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Note

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Synthesis of 1,4-Benzodiazepine-2,5-diones by Base Promoted Ring Expansion of 3-Aminoquinoline-2,4-diones

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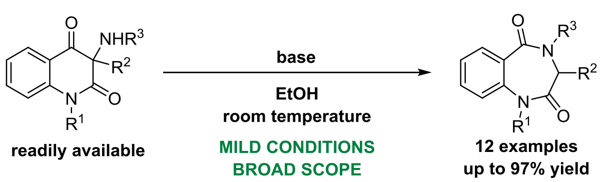
TOC Graphics



Abstract: An unprecedented reactivity of 3-aminoquinoline-2,4-diones is reported. Under basic conditions these compounds undergo molecular rearrangement to furnish 1,4-benzodiazepine-2,5-diones. The transformations take place under mild reaction conditions by using 1,1,3,3-tetramethylguanidine (TMG), NaOEt, or benzyltrimethylammonium hydroxide (Triton B) as a base. A proposed mechanism of the rearrangement and the conformational equilibrium of 1,4-benzodiazepine-2,5-dione rings are discussed.

The 1,4-benzodiazepine-2,5-dione scaffold, a subset of the 1,4-benzodiazepines, comprises a privileged structure and numerous derivatives have been found to exhibit a diverse array of biological activities.[1–5] These activities include: histone deacetylase inhibition (Figure 1, structure I);[6] anticholinesterase activity (II, R= H, R' = Br);[7] melanocortin agonist activity;[8] endothelin receptor antagonism (III);[9] glycoprotein IIb-IIIa antagonism (IV);[10,11] antagonism of the HDM2-p53 interaction (V);[12,13] anxiolytic activity;[14] anti-leishmanial activity;[15] and herbicidal activity.[16] The 1,4-benzodiazepine-2,5-dione motif appears in natural products including cyclopenin[17,18] (**II**; R = CH_3, R' = H, Ar = C_6H_5), cyclopenol[17] (**II**; R = CH_3, R' = H, Ar = 3-OH-C_6H_4), and cyclopeptin (**VI**).[19] They were predicted to be biosynthesized by the condensation of anthranilic acid and an amino acid.[20] In addition to diverse biological activities, 1,4-benzodiazepine-2,5-diones found widespread applications as intermediates in the preparation of products of medicinal interest.[21,22]

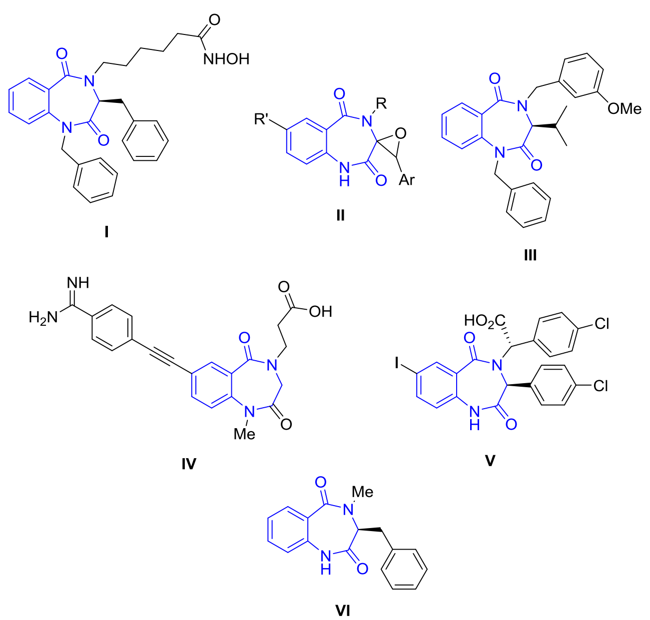


Figure 1. Selected 1,4-benzodiazepine-2,5-diones of biological relevance.

The synthesis of 1,4-benzodiazepine-2,5-dione has been reviewed.[1,23] There are two major strategies for their preparation. One relies on the condensation of an anthranilic acid or its derivative, e.g. isatoic anhydride, with α-amino acid (Figure 2a). Another versatile route takes advantage of Ugi reaction, a four component reaction of substituted *N*-Boc-protected anthranilic acid with an aldehyde, an amine, and an isonitrile to form bis-amide (Figure 2b).[24] Subsequent *N*-Boc-deprotection and condensation of the bis-amide Ugi product generates the 1,4-benzodiazepine-2,5-dione ring skeleton. With some exceptions,[25,26] this procedure has been largely executed to give N1 unsubstituted products (R^1 = H). After ring formation, late stage, selective alkylation (N1/N3) to form the desired product can sometimes be challenging.[27] High-throughput synthetic protocols have been realized by a combinatorial approach.[1,8,28–32]

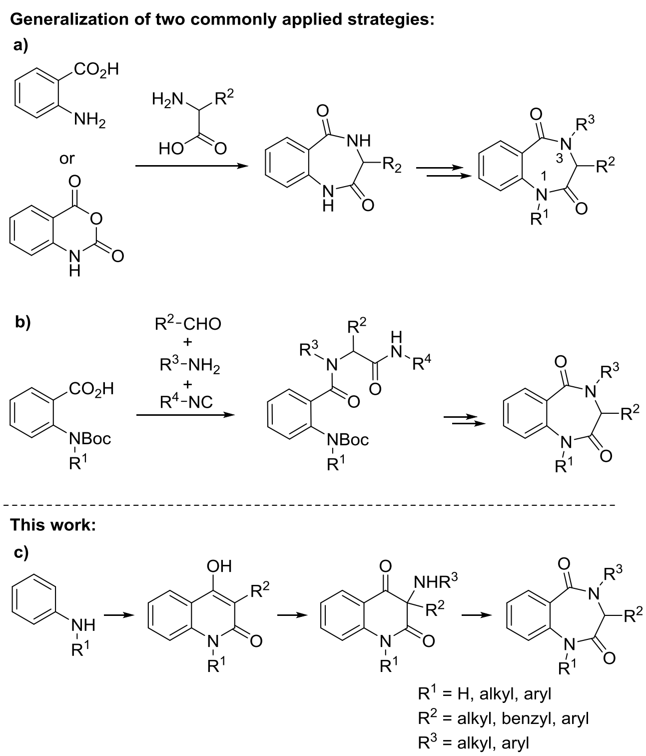
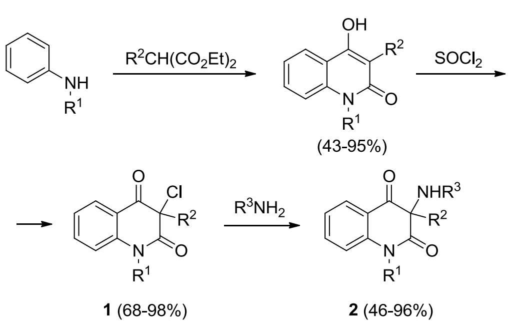


Figure 2. Approaches to 1,4-benzodiazepine-2,5-diones.

Due to the remarkable synthetic and biological relevance of 1,4-benzodiazepine-2,5-diones and related compounds there is an urge to discover new strategies for their preparation. As a part of our interest in the chemistry of quinoline-2,4(1*H*,3*H*)-diones,[33–42] herein we report a novel, approach to this scaffold that is based on a rearrangement of 3-aminoquinoline-2,4(1*H*,3*H*)-diones (Figure 2c). In a simple four-step protocol this method employs anilines as starting substrates. An advantage of the method over those from Figure 2a–b is a broad availability of aniline derivatives in comparison to anthranilic acids and isatoic anhydrides, both, synthetically and commercially. It readily provides the 1,4-benzodiazepine-2,5-dione ring functionalized at N1 and N3 with an alkyl or aryl moiety. Optimization of the reaction conditions as well as the scope of the reaction is reported.

Differently functionalized starting compounds required for this study were prepared in three simple steps starting from commercially available anilines and diethyl malonates to initially afford 4-hydroxy-2(1*H*)-quinolones (Scheme 1). Chlorination of 4-hydroxy-2(1*H*)-quinolones with sulfuryl chloride gave 3-chloroquinolin-2,4(1*H*,3*H*)-diones **1**,[43,44] which subsequently readily underwent nucleophilic displacement of the chlorine atom with selected primary amines into 3-aminoquinoline-2,4(1*H*,3*H*)-diones **2**.[45]

Scheme 1. Preparation of compounds 1 and 2

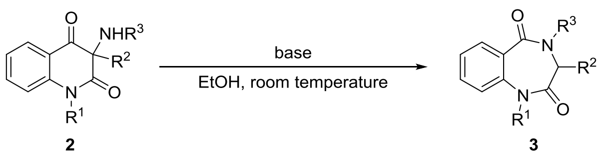


2	R1	R2	R3	2	R1	R2	R3
a	Me	Ph	*c*-Hex	**g**	Ph	Ph	Me
b	Me	Ph	Me	**h**	H	Ph	Me
c	Me	Ph	Ph	**i**	H	Ph	Bu
d	Me	Me	*c*-Hex	**j**	H	Et	Bu
e	Me	Bn	Bu	**k**	H	Bu	Bu
f	Ph	Ph	*c*-Hex	**l**	H	Bn	Me

Investigating the scope of the Wittig olefination at the C-3 carbonyl atom of 3-aminoquinoline-2,4(1*H*,3*H*)-diones, we have previously made a preliminary observation that these compounds are capable of ring expansion into 1,4-benzodiazepine-2,5-diones.[46] In one instance the treatment of a selected 3-aminoquinoline-2,4(1*H*,3*H*)-dione with ethyl (triphenylphosphoranylidene)acetate ($Ph_3P{=}CHCO_2Et$) in xylene at elevated temperature unexpectedly resulted in its rearrangement into 1,4-benzodiazepine-2,5-dione instead of the anticipated olefination.

It is reasonable to assume that in the presence of $Ph_3P{=}CHCO_2Et$ the rearrangement was enabled by the assistance of a relatively basic Wittig reagent (pK_a[47] of the conjugated acid, $Ph_3P^+CH_2CO_2Et$, measured in DMSO = 8.50). To find out whether 3-aminoquinoline-2,4(1*H*,3*H*)-diones are in general susceptible to base mediated transformations into 1,4-benzodiazepine-2,5-diones, we initially conducted some base screening experiments with compound **2a** as a model substrate. As the above mentioned heating in xylene in the presence of a phophonium ylide would unlikely find practical applications, we decided to test amine bases including 4-dimethylaminopyridine (DMAP), triethylamine, piperidine, butylamine and 1,1,3,3-tetramethylguanidine (TMG) in ethanol as the reaction solvent (Table 1). Whereas DMAP completely failed to react with **2a**, triethylamine resulted in a complex mixture of products, as judged by TLC analyses of the crude reaction mixtures. In contrast, piperidine, butylamine, and TMG afforded the desired (**3a**) in low to moderate yield. Out of these three bases, TMG was the most effective. It appeared that the efficiency of this rearrangement correlated with its basic character (pK_a data of conjugated acids in water for DMAP = 9.60;[48] triethylamine = 10.68;[49] piperidine = 11.12;[50] butylamine = 10.6;[50] TMG (pK_a = 13.6[51], 15.2[52]). We next explored sodium ethoxide and Cs_2CO_3 as alternative non-amine bases and found out to perform similarly as TMG. Finally, benzyltrimethylammonium hydroxide (Triton B), a source of hydroxide ion that is soluble in organic solvents turned out to be superior. Triton B, TMG and NaOEt were thus selected for the subsequent substrate scope screening experiments. The results are shown in Table 1.

Table 1. Rearrangements of compounds **2** into **3**



Entry	**2**	R^1	R^2	R^3	Base	Equiv.	*t* (h)	**3**	Yield[a] (%)
1	**2a**	Me	Ph	c-Hex	DMAP	0.7	[b]	**3a**	0
2	**2a**	Me	Ph	c-Hex	Triethylamine	1.1	48	**3a**	[c]
3	**2a**	Me	Ph	c-Hex	Piperidine	1.0	[b]	**3a**	26
4	**2a**	Me	Ph	c-Hex	Butylamine	1.6	[b]	**3a**	41
5	**2a**	Me	Ph	c-Hex	TMG	1.0	72	**3a**	46
6	**2a**	Me	Ph	c-Hex	TMG	0.3	4[d]	**3a**	73
7	**2a**	Me	Ph	c-Hex	NaOEt	2.3	4	**3a**	68
8	**2a**	Me	Ph	c-Hex	NaOEt	0.2	1	**3a**	35[e]
9	**2a**	Me	Ph	c-Hex	Cs_2CO_3[f]	0.2	35[g]	**3a**	46
10	**2a**	Me	Ph	c-Hex	Triton B	0.2	1	**3a**	95
11	**2b**	Me	Ph	Me	TMG	2.2	23	**3b**	77
12	**2c**	Me	Ph	Ph	TMG	2.2	10	**3c**	76
13	**2d**	Me	Me	c-Hex	Triton B	0.2	1	**3d**	97
14	**2e**	Me	Bn	Bu	NaOEt	2.5	30	**3e**	68
15	**2e**	Me	Bn	Bu	Triton B	0.2	1	**3e**	94
16	**2f**	Ph	Ph	c-Hex	TMG	2.2	5[d]	**3f**	67
17	**2f**	Ph	Ph	c-Hex	Triton B	0.2	1	**3f**	34[e]
18	**2f**	Ph	Ph	c-Hex	Triton B	0.2	4	**3f**	65[e]
19	**2g**	Ph	Ph	Me	TMG	2.2	16	**3g**	97
20	**2g**	Ph	Ph	Me	Triton B	0.2	1	**3g**	90
21	**2h**	H	Ph	Me	TMG	2.2	32	**3h**	59
22	**2i**	H	Ph	Bu	NaOEt	2.3	12	**3i**	44
23	**2j**	H	Et	Bu	NaOEt	2.3	[h]	**3j**	58
24	**2k**	H	Bu	Bu	NaOEt	2.3	48	**3k**	71
25	**2k**	H	Bu	Bu	Triton B	2.5	24	**3k**	43[e]
26	**2k**	H	Bu	Bu	Triton B	2.5	72	**3k**	83[e]
27	**2k**	H	Bu	Bu	Triton B	0.2	24	**3k**	9[e]

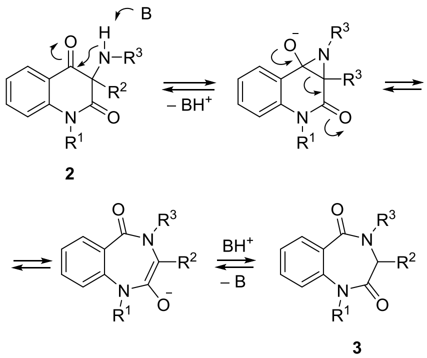
28	**2l**	H	Bn	Me	NaOEt	2.3	51	**3l**	40

[a]Yield of isolated pure product is given. [b]24 hours at rt and then heated at 50 °C for 30 h. [c]Complex mixture of products. [d]Reflux. [e]Conversion based on ^{1}H NMR integration. [f]DMF used as a solvent. [g]15 h at rt, then 14 h at 80 °C, then 6 h at 90 °C. [h]24 h at rt, then 4 h at 50 °C, then 4 h at 65 °C.

In the case of N1 substituted substrates **2a**–**2g** (R^1 = alkyl or phenyl) catalytic amounts of TMG, NaOEt or Triton B could be employed for the rearrangement into **3**. However, the reactions with TMG and NaOEt were too slow and/or resulted in unacceptably low conversions for practical applications in preparative purposes. For the rearrangement of these substrates Triton B was found to be superior. It is also noteworthy that the reactions with Triton B were extremely clean as no side products could be detected by TLC or NMR analyses of the crude reaction mixtures. A simple extractive workup was only required to isolate pure products that needed no further chromatographic purification. In contrast, for N1 unsubstituted analogues **2h**–**2l** (R^1 = H) an excess of a base (NaOEt) had to be applied for an efficient rearrangement.

The proposed reaction mechanism that accounts for the rearrangement of **2** into **3** is shown in Scheme 2. The base assisted intramolecular addition of the 3-amino nitrogen atom to the C-4 carbonyl group results in the formation of aziridine oxo-anion, which then undergoes cleavage of C-3/C-4 bond, followed by protonation. It is interesting to note that a reverse reaction, i.e., ring contraction of some 1,4-benzodiazepine-2,5-diones into the corresponding 3-aminoquinoline-2,4(1*H*,3*H*)-diones, was recently reported by the groups of Dewynter[53] and Carlier.[54] The transformation was achieved by using LiHMDS or KHMDS at –78 °C.

Scheme 2. Proposed mechanism



The chemical compositions of all the compounds under investigation were confirmed by standard spectroscopic and analytical methods. Structure elucidation of compounds **3** as well as the assignments of proton and carbon resonances was performed by using 2D NMR experiments. ^{1}H NMR spectra of C3-alkyl and C3-benzyl derivatives **3d**, **3e**, **3j**–**3l**, recorded in DMSO-d_6 at 296 K, exhibited split signal patterns. This suggested the presence of two conformers that are slowly interconverting on the NMR time scale and was confirmed by variable-temperature (VT) ^{1}H NMR experiments. VT ^{1}H NMR spectra of compound **3l** in the temperature range of 293–353 K are shown in Figure 3. The spectrum at 293 K, in the slow exchange regime, is consistent with the presence of two isomers of the compound **3l**. At increase in the temperature, the broadening of the resonances occurs with the subsequent appearance of the average resonance above 323 K, where fast ring inversion takes place. The VT ^{1}H NMR spectra could be rationalized by the 1,4-benzodiazepine-2,5-dione seven-membered ring interconversion in which the C3 substituent has either pseudoequatorial or pseudoaxial orientation thus providing two pairs of enantiomers (*P*)-(*S*)-**3** / (*M*)-(*R*)-**3** and (*P*)-(*R*)-**3** / (*M*)-(*S*)-**3** in two diastereomeric forms (*P*)-(*R*)-**3** / (*M*)-(*S*)-**3** and (*M*)-(*R*)-**3** / (*P*)-(*S*)-**3**, respectively (Figure 4). The existence of two conformers in DMSO-d_6 at 296 K through the split signal patterns was also evident from ^{13}C NMR spectra and 2D NMR spectra. In contrast to the C3-benzyl and C3-alkyl derivatives **3d**, **3e**, **3j**–**3l** the NMR spectra of the C3-phenyl substituted products **3a**–**3c**, **3f**–**3i**, indicated a single set of resonances. The conformational behavior is consistent with that observed in related 1,4-benzodiazepine-2,5-diones.[6,11,53–57]

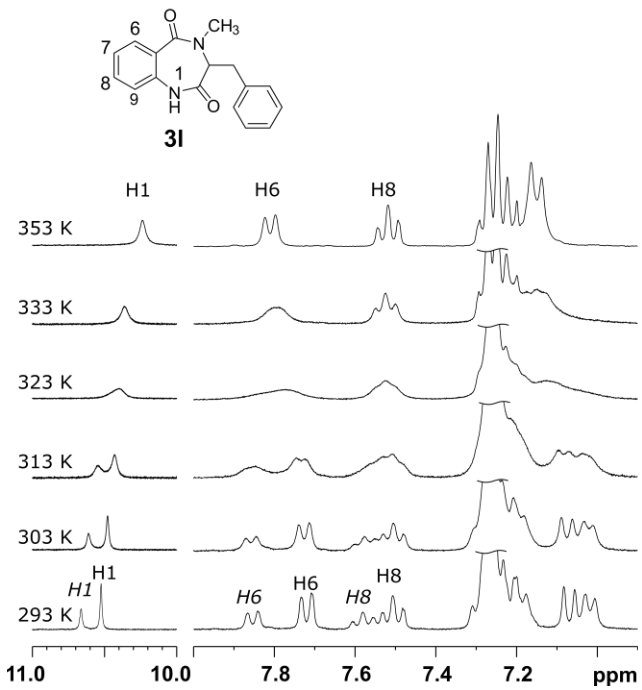


Figure 3. Selected parts of VT ^{1}H NMR spectra of **3l** in DMSO-d_6.

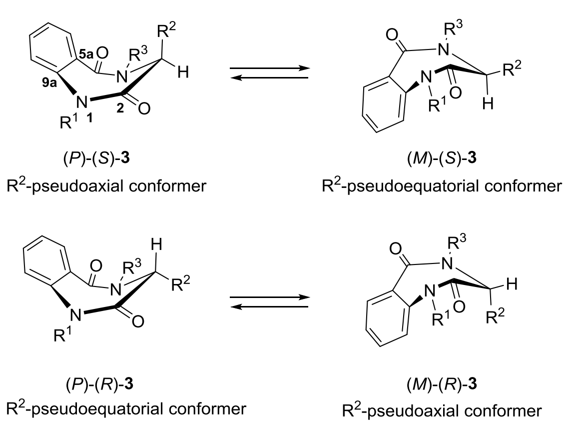


Figure 4. Conformational equilibrium in 1,4-benzodiazepine-2,5-dione ring at racemic compounds **3**. Conformational assignment (*M*/*P*) followed an earlier proposal to designate the

sense of conformational chirality of the benzodiazepine ring and is based on the sign of the 2–1–9a–5a dihedral angle (*M* = minus, P = positive).[58,59]

In conclusion, a novel approach to 1,4-benzodiazepine-2,5-dione scaffold is reported. It is based on a molecular rearrangement of easily available 3-aminoquinoline-2,4(1*H*,3*H*)-diones in the presence of base, such as benzyltrimethylammonium hydroxide (Triton B), 1,1,3,3-tetramethylguanidine (TMG) or NaOEt. The transformations proceed under mild reaction conditions in environmentally-friendly ethanol as a reaction solvent, at room temperature. In contrast to the known methods, this approach does not require N1/N3 post alkylation of the 1,4-benzodiazepine-2,5-dione parent ring.

Experimental Section

General Experimental Methods. The reagents and solvents were used as obtained from the commercial sources. Compounds **1a**,[43,45] **1d**,[60] **1e**,[61] **1f**,[61] **1h**,[45] **1j**,[43] **1k**,[43,61] and **1l**,[43,45,61] were prepared as described in the literature. Column chromatography was carried out on Silica gel 60 (particle size 0.063–0.2 mm, activity acc. Brockmann and Schodder 2–3). Melting points were determined on the microscope hot stage, and are uncorrected. TLC was carried out on TLC-cards with a fluorescent indicator, visualization was accomplished with UV light (254 nm). NMR spectra were recorded with a 500 MHz NMR instrument operating at 500 MHz (^{1}H), 126 MHz (^{13}C) and 51 MHz (^{15}N) at 300 K. Proton spectra were referenced to TMS as internal standard, in some cases to the residual signal of DMSO-d_6 (at δ 2.50 ppm). Carbon chemical shifts were determined relative to the ^{13}C signal of DMSO-d_6 (39.5 ppm). ^{15}N chemical shifts were extracted from ^{1}H–^{15}N *gs*-HMBC spectra (with 20 Hz digital resolution in the indirect dimension and the parameters adjusted for a long-range ^{1}H–^{15}N coupling constant of 5 Hz) determined with respect to external nitromethane and are corrected to external ammonia by addition of 380.5 ppm. Nitrogen chemical shifts are reported to one decimal place as measured of the spectrum, however, the data should not be considered to be more accurate than ±0.5 ppm because of the digital resolution limits of the experiment. Chemical shifts are given on the δ scale (ppm). Coupling constants (*J*) are given in Hz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broadened). The numbering used for the assignment of NMR signals is as follows: quinoline-2,4(1*H*,3*H*)-dione ring (**2**) and 1,4-benzodiazepine-2,5-dione (**3**), simple figures, R^1-substituent primed figures; R^2-substituent, double primed figures; R^3-substituent, triple primed figures. NMR peak assignments are based on the analyses of ^{1}H–^{1}H *gs*-COSY, ^{1}H–^{13}C *gs*-HSQC, ^{1}H–^{13}C *gs*-HMBC and ^{1}H–^{15}N *gs*-HMBC 2D NMR spectra. Infrared spectra were recorded on a FT-IR spectrometer using samples in potassium bromide disks and only the strongest/structurally most important peaks are listed. Electron impact mass spectra (EI) were recorded at 70 eV. High-resolution mass spectra (HRMS) were obtained with a time-of-flight (TOF) mass spectrometer equipped with an electrospray source at atmospheric pressure ionization (ESI). Elemental analyses (C, H, N) were performed with a CHNS/O Analyzer.

Synthesis of 3-aminoquinoline-2,4(1*H*,3*H*)-diones 2. 3-Aminoquinoline-2,4(1*H*,3*H*)-diones **2** were prepared from 3-chloroquinolin-2,4(1*H*,3*H*)-diones **1** according to the procedures described in the literature.[45] Spectroscopic and analytical data for compounds **2a**,[45] **2b**,[45] **2c**,[45] **2e**,[42] **2h**,[45] ~~**2g**,[45]~~ **2i**,[45] **2k**,[45] and **2l**[45] were in agreement with the literature data. Spectroscopic and analytical data of new compounds **2d**, **2f**, **2g**, and **2j** are reported below.

*3-(Cyclohexylamino)-1,3-dimethylquinoline-2,4(1H,3H)-dione (**2d**).* Compound **2d** (1.67 g, 58.3 mmol, 58%) was prepared from **1d** (2.24 g, 10.0 mmol). Beige solid, mp 78–81 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.88–1.09 (m, 5H), 1.32 (s, 3H), 1.40–1.60 (m, 5H), 2.34 (br s, 1H), 2.38–2.45 (m, 1H), 3.21 (s, 3H), 7.24 (dd, 1H, J = 7.4 Hz, 7.4 Hz), 7.40 (d, 1H, J = 8.4 Hz), 7.75 (ddd, 1H, J = 8.7, 7.0, 1,6 Hz), 7.91 (dd, 1H, J = 7.7, 1.6 Hz); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.7, 25.4, 26.6, 29.8, 34.0, 34.5, 52.8, 67.6, 115.8, 119.4, 122.9, 127.4, 136.4, 142.7, 173.1, 195.4; two ^{13}C resonances are overlapped; IR (cm^{-1}): ν 3326, 2924, 2854, 1693, 1658, 1597, 1491, 1468, 1363, 1345, 1298, 1101, 762, 579, 418; MS (EI) *m/z* (%): 286 (2, [M]$^+$), 243 (34), 214 (22), 191 (36), 189 (19), 160 (16), 98 (89), 83 (42), 71 (16); HRMS (ESI+): *m/z* calcd for $C_{17}H_{23}N_2O_2^+$ [M + H]$^+$ 287.1754, found 287.1751. Anal. calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30, H, 7.74, N, 9.78%. Found: C, 71.60, H, 7.99, N, 9.80.

*3-(Cyclohexylamino)-1,3-diphenylquinoline-2,4(1H,3H)-dione (**2f**).* Compound **2f** (3.91 g, 9.5 mmol, 96%) was prepared from **1f** (3.44 g, 9.9 mmol). Beige solid, mp 86–92 °C (benzene); ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.98–1.15 (m, 5H), 1.45 (br s, 1H), 1.53–1.64 (m, 3H), 1.77 (d, 1H, J = 10.1 Hz), 2.60–2.67 (m, 1H, H1'''), 6.37 (d, 1H, J = 8.3 Hz, H8), 7.16 (dd, 1H, J = 7.3, 7.2 Hz, H6), 7.29–7.35 (m, 2H, H4', H3'), 7.35–7.40 (m, 2H, H3'', H5''), 7.45–7.53 (m, 4H, H7, H2'', H6'', H3'), 7.58 (dd, 1H, J = 7.4, 7.4 Hz, H4'), 7.61–7.71 (m, 2H, H2', H6'), 7.86 (dd, 1H, J = 7.8, 1.5 Hz, H5); NH proton not found, probably in fast exchange with HOD; ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.97, 25.00, 25.4, 34.5, 34.8, 53.0 (C1'''), 75.7 (C3), 116.7 (C8), 119.9 (C4a), 123.5 (C6), 126.7 (C2'', C6''), 127.8 (C5), 128.6 (C4''), 128.7 (C3' or C5'), 128.9 (C3'', C5''), 129.0 (C4'), 129.2 (C5' or C3'), 130.3 (C2' or C6'), 130.6 (C6' or C2'), 136.1 (C7), 137.3 (C1'), 138.4 (C1''), 143.0 (C8a), 172.2 (C2), 192.7 (C4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 151.4 (N1); IR (cm^{-1}): ν 2924, 2850, 1705, 1672, 1599, 1491, 1461, 1332, 1301, 1240, 757, 717, 695;

MS (EI) *m/z* (%): 411 (4, $[M + 1]^+$), 410 (12, $[M]^+$), 367 (14), 316 (11), 313 (26), 312 (25), 196 (14), 186 (16), 104 (100), 98 (82), 77 (12); HRMS (ESI+): *m/z* calcd for $C_{27}H_{27}N_2O_2^+$ $[M + H]^+$ 411.2067, found 411.2062 Anal. Calcd for $C_{27}H_{26}N_2O_2$ (410.51): C 79.00, H 6.38, N 6.82; found: C 78.92, H 6.44, N 6.99.

*3-(Methylamino)-1,3-diphenylquinoline-2,4(1H,3H)-dione (**2g**).* Compound **2g** (1.58 g, 4.6 mmol, 90%) was prepared from **1f** (1.79 g, 5.1 mmol). White solid, mp 142–149 °C (ethanol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.26 (s, 3H, H'''), 2.98 (br s, 1H, NH), 6.34 (d, 1H, *J* = 8.3 Hz, H8), 7.14 (dd, 1H, *J* = 7.5, 7.4 Hz, H6), 7.32 (dd, 1H, *J* = 7.2, 7.2 Hz, H4''), 7.39 (dd, 2H, *J* = 7.6, 7.6 Hz, H3'', H5''), 7.40–7.50 (m, 5H, H7, H3', H5', H2'', H6''), 7.57 (dd, 1H, *J* = 7.4, 7.4 Hz, H4'), 7.60–7.70 (m, 2H, H2', H6'), 7.82 (dd, 1H, *J* = 7.8, 1.2 Hz, H5); ^{13}C NMR (126 MHz, DMSO-d_6) δ 31.7 (C'''), 78.0 (C3), 116.6 (C8), 120.6 (C4a), 123.3 (C6), 126,8 (C2'', C6''), 127.5 (C5), 128.7 (C4''), 128.9 (C3'', C5''), 129.0 (C4'), 129.1 (C3', C5'), 130.4 (C2'', C6''), 135.9 (C7), 137.3 (C1''), 137.4 (C1'), 143.0 (C8a), 171.2 (C2), 192.7 (C4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 34.2 (NH), 152.1 (N1); IR (cm^{-1}): ν 3342, 3062, 2953, 2853, 2793, 1701, 1670, 1598, 1491, 1461, 1336, 1301, 1247, 763, 735, 690, 598, 537, 518; MS (EI) *m/z* (%):343 (6, $[M + 1]^+$), 342 (23, $[M]^+$), 313 (14), 312 (11), 119 (11), 118 (100), 104 (12), 77 (19); HRMS (ESI+): *m/z* calcd for $C_{22}H_{19}N_2O_2^+$ $[M + H]^+$ 343.1441, found 343.1440. Anal. calcd. for $C_{22}H_{18}N_2O_2$ (342.39): C, 77.17, H, 5.30, N, 8.18; found: C, 76.89, H, 5.25, N, 8.07.

*3-(Butylamino)-3-ethylquinoline-2,4(1H,3H)-dione (**2j**)* Compound **2j** (597 mg, 2.3 mmol, 46%) was prepared from **1j** (1.12 g, 5.0 mmol). Yellowish solid, mp 86–89 °C (cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.71 (t, 3H, *J* = 7.4 Hz), 0.81 (t, 3H, *J* = 7.2 Hz), 1.20–1.29 (m, 2H), 1.29–1.36 (m, 2H), 1.68–1.82 (m, 2H), 2.17–2.33 (m, 3H), 7.09 (d, 1H, *J* = 8.0 Hz), 7.11 (dd, 1H, *J* = 7.6 Hz), 7.60 (dd, 1H, *J* = 7.6 Hz), 7.75 (d, 1H, *J* = 7.7 Hz), 10.94 (s, 1H). ^{13}C NMR

(126 MHz, DMSO-d_6) δ 7.8, 13.8, 19.8, 32.2, 32.8, 44.1, 73.5, 116.3, 119.3, 122.6, 126.6, 136.3, 141.7, 172.8, 196.5. IR (cm^{-1}): ν 3305, 2963, 2925, 2872, 1706, 1695, 1670, 1650, 1609, 1593, 1485, 1435, 1369, 757, 666. HRMS (ESI+): *m/z* calcd for $C_{15}H_{21}N_2O_2^+$ $[M + H]^+$ 261.1598, found 261.1596. Anal. Calcd for $C_{15}H_{20}N_2O_2$ (260.33): C 69.20, H 7.74, N 10.76; found: C 68.98, H 7.88, N 10.53.

Rearrangement of 3-aminoquinoline-2,4(1*H*,3*H*)-diones 2 into 1,4-benzodiazepine-2,5-diones 3.

*General procedure for rearrangement of **2** into **3**:* A mixture of 3-aminoquinoline-2,4-(1*H*,3*H*)-dione (**2**, 0.9 mmol) and a base in ethanol (9 mL) was stirred at room temperature for given time (see Table 1). Details of isolation are described below.

With benzyltrimethylammonium hydroxide (Triton B) as a base: A mixture of 3-aminoquinoline-2,4-(1*H*,3*H*)-dione (**2**, 0.9 mmol) and Triton B (34 mg, 0.2 mmol; as 84 mg of 40 wt. % solution in methanol) in ethanol (9 mL) was stirred for 1 hour at room temperature. The reaction mixture was at room temperature concentrated under reduced pressure. The crude product was dissolved in ethyl acetate (30 mL), washed with water (2 × 15 mL), brine (15 mL), dried over sodium sulfate and evaporated to dryness to afford pure products **3** in excellent isolated yield (Table 1, entries 10, 13, 15, 20) or ratio of conversion (Table 1, entries 17, 18, 25–27) which was determined by ^{1}H NMR integration.

With TMG as base: A mixture of 3-aminoquinoline-2,4-(1*H*,3*H*)-dione (**2**, 0.9 mmol) and TMG (230 mg, 2.0 mmol) in ethanol (9 mL) was stirred at room temperature until completion as judged by TLC analysis (Table 1). The precipitated crude product was collected by filtration, washed with water (2 × 2 mL) and recrystallized from ethanol to afford pure 1,4-benzodiazepine-2,5-dione **3**.

With NaOEt as base: A mixture of 3-aminoquinoline-2,4-(1*H*,3*H*)-dione (**2**, 0.9 mmol) and 0.5 M solution of NaOEt (4.5 mL, 2.25 mmol) was stirred at room temperature under exclusion of atmospheric moisture (the flask equipped with drying tube filled with potassium hydroxide) until completion as judged by TLC analysis (Table 1). The isolation of 1,4-benzodiazepine-2,5-diones **3** from the reaction mixture was done as follows.

From **2a** or **2e**: The reaction mixture was filtered. The filter cake was washed with water (2 mL) and dried at 50 °C to afford pure **3a** (212 mg, 68%) or **3e** (206 mg, 68%).

From **2i** and **2l**: The reaction mixture was acidified with 1M HCl to Congo red and concentrated *in vacuo*. The oily residue was triturated with water (1 mL) and the resulting precipitate was collected by filtration. The filter cake was washed with water and dried at 50 °C to afford pure **3i** (121 mg, 44%) or **3l** (100 mg, 40%).

From **2j** or **2k**: The reaction mixture was acidified with 1M HCl to Congo red and extracted with dichloromethane (3 × 9 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The residue was subjected to column chromatography on silica gel using: (*i*) benzene as an eluent to isolate product **3j**, which was additionally crystallized from a mixture of hexane and benzene to obtain pure **3j** (136 mg, 58%); (*ii*) chloroform as an eluent to provide pure **3k** (185 mg, 71%).

*4-Cyclohexyl-1-methyl-3-phenyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3a**).* Triton B: 298 mg, 95% yield; TMG: 232 mg, 74% yield; NaOEt: 212 mg, 68% yield. White solid, mp 192–193 °C (benzene/cyclohexane). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.11–1.22 (m, 1H, cyclohexyl), 1.32–1.89 (m, 9H, cyclohexyl), 3.37 (s, 3H, H1'), 4.73–4.81 (m, 1H, H1''' of cyclohexyl), 5.59 (s, 1H, H3), 6.87 (d, 2H, *J* = 7.7 Hz, H2'', H6''), 6.95 (dd, 1H, *J* = 7.5, 7.5 Hz, H7), 6.99 (t, 1H, *J* = 6.8 Hz, H4''), 7.03 (d, 1H, *J* = 8.5 Hz, H9), 7.06 (dd, 2H, *J* = 7.5, 7.5 Hz, H3'', H5''), 7.21 (ddd, 1H, *J* = 8.5, 7.0, 1.6 Hz, H8), 7.38 (dd, 1H, *J* = 7.8, 1.5 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.6, 25.3, 25.4, 29.1, 30.4, 35.1 (C1'), 54.3 (C1'''), 61.1 (C3), 120.7 (C9), 124.0 (C2'', C6''), 124.6 (C7), 126.9 (C4''), 128.1 (C3'', C5''), 129.8 (C6), 129.9 (C5a), 131.4 (C8), 135.0 (C1''), 138.9 (C9a), 165.8 (C5), 170.3 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 124.3 (N1), 143.3 (N4); IR (cm^{-1}): ν 2936, 2856, 1664, 1629, 1601, 1493, 1475, 1457, 1432, 1366, 1246, 1145, 715; MS (EI) *m/z* (%):349 ([M + 1]$^+$, 12), 348 ([M]$^+$, 49), 291 (48), 266 (43), 251 (68), 161 (65), 132 (44), 105 (60), 104 (100), 55 (42); HRMS (ESI+): *m/z* calcd for $C_{22}H_{25}N_2O_2^+$ [M + H]$^+$ 349.1911, found 349.1907. Anal. Calcd for $C_{22}H_{24}N_2O_2$ (348.74): C, 75.83; H, 6.94; N, 8.04%. Found: C, 75.62; H, 6.96; N, 8.07%.

*3,4-Dihydro-1,4-dimethyl-3-phenyl-1H-benzo[e][1,4]diazepine-2,5-dione (**3b**)*. TMG: 194 mg, 77% yield. White solid, mp 183–186 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.38 (s, 3H, H1'), 3.41 (s, 3H, H1'''), 5.64 (s, 1H, H3), 6.83 (d, 2H, *J* = 7.8 Hz, H2'', H6''), 6.96 (dd, 1H, *J* = 7.5, 7.5 Hz, H7), 7.01 (t, 1H, *J* = 7.3 Hz, H4''), 7.08 (dd, 2H, *J* = 7.7, 7.7 Hz, H3'', H5''), 7.10 (d, 1H, *J* = 8.0 H, H9), 7.26 (ddd, 1H, *J* = 7.7, 7.7, 1.2 Hz, H8), 7.38 (dd, 1H, *J* = 7.8, 1.0 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 35.3 (C1'), 38.2 (C1'''), 68.0 (C3), 121.0 (C9), 123.9 (C2'', C6''), 124.8 (C7), 127.1 (C4''), 128.3 (C3'', C5''), 129.1 (C5a), 129.6 (C6), 131.6 (C8), 134.6 (C1''), 139.2 (C9a), 166.3 (C5), 169.3 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 119.2 (N4), 124.0 (N1); IR (cm^{-1}): ν 2933, 2852, 1702, 1670, 1602, 1473, 1443, 1356, 1307, 1124, 1098, 765, 704, 647; MS (EI) *m/z* (%):281 (8, [M + 1]$^+$, 280 (42, [M]$^+$), 175 (46), 161 (36), 133 (38), 120 (100), 118 (91), 105 (46), 104 (45), 78 (23), 77 (27); HRMS (ESI+): *m/z* calcd for $C_{17}H_{17}N_2O_2^+$ [M + H]$^+$ 281.1285, found 281.1283. Anal. Cald. for $C_{17}H_{16}N_2O_2$ (280.33): C 72.84, H 5.75, N 9.99, found C 72.76, H 5.77, N 10.04.

*3,4-Diphenyl-1-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3c**).* TMG: 234 mg, 76% yield. White solid, mp 202–204 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.48 (s, 3H, H1'), 5.78 (s, 1H, H3), 7.03 (dd, 1H, J = 7.6, 7.6 Hz, H7), 7.06 (d, 2H, J = 7.8 Hz, H2'', H3''), 7.07 (t, 1H, J = 7.8 Hz, H4''), 7.14 (dd, 2H, J = 7.5, 7.5 Hz, H3'', H5''), 7.16 (d, 1H, J = 8.3 Hz, H9), 7.32 (ddd, 1H, J = 8.5, 7.0, 1.4 Hz, H8), 7.36–7.41 (m, 1H, H4'''), 7.46 (dd, 1H, J = 7.8, 1.2 Hz, H6), 7.49–7.54 (m, 4H, H2''', H3''', H5''', H6'''); ^{13}C NMR (126 MHz, DMSO-d_6) δ 35.4 (C1'), 69.9 (C3), 121.3 (C9), 124.0 (C2'', C6''), 125.0 (C7), 126.1 (C2''', C6'''), 127.3 (C4'''), 127.4 (C4''), 128.5 (C3'', C5''), 129.4 (C5a, C3''', C5''), 129.9 (C6), 132.1 (C8), 134.2 (C1''), 139.2 (C9a), 143.8 (C1'''), 165.7 (C5), 169.1 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 124.1 (N1), 139.2 (N4); IR (cm^{-1}): ν 3064, 1667, 1654, 1600, 1494, 1473, 1458, 1417, 1369, 1243, 764, 712, 698, 614, 545, 524; HRMS (ESI+): *m/z* calcd for $C_{22}H_{19}N_2O_2^+$ $[M + H]^+$ 343.1441, found 343.1441. Anal. Calcd for $C_{22}H_{18}N_2O_2$ (342.40) C, 77.17; H, 5.30; N, 8.18%. Found: C, 77.47; H, 5.35; N 8.22.

*4-Cyclohexyl-1,3-dimethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3d**).* Triton B: 250 mg, 97% yield; White solid, mp 120–124 °C (hexane). Major isomer : minor isomer = 88 : 12. *Major isomer:* ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.89 (d, 3H, 7.5 Hz, 3-H''), 1.00–1.83 (m, 10H, H2''', H3''', H4''', H5''', H6'''), 3.30 (s, 3H, H1'), 4.41 (q, 1H, J = 7.5 Hz, H3), 4.53–4.60 (m, 1H, H1'''), 7.31 (dd, 1H, J = 7.4 Hz, H7), 7.38 (d, 1H, J = 8.2 Hz, H9), 7.60 (ddd, 1H, J = 7.8, 7.7, 1.3 Hz, H8), 7.68 (dd, 1H, J = 7.8, 1.3 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 16.0 (C1''), 24.7, 25.2, 25.3, 29.3, 29.8, 35.2 (C1'), 53.6 (C3), 54.2 (C1'''), 121.1 (C9), 125.1 (C7), 129.4 (C5a), 130.2 (C6), 132.0 (C8), 139.2 (C9a), 164.7 (C5), 170.9 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 123.0 (N1), 146.9 (N4); *Minor isomer:* ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.00–1.83

(m, 10H, H2''', H3''', H4''', H5''', H6'''), 1.36 (d, 3H, *J* = 6.8 Hz, H''), 3.26–3.31 (m, 1H, H1'''), 3.31 (s, 3H, H1'), 4.23 (q, 1H, *J* = 6.8 Hz, H3), 7.29 (dd, 1H, *J* = 7.4 Hz, H7), 7.38 (d, 1H, *J* = 8.2 Hz, H9), 7.57 (ddd, 1H, *J* = 7.8, 7.7, 1.3 Hz, H8), 7.68 (dd, 1H, *J* = 7.8, 1.3 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 12.5 (C1''), 25.0, 25.8, 28.5, 30.7, 34.1 (C1'), 51.0 (C3), 55.0 (C1'''), 121.0 (C9), 124.9 (C7), 129.7 (C5a), 130.1 (C6), 131.7 (C8), 140.4 (C9a), 167.4 (C5), 170.5 (C2), one resonance belonging to cyclohexane ring not visible; ^{15}N NMR (51 MHz, DMSO-d_6) δ 142.0 (N4); IR (cm^{-1}): *v* 2931, 2918, 2850, 1678, 1636, 1601, 1454, 1423, 1377, 1368, 1318, 1248, 1138, 794, 766, 713; HRMS (ESI+): *m/z* calcd for $C_{17}H_{23}N_2O_2^+$ [M + H]$^+$ 287.1754, found 287.1753. Anal. calcd for $C_{17}H_{22}N_2O_2$ (286.37): C, 71.30, H, 7.74, N, 9.78%. Found: C, 71.10, H, 8.00, N, 9.69%.

*3-Benzyl-4-butyl-3,4-dihydro-1-methyl-1H-benzo[e][1,4]diazepine-2,5-dione (**3e**).* Triton B: 286 mg, 94% yield; NaOEt: 206 mg, 68% yield. Pale yellow solid, mp 135–136 °C. Major isomer : minor isomer = 53 : 47. *Major isomer:* ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.87 (t, 3H, *J* = 7.3 Hz, H4'''), 1.11–1.26 (m, 2H, H3'''), 1.39–1.49 (m, 1H, H2'''), 1.49–1.59 (m, 1H, H2'''), 3.13 (ddd, 1H, *J* = 13.9, 8.8, 4.5 Hz, H1'''), 3.22 (dd, 1H, *J* = 14.5, 7.3 Hz, $PhCH_2$), 3.32–3.38 (m, 1H, $PhCH_2$), 3.31 (s, 3H, H1'), 3.89 (ddd, 1H, *J* = 14.0, 8.2, 8.1 Hz, H1'''), 4.46 (t, 1H, *J* = 7.5 Hz, H3), 7.15–7.20 (m, 1H, H4''), 7.20–7.29 (m, 4H, H2'', H3'', H5'', H6''), 7.34 (dd, 1H, *J* = 7.5, 7.5 Hz, H7), 7.40 (d, 1H, *J* = 8.3 Hz, H9), 7.59 (ddd, 1H, *J* = 7.7, 7.7, 1.4 Hz, H8), 7.71 (dd, 1H, *J* = 7.7, 1.5 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.6 (C4'''), 19.4 (C3'''), 29.9 (C2'''), 31.8 ($PhCH_2$), 34.4 (C1'), 41.3 (C1'''), 55.8 (C3), 121.4 (C9), 125.3 (C7), 126.5 (C4''), 128.4 (C3'', C5''), 128.9 (C2'', C6''), 129.1 (C5a), 129.7 (C6), 132.0 (C8), 137.2 (C1''), 140.4 (C9a), 167.2 (C5), 169.7 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 125.6 (N1), 132.0 (N4); *Minor isomer*: ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.82 (t, 3H, *J* = 7.3 Hz, H4'''), 1.11–1.26 (m, 2H, H3'''), 1.28–1.39

(m, 2H, H2'''), 2.44 (dd, 1H, *J* =13.4, 9.3 Hz, $PhCH_2$), 2.49–2.55 (m, 1H, $PhCH_2$), 2.99 (ddd, 1H, *J* = 13.4, 8.1, 5.6 Hz, H1'''), 3.31 (s, 3H, H1'), 3.68 (ddd, 1H, *J* = 13.3, 7.8, 7.5 Hz, H1'''), 4.41 (t, 1H, *J* = 8.9 Hz, H3), 6.96 (d, 2H, *J* = 7.1 Hz, H2''), 7.20–7.29 (m, 3H, H3'', H4'', H5''), 7.41 (dd, 1H, *J* = 7.5, 7.5 Hz, H7), 7.50 (d, 1H, *J* = 8.2 Hz, H9), 7.70 (ddd, 1H, *J* = 7.4, 7.4, 1.4 Hz, H8), 7.79 (dd, 1H, *J* = 7.7, 1.3 Hz, H6); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.6 (C4'''), 19.2 (C3'''), 29.1 (C2'''), 34.3 ($PhCH_2$), 35.4 (C1'), 49.5 (C1'''), 66.0 (C3), 121.5 (C9), 125.4 (C7), 126.9 (C4''), 128.5 (C3'', C5''), 128.9 (C2'', C6''), 129.3 (C5a), 130.1 (C6), 132.4 (C8), 136.0 (C1''), 139.4 (C9a), 165.0 (C5), 169.2 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 124.4 (N1), 131.8 (N4); IR (cm^{-1}): ν 2951, 2866, 1676, 1640, 1629, 1602, 1459, 1408, 1384, 760, 707; HRMS (ESI+): *m/z* calcd for $C_{21}H_{25}N_2O_2^+$ $[M + H]^+$ 337.1911, found 337.1909. Anal. Calcd for $C_{21}H_{24}N_2O_2$ (336.43): C, 74.97; H, 7.19; N, 8.33%. Found: C, 74.67; H, 7.43; N, 8.26%.

*4-Cyclohexyl-1,3-diphenyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3f**).* TMG: 247 mg, 67% yield. Yellow solid, mp 224–227 °C (ethanol). ^{1}H NMR (DMSO-d_6, 500 MHz): 1.10–1.21 (m, 1H, cyclohexyl), 1.31–1.48 (m, 2H, cyclohexyl), 1.50–1.84 (m, 6H, cyclohexyl), 1.84–1.92 (m, 1H, cyclohexyl), 4.81–4.89 (m, 1H, H1'''), 5.72 (s, 1H, H3), 6.32 (d, 1H, *J* = 8.1 Hz, H9), 6.94 (dd, 1H, *J* = 7.5, 7.5 Hz, H7), 7.01–7.06 (m, 2H, H8, H4''), 7.08–7.15 (m, 4H, H2'', H3'', H5'', H6''), 7.31 (d, 2H, *J* = 7.4 Hz, H2', H6'), 7.40 (t, 1H, *J* = 7.4 Hz, H4'), 7.47 (dd, 1H, *J* = 7.9, 1.5 Hz, H6), 7.50 (dd, 2H, *J* = 7.9, 7.6 Hz, H3', H5'); ^{13}C NMR (DMSO-d_6, 126 MHz) 24.6, 25.3, 25.4, 29.0, 30.4, 54.6 (C1'''), 61.3 (C3), 123.2 (C9), 124.1 (C2'', C6''), 125.0 (C7), 127.1 (C4''), 127.8 (C4'), 128.3 (C3'', 5''), 128.5 (C2', C6'), 129.5 (C3', C5'), 130.1 (C6), 130.6 (C5a), 131.3 (C8), 134.8 (C1''), 138.5 (C9a), 140.7 (C1'), 165.6 (C5), 169.2 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 142.0 (N4), 145.3 (N1); IR (cm^{-1}): ν 2918, 2848, 1668, 1640, 1602, 1493, 1456, 1426, 1353, 1238, 1149, 765, 708, 693, 568; MS (EI) *m/z* (%): (411 5, $[M + 1]^+$), (410 (16, $[M]^+$), 328 (32), 327 (19), 313 (34), 305 (19), 291 (65), 223 (34), 196 (23), 195 (100), 167 (37), 132 (25), 77 (19); HRMS (ESI+): *m/z* calcd for $C_{27}H_{27}N_2O_2^+$ ([M + H]$^+$) 411.2067, found 411.2065. Anal. Calcd for $C_{27}H_{26}N_2O_2$ (410.52): C 79.00, H 6.38, N 6.82, found: C 79.11, H 6.29, N 6.76.

*1,3-Diphenyl-4-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3g**).* Triton B: 276 mg, 90% yield; TMG: 298 mg, 97% yield. Yellow solid, mp 84–89 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.47 (s, 3H, H1'''), 5.77 (s, 1H, H3), 6.36 (d, 1H, J = 8.2 Hz, H9), 6.96 (dd, 1H, J = 7.5, 7.5 Hz, H7), 7.03–7.10 (m, 4H, H8, H2'', H4'', H6''), 7.15 (dd, 2H, J = 7.6, 7.6 Hz, H3'', H5''), 7.33 (d, 2H, J = 7.5 Hz, H2', H6'), 7.40 (t, 1H, J = 7.5 Hz, H4'), 7.47 (dd, 1H, J = 7.9, 1.4 Hz, H6), 7.50 (dd, 2H, J = 7.5 Hz, H3', H5'); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.2 (C1'''), 68.1 (C3), 123.4 (C9), 123.9 (C2'', C6''), 125.1 (C7), 127.3 (C4''), 127.8 (C4'), 128.5 (C3'', C5''), 128.6 (C2', C6'), 129.5 (C3', C5'), 129.8 (H6), 129.9 (C5a), 131.5 (C8), 134.4 (C1''), 138.8 (C9a), 140.8 (C1'), 166.2 (C5), 168.0 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 118.4 (N4), 145.8 (N1); IR (cm^{-1}): ν 3061, 2929, 1678, 1643, 1601, 1492, 1450, 1396, 1352, 1243, 1162, 758, 711, 695 595, 529; MS (EI) *m/z* (%): (8, [M + 1]$^+$), 342 (34, [M]$^+$), 237 (40), 223 (40), 196 (24), 195 (100), 167 (32), 118 (16), 77 (22); HRMS (ESI+): *m/z* calcd for $C_{22}H_{19}N_2O_2^+$ ([M + H]$^+$) 343.1441, found 343.1439.

*3,4-Dihydro-4-methyl-3-phenyl-1H-benzo[e][1,4]diazepine-2,5-dione (**3h**).* TMG: 142 mg, 59% yield. White solid, mp 249–252 °C; mp[62] 242–244 °C (DMF/water). ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.46 (s, 3H, H1'''), 5.55 (s, 1H, H3), 6.93 (d, 1H, J = 8.1 Hz, H9), 6.98 (dd, 1H, J = 7.5, 7.5 Hz, H7), 7.00–7.08 (m, 2H, H2'', H6''), 7.14 (t, 1H, J = 7.2 Hz, H4''), 7.22 (dd, 2H, J = 7.6, 7.6 Hz, H3'', H5''), 7.28 (dd, 1H, J = 7.4, 7.4 Hz, H8), 7.54 (d, 1H, J = 7.7 Hz, H6), 10.80 (br s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 38.6 (br, C1'''), 67.5 (br, C3), 119.9 (C9), 123.6 (C7), 124.3 (br, C2'', C6''), 126.7 (C5a), 127.4 (C4''), 128.4 (C3'', C5''), 130.3 (C6), 131.7

(C8), 134.3 (br, C1''), 135.2 (C9a), 166.4 (C5), 170.3 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 116.4 (N4), 135.7 (N1); IR (cm^{-1}): ν 3143, 2920, 1687, 1618, 1488, 1448, 1396, 1373, 1246, 1168, 795, 760, 728, 693, 495; MS (EI) *m/z* (%):267 (15, $[M + 1]^+$), 266 (81, $[M]^+$), 161 (100), 146 (13), 120 (60), 119 (43), 118 (44), 92 (32), 91 (14), 77 (12), 42 (21); HRMS (ESI+): *m/z* calcd for $C_{16}H_{15}N_2O_2^+$ $[M + H]^+$ 267.1128, found 267.1129. Anal Calcd for $C_{16}H_{14}N_2O_2$ (266.29): C 72.17, H 5.30, N 10.52%, found C 72.02, H 5.26, N 10.59.

*4-Butyl-3-phenyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3i**).* NaOEt: 121 mg, 44% yield. Brownish solid, mp 166–170 °C (ethyl acetate); mp[46] 159–163 °C (benzene/hexane) ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.92 (t, 3H, *J* = 7.3 Hz, H4'''), 1.34 (tq, 2H, *J* = 7.3, 7.3 Hz, H3'''), 1.58–1.71 (m, 2H, H2'''), 3.53 (ddd, 1H, *J* = 13.7, 7.7, 5.4 Hz, H1'''a), 4.07–4.17 (m, 1H, H1'''b), 5.47 (s, 1H, H3), 6.83 (d, 1H, *J* = 8.0 Hz, H9), 6.90 (dd, 1H, *J* = 7.5, 7.5 Hz, H7), 6.96 (br d, 2H, *J* = 6.9 Hz, H2'', H6''), 7.05 (t, 1H, *J* = 7.1, H4''), 7.14 (dd, 2H, *J* = 7.5, 7.5 Hz, H3'', H5''), 7.19 (dd, 1H, *J* = 7.5, 7.5 Hz, H8), 7.46 (d, 1H, *J* = 7.7 Hz, H6), 10.70 (s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6 δ 13.7 (C4'''), 19.4 (C3'''), 29.9 (C2'''), 49.7 (C1'''), 66.1 (C3), 119.9 (C9), 123.6 (C7), 124.2 (br, C2'', C6''), 127.3 (C4'', C5a), 128.4 (C3'', C5''), 130.3 (C6), 131.6 (C8), 134.5 (C1''), 135.1 (C9a), 166.1 (C5), 170.8 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 128.5 (N4), 135.5 (N1); IR (cm^{-1}): ν 3206, 3085, 2955, 2926, 2859, 1675, 1630, 1606, 1484, 1461, 1450, 1434, 1400, 765, 735; HRMS (ESI+): *m/z* calcd for $C_{19}H_{21}N_2O_2^+$ $[M + H]^+$ 309.1598, found 309.1594. Anal. Calcd for $C_{19}H_{20}N_2O_2$ (308.38): C, 74.00; H, 6.54; N, 9.08%. Found: C, 73.70; H, 6.67; N, 9.01%.

*4-Butyl-3-ethyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3j**).* NaOEt: 136 mg, 58% yield. Colorless solid, mp 98–104 °C (benzene/hexane). Major isomer : minor isomer = 59 : 41. *Major isomer:* ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.76 (t, 3H, *J* = 7.4 Hz, H2''), 0.89 (t, 3H, *J*

= 7.3 Hz, H4'''), 1.23–1.31 (m, 2H, H3'''), 1.31–1.42 (m, 2H, H1''), 1.49–1.56 (m, 2H, H2'''), 3.19–3.27 (m, 1H, H1'''a), 3.90–4.01 (m, 2H, H3, H1'''b), 7.08 (d, 1H, *J* = 8.1 Hz, H9), 7.17 (dd, 1H, *J* = 7.5, 7.5 Hz, H7), 7.47 (dd, 1H, *J* = 7.7, 7.7 H, H8), 7.73 (d, 1H, *J* = 7.8 Hz, H6), 10.50 (br s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.3 (C2''), 13.7 (C4'''), 19.3 (C3'''), 21.9 (C1''), 29.7 (C2'''), 49.8 (C1'''), 65.4 (C3), 119.9 (C9), 123.7 (C7), 126.6 (C5a), 130.7 (C6), 132.2 (C8), 135.5 (C9a), 164.9 (C5), 171.2 (C2); *Minor isomer:* ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.84 (t, 3H, *J* = 7.1 Hz, H2''), 0.89 (t, 3H, *J* = 7.3 Hz, H4'''), 1.16–1.23 (m, 2H, H3'''), 1.41–1.49 (m, 2H, H2'''), 1.74–1.84 (m, 1H, H1''a), 1.92–2.03 (m, 1H, H1''b), 3.00–3.09 (m, 1H, H1'''a), 3.83 (t, 1H, J = 7.2 Hz, H3), 3.90–4.01 (m, 1H, H1'''b), 7.08 (d, 1H, *J* = 8.1 Hz, H9), 7.21 (dd, 1H, *J* = 7.6, 7.6 Hz, H7), 7.49 (dd, 1H, *J* = 7.8, 7.8 Hz, H8), 7.73 (d, 1H, *J* = 7.8 Hz, H6), 10.50 (br s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 10.9 (C2''), 13.6 (C4'''), 19.1 (C1''), 19.5 (C3'''), 30.2 (C2'''), 41.0 (C1'''), 56.3 (C3), 120.5 (C9), 123.9 (C7), 127.3 (C5a), 130.7 (C6), 131.8 (C8), 136.7 (C9a), 167.4 (C5), 170.9 (C2); IR (cm^{-1}): ν 3223, 3169, 2956, 2930, 2871, 1709, 1616, 1604, 1482, 1414, 1391, 1220, 767, 757; HRMS (ESI+): *m/z* calcd for $C_{15}H_{21}N_2O_2^+$ [M + H]$^+$ 261.1598, found 261.1601. Anal. Calcd. for $C_{15}H_{20}N_2O_2$ (260.33): C, 69.20; H, 7.74; N, 10.76%. Found: C, 69.13; H, 7.73; N, 10.62%.

*3,4-Dibutyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3k**).* NaOEt: 185 mg, 71% yield, colorless oil. Major isomer : minor isomer = 61 : 39. *Major isomer:* ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.69 (t, 3H, *J* = 7.1 Hz, H4''), 0.89 (t, 3H, *J* = 7.4 Hz, H4'''), 1.05–1.57 (m, 10H, H3'', H2'', H1'', H3''', H2'''), 3.16–3.26 (m, 1H, H1'''), 3.94 (dd, 1H, *J* = 7.6, 7.6 Hz, H1'''), 4.00 (dd, 1H, *J* = 8.5, 8.5 Hz, H3), 7.08 (d, 1H, *J* = 7.9 Hz, H9), 7.18 (ddd, 1H, *J* = 7.2, 7.2, 0.6 Hz, H7), 7.48 (ddd, 1H, *J* = 7.4, 7.4, 1.4 Hz, H8), 7.72 (d, 1H, *J* = 7.9 Hz, H6, H6), 10.49 (s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.5 (C4''), 13.7 (C4'''), 19.3 (C3'''), 21.5 (C3''), 27.6 (C2''), 28.2 (C1''), 29.7 (C2'''), 49.8 (C1'''), 64.2 (C3), 120.0 (C9), 123.8 (C7), 126.7 (C5a), 130.7 (C6), 132.2 (C8), 135.6 (C9a), 165.0 (C5), 171.3 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 129.2 (N4), 135.5 (N1); *Minor isomer:* ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.85 (t, 6H, *J* = 7.3 Hz, H4'', H4'''), 1.05–1.57 (m, 10H, H3'', H2'', H3''', H2'''), 1.69–1.81 (m, 1H, H1''), 1.88–2.00 (m, 1H, H1''), 2.98–3.08 (m, 1H, H1'''), 3.88 (dd, 1H, *J* = 7.3, 7.3 Hz, H3), 3.97 (dd, 1H, *J* = 7.5, 7.5 Hz, H1'''), 7.07 (d, 1H, *J* = 8.0 Hz, H9), 7.21 (dd, 1H, *J* = 7.8, 7.8 Hz, H7), 7.49 (ddd, 1H, *J* = 7.4, 7.4, 1.3 Hz, H8), 10.49 (s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 13.6 (C4'''), 13.8 (C4''), 19.5 (C3'''), 22.1 (C3''), 25.4 (C1''), 28.1 (C2''), 30.2 (C2'''), 41.1 (C1'''), 54.9 (C3), 120.5 (C9), 124.0 (C7), 127.3 (C5a), 130.7 (C6), 131.9 (C8), 136.7 (C9a), 167.5 (C5), 171.0 (C2); ^{15}N NMR (51 MHz, DMSO-d_6) δ 137.4 (N1); IR (cm^{-1}): ν 3221, 2958, 2930, 2871, 1689, 1636, 1620, 1484, 1437, 1380, 1164, 760, 703, 526; HRMS (ESI+): *m/z* calcd for $C_{17}H_{25}N_2O_2^+$ [M + H]$^+$ 289.1911, found 289.1909.

*3-Benzyl-4-methyl-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**3l**).* NaOEt: 100 mg, 40% yield. Brownish solid, mp 121–124 °C; mp[63] 100.5–103 °C (acetone/hexane). Major isomer : minor isomer = 62 : 38. *Major isomer:* ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.95 (s, 3H, H1'''), 3.21 (dd, 1H, *J* = 14.4, 7.5 Hz, $PhCH_2$), 3.29 (dd, 1H, *J* = 14.4, 7.6 Hz, $PhCH_2$), 4.33 (t, 1H, *J* = 7.4 Hz, H3), 7.08 (d, 1H, *J* = 8.1 Hz, H9), 7.16–7.32 (m, 6H, H7, H2'', H3'', H4'', H5'', H6''), 7.50 (dd, 1H, *J* = 7.3, 7.3 Hz, H8), 7.73 (d, 1H, *J* = 7. 6 Hz, H6), 10.51 (br s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 28.7 (C1'''), 31.4 ($PhCH_2$), 56.0 ($PhCH_2$), 120.7 (C9), 124.1, 126.5, 127.0, 128.4, 129.0, 130.7 (C6), 132.0 (C8), 136.6 (C9a), 137.4, 167.6, 169.2 (C2). ^{15}N NMR (51 MHz, DMSO-d_6) δ 117.3 (N4), 136.9 (N1). *Minor isomer:* ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.62 (dd, 1H, *J* = 13.2, 10.2 Hz, $PhCH_2$), 2.72 (dd, 1H, *J* = 13.3 H, 7.8 Hz, $PhCH_2$), 2.88 (s, 3H, H1'''), 4.32 (t, 1H, *J* = 7.8 Hz, H3), 7.02 (d, 2H, *J* = 7.2 Hz, H2'', H6''), 7.16–7.32 (m, 5H, H7, H9, H3", H4", H5"), 7.58 (dd, 1H, *J* = 7.4, 7.4 Hz, H8), 7.86 (d, 1H, *J* = 7.7 Hz, H6), 10.65 (br s, 1H, H1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 33.7 (PhCH$_2$), 38.7 (C1'"), 67.1 (C3), 120.2 (C9), 124.0, 126.4, 126.9, 128.5, 128.9, 131.0 (C6), 132.5 (C8), 135.6 (C9a), 136.0, 165.2, 169.8 (C2). ^{15}N NMR (51 MHz, DMSO-d_6) δ 115.5 (N4), 136.6 (N1); IR (cm^{-1}): ν 3602, 3084, 2904, 1691, 1613, 1607, 1482, 1454, 1436, 1396, 755, 700, 525, 499; HRMS (ESI+): *m/z* calcd for $C_{17}H_{17}N_2O_2^+$ $[M + H]^+$ 281.1285, found 281.1283. Anal. Calcd for $C_{17}H_{16}N_2O_2$ (280.32): C, 72.84; H, 5.75; N, 9.99%. Found: C, 72.58; H, 5.98; N, 9.83%.

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