenzyl)-1,2-dihydro-2,2-dimethyl-4*H*-benzo[*e*][1,4]diazepine-3,5-dione (11g)

Yield 0.24 g (75%); white crystals; mp 120–122 °C. IR (KBr): 3329 (NH), 1694 (C=O), 1609 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 6 H, CH_3), 3.77 (s, 3 H, OCH_3), 4.42 (s, 1 H, NH), 5.12 (s, 2 H, NCH_2), 6.70 (d, *J* = 8.1 Hz, 1 H, H_9), 6.82 (d, *J* = 8.5 Hz, 2 H, $H_{3'}$, $H_{5'}$), 6.91 (t, *J* = 7.6 Hz, 1 H, H_7), 7.31–7.34 (m, 3 H, H_8, $H_{2'}$, $H_{6'}$), 8.20 (dd, *J* = 7.6, 1.4 Hz, 1 H, H_6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.4, 48.7, 55.1, 57.7, 113.6, 114.1, 118.4, 118.8, 119.4, 129.4, 130.2, 133.4, 134.0, 144.5, 158.5, 167.8, 173.0. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.50; H, 6.44; N, 8.80.

4-(4-Methoxybenzyl)-2-ethyl-1,2-dihydro-2-methyl-4*H*-benzo[*e*][1,4]diazepine-3,5-dione (11h)

Yield 0.24 g (70%); white crystals; mp 110–111 °C. IR (KBr): 3320 (NH), 1698 (C=O), 1617 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.71 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.47 (s, 3 H, CH_3), 1.67 (dq, *J* = 14.8, 7.4 Hz, 1 H, CH_2CH_3), 1.76 (dq, *J* = 14.8, 7.4 Hz, 1 H, CH_2CH_3), 3.76 (s, 3 H, OCH_3), 4.43 (s, 1 H, NH), 5.09 (d, *J* = 14.0 Hz, 1 H, NCH_2), 5.15 (d, *J* = 14.0 Hz, 1 H, NCH_2), 6.71 (d, *J* = 7.3 Hz, 1 H, H_9), 6.81 (d, *J* = 8.6 Hz, 2 H, $H_{3'}$, $H_{5'}$), 6.90 (t, *J* = 7.3 Hz, 1 H, H_7), 7.32 (dt, *J* = 7.3, 1.5 Hz, 1 H, H_8), 7.36 (d, *J* = 8.6 Hz, 2 H, $H_{2'}$, $H_{6'}$), 8.19 (dd, *J* = 7.3, 1.5 Hz, 1 H, H_6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.4, 23.1, 26.9, 48.7, 55.1, 60.9, 113.5, 118.3, 118.8, 119.3, 129.8, 130.2, 133.2, 134.0, 144.3, 158.5, 167.7, 173.1. MS: *m/z* (%) = 338 (76 $[M^+]$, 281 (20), 217 (20), 174 (59), 146 (52), 121 (100), 77 (25). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.15; H, 6.80; N, 8.35.

4-[(Furan-2-yl)-methyl]-1,2-dihydro-2,2-dimethyl-4*H*-benzo[*e*][1,4]diazepine-3,5-dione (11i)

Yield 0.18 g (65%); white crystals; mp 103–105 °C. IR (KBr): 3366 (NH), 1695 (C=O), 1625 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.45 (s, 6 H, CH_3), 4.37 (s, 1 H, NH), 5.17 (s, 2 H, NCH_2), 6.28–6.29 (m, 2 H, furan), 6.71 (dd, *J* = 7.6, 0.9 Hz, 1 H, H_9), 6.92 (dt, *J* = 7.6, 0.9 Hz, 1 H, H_7), 7.30 (dd, *J* = 3.0, 1.0 Hz, 1 H, furan), 7.34 (dt, *J* = 7.6, 1.4 Hz, 1 H, H_8), 8.21 (dd, *J* = 7.6, 1.4 Hz, 1 H, H_6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.5, 42.1, 57.8, 108.1, 110.2, 118.2, 118.9, 119.6, 133.5, 134.1, 141.6, 144.6, 151.4, 167.2, 173.2. MS: *m/z* (%) = 284 (35) $[M^+]$, 257 (15), 241 (20), 203 (20), 160 (100), 132 (90), 96 (71), 53 (28). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.66; H, 5.86; N, 10.00.

2-Ethyl-4-[(furan-2-yl)-methyl]-1,2-dihydro-2-methyl-4*H*-benzo[*e*][1,4]diazepine-3,5-dione (11j)

Yield 0.18 g (60%); white crystals; mp 102–104 °C. IR (KBr): 3336 (NH), 1697 (C=O), 1621 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.73 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.49 (s, 3 H, CH_3), 1.66 (dq, *J* = 14.8, 7.4 Hz, 1 H, CH_2CH_3), 1.80 (dq, *J* = 14.8, 7.4 Hz, 1 H, CH_2CH_3), 4.37 (s, 1 H, NH), 5.09 (d, *J* = 14.7 Hz, 1 H, NCH_2), 5.23 (d, *J* = 14.7 Hz, 1 H,

NCH_2), 6.28–6.31 (m, 2 H, furan), 6.72 (d, J = 8.0 Hz, 1 H, H_9), 6.91 (t, J = 7.7 Hz, 1 H, H_7), 7.31–7.35 (m, 2 H, H_8, furan), 8.20 (d, J = 7.7 Hz, 1 H, H_6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.3, 23.2, 26.9, 42.1, 61.1, 108.5, 110.2, 118.1, 118.9, 119.5, 133.3, 134.1, 141.5, 144.4, 151.4, 167.1, 173.1. MS: *m/z* (%) = 298 (65) [M^+], 271 (14), 241 (42), 217 (26), 174 (97), 146 (75), 81 (100), 53 (45). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.25; H, 5.90; N, 9.15.

4-(3,5-Dimethoxyphenethyl)-1,2-dihydro-2,2-dimethyl-4*H*-benzo[*e*][1,4]diazepine-3,5-dione (11k) Yield 0.26 g (70%); white crystals; mp 125–127 °C. IR (KBr): 3367 (NH), 1687 (C=O), 1634 (C=O) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (s, 6 H, CH_3), 2.88 (t, J = 7.8 Hz, 2 H, NCH_2CH_2), 3.85 (s, 6 H, OCH_3), 4.13 (t, J = 7.8 Hz, 2 H, NCH_2CH_2), 4.45 (s, 1 H, NH), 6.72–6.80 (m, 4 H, H_9, $H_{2'}$, $H_{4'}$, $H_{6'}$), 6.90 (t, J = 7.5 Hz, 1 H, H_7), 7.32 (t, J = 7.5 Hz, 1 H, H_8), 8.12 (d, J = 7.5 Hz, 1 H, H_6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.5, 34.9, 48.2, 55.7, 55.8, 57.8, 111.1, 112.1, 118.8, 119.5, 120.7, 132.4, 133.1, 134.0, 144.4, 147.4, 148.6, 168.1, 173.2. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.15; H, 6.30; N, 7.77.