

A One-Pot Transition-Metal-Free Tandem Process to 1,4-Benzodiazepine Scaffolds

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Abstract: An efficient and practical method for the synthesis of 1,4-benzodiazepines is reported. This methodology offers a transition-metal-free tandem process in one pot. This process is applicable to the construction of a wide variety of 1,4-benzodiazepines and other tricyclic systems with high potential biological and pharmacological activities.

Key words: 1,4-benzodiazepines, pyridazinobenzodiazepines, one-pot reaction, transition-metal-free tandem process

The synthesis of heterocycles² is currently regarded as one of the primary challenges in medicinal chemistry. 1,4-Benzodiazepines have received considerable attention because of their biological activities such as antidepressant,³ anti-inflammatory,⁴ antagonist,⁵ antimicrobial,⁶ anti-HIV agents,⁷ and antihypertensive⁸ activities. The 1,4-benzodiazepine moiety is also a pivotal intermediate for the production of the medicines, which are currently marketed including olanzapine, clozapine, and virmune (Figure 1).⁹ Pyridazinone derivatives still play an important role in medicinal chemistry owing to their biological activities,¹⁰ including antimicrobial,¹¹ pesticide,¹² analgesic,¹³ herbicidal,¹⁴ and anticancer¹⁵ activities.

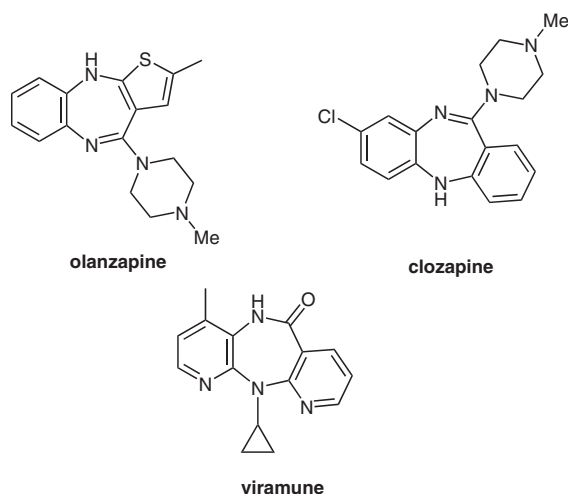
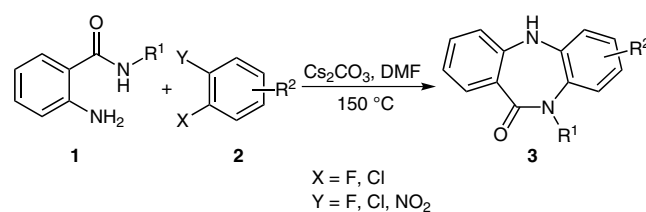


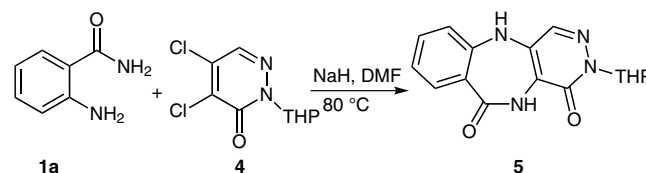
Figure 1 Structures of olanzapine, clozapine and virmune

To date, several methods have been reported for the synthesis of these 1,4-benzodiazepine scaffolds.¹⁶ Wang et al. described the synthesis of these tricyclic compounds in chlorobenzene using ortho-substituted benzoic acids and benzene-1,2-diamine in the presence of copper.¹⁷ Joshua and co-workers reported the synthesis of a tricyclic lactam by coupling 2,5-dibromonitrobenzene with anthranilic acid via multiple steps.¹⁸ Diao and Ma developed a new copper-catalyzed strategy to construct these compounds from ortho-substituted aryl bromides and primary amines.¹⁹ However, these procedures suffer from some disadvantages such as complex manipulation²⁰ and the use of transition metal catalyst.²¹ Additionally, to the best of our knowledge, fused pyridazinobenzodiazepines have not been reported. We believe these to be valuable intermediates in medicinal chemistry.

Herein, we report an effective metal-free process for the synthesis of 1,4-benzodiazepines and fused pyridazinobenzodiazepines. Substituted benzenes **2** and N-substituted 2-aminobenzamides **1** were used as substrates in the presence of cesium carbonate (Scheme 1). 2-Aminobenzamide (**1a**) and 4,5-dichloro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (**4**) as substrates, sodium hydride as the base, and DMF as the solvent were used to synthesize the fused pyridazinobenzodiazepine **5** (Scheme 2).



Scheme 1 One-pot synthesis of 1,4-benzodiazepines



Scheme 2 One-pot synthesis of a pyridazinobenzodiazepine

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Initially, the 2-aminobenzamide (**1a**) and 2,3-difluorobenzonitrile (**2e**) were chosen as models to determine the optimized conditions. As shown in Table 1, the reaction temperature, base, and solvent were investigated. The preliminary study was conducted using K_2CO_3 as the base and DMF as the solvent at room temperature for 48 hours, but the desired product **3d** was not obtained. Increasing the temperature to 150 °C led to the desired product in 30% yield (Table 1, entry 2). Next, the reaction was carried out using various bases, and Cs_2CO_3 provided the highest yields (Table 1, entries 1–4). When strong base such as NaH or *t*-BuOK was used in the reaction, no desired **3d** was obtained (Table 1, entries 1, 4, 7, and 8). Finally, the solvents DMF and DMSO were investigated using Cs_2CO_3 as the base (Table 1, entries 3 and 6). To our delight, the desired product **3d** was obtained in 54% yield when DMF was used.

The optimized conditions (Table 1, entry 3) were applied to a variety of compounds **2**, and the results are summarized in Table 2. As observed in Table 2, the reaction proceeded well with substituted benzenes and *N*-substituted 2-aminobenzamides to give a range of 1,4-benzodiazepines.²² When **1** was reacted with benzenes containing electron-withdrawing groups (halogen, nitro, cyano, and trifluoromethyl), the corresponding products **3** were generated in moderate to good yields (Table 2, entries 1–6, 8, and 11). Moreover, the reaction was also applied to 2-fluoro-1-methyl-3-nitrobenzene (**2g**) bearing an electron-donating group, affording the desired product **3f** in 67% yield (Table 2, entry 7). Further, 2-amino-*N*-methylbenz-

Table 1 Reaction Conditions and Yields for the Synthesis of **3d**

Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%)
1	NaH	DMF	150	8	0
2	K_2CO_3	DMF	150	12	30
3	Cs_2CO_3	DMF	150	8	54
4	<i>t</i> -BuOK	DMF	150	12	0
5	K_2CO_3	DMSO	150	12	28
6	Cs_2CO_3	DMSO	150	6	52
7	<i>t</i> -BuOK	DMSO	150	12	0
8	NaH	DMSO	150	8	0

amide (**1b**) possessing an electron-donating group was reacted with **2e** under the same conditions to afford the corresponding product **3i** in excellent yield (Table 2, entry 11).

Table 2 Synthesis of 1,4-Benzodiazepines **3**^a

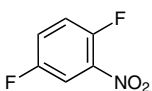
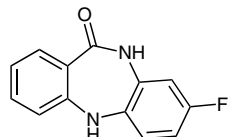
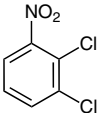
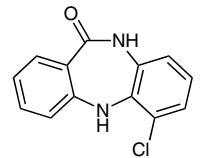
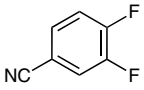
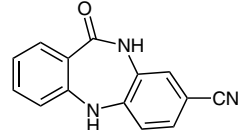
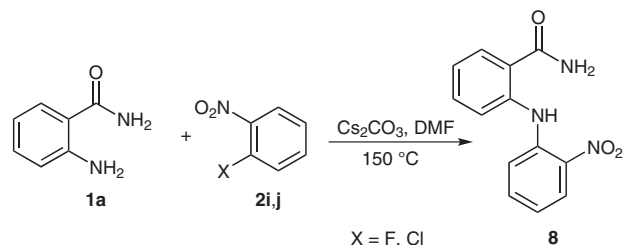
Entry	1	R^1	2	Time (h)	Product 3	Yield (%) ^b
1	1a	H	2a 	7	3a 	68
2	1a	H	2b 	7	3b 	56
3	1a	H	2c 	7.5	3c 	51

Table 2 Synthesis of 1,4-Benzodiazepines **3**^a (continued)

Entry	1	R ¹	2	Time (h)	Product 3	Yield (%) ^b
<p style="text-align: center;">X = F, Cl Y = F, Cl, NO₂</p>						
4	1a	H	2d 	5.5	3c 	60
5	1a	H	2e 	6.5	3d 	54
6	1a	H	2f 	6	3e 	47
7	1a	H	2g 	5.5	3f 	67
8	1a	H	2h 	6	3g 	60
9	1a	H	2i 	6	3h 	trace
10	1a	H	2j 	6.5	3h 	trace
11	1b	Me	2e 	5	3i 	90

^a Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), Cs₂CO₃ (3 mmol), DMF (10 mL), 150 °C, 5–7.5 h.^b Isolated yield.

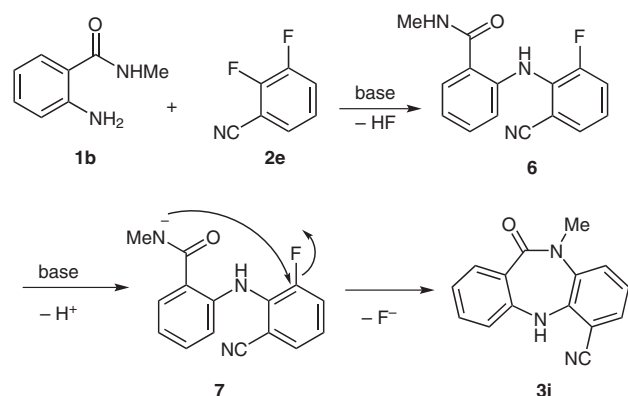
As shown in Table 2, the reactant with nitro group (Table 2, entries 9 and 10) could afford **3h**,^{21,22a} but their yields were much lower than the substrates having a strong electron-donating group. The tricyclic product **3h** was obtained only in trace amounts and was confirmed by HRMS analysis. Conversely, the mono-substituted product **8** was mainly obtained (Scheme 3).



Scheme 3 Reaction of **1a** with **2i** and **2j**

After the synthesis of 1,4-benzodiazepines **3**, this methodology was explored for the preparation of fused pyridazinobenzodiazepines **5**. Thus, 4,5-dichloro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (**4**) could be employed to construct 2-(tetrahydro-2H-pyran-2-yl)-5,11-dihydro-1H-benzo[e]pyridazino[4,5-b][1,4]diazepine-1,10(2H)-dione (**5**) in the presence of cesium carbonate in DMF at 120 °C in 54% yield. By comparison of various reaction conditions, we found that NaH in DMF at 80 °C was the most efficient system, giving the tricyclic product **5** in 84% yield (Scheme 2).

Based on the experimental results, a proposed reaction mechanism of the one-pot formation of **3i** is outlined in Scheme 4. The reaction of **1b** with **2e** yielded compound **6** by nucleophilic aromatic substitution. The next step was the formation of intermediate **7**. Finally, intermediate **7** underwent an intramolecular nucleophilic displacement of halogen anion by a nitrogen anion to yield compound **3i**. To support this mechanism, the structure of **3i** was unambiguously proved by single crystal X-ray analysis (Figure 2).



Scheme 4 A proposed reaction mechanism

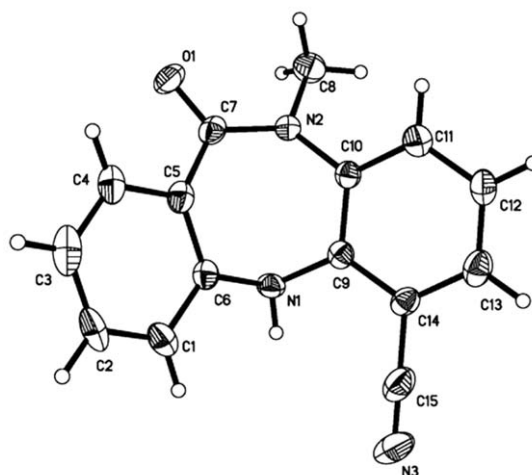


Figure 2 Single crystal X-ray structure of **3i**

In summary, we have developed a simple and efficient approach for the synthesis of 1,4-benzodiazepines in moderate to good yields. The prominent features of this methodology are mild and metal catalyst-free reaction conditions. On the basis of the related work, a facile method was discovered for assembling 2-(tetrahydro-2H-pyran-2-yl)-5,11-dihydro-1H-benzo[e]pyridazino[4,5-b][1,4]diazepine-1,10(2H)-dione in high yield. Importantly, this method has high potential uses in the synthesis of biologically relevant compounds. Further investigation for broadening the application of this methodology is currently underway in our laboratory.

2-Amino-*N*-methylbenzamide (**1b**)²³ and 4,5-dichloro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (**4**)²⁴ were prepared according to literature procedures. All other commercial reagents were used without further purification. Petroleum ether (PE) refers to the fraction boiling in the 60–90 °C range. All the reactions were conducted under N₂ atmosphere and monitored by TLC. Melting points were determined on an XD-4 digital micro melting point apparatus. ¹H NMR spectra were recorded at 300 MHz on a Bruker Avance 300 spectrometer with TMS as the internal standard and CDCl₃ or DMSO-*d*₆ as solvent. ¹³C NMR spectra were obtained on a Bruker Avance 300 (75 MHz) spectrometer with TMS as the internal standard and CDCl₃ or DMSO-*d*₆ as solvent. ¹⁹F NMR spectra were obtained in DMSO-*d*₆ on a Bruker Avance 300 (282 MHz) spectrometer. High-resolution mass spectra (HRMS) were obtained on a Q-TOF6510 spectrograph (Agilent). Single crystal X-ray diffraction were performed on a Rigaku RAXIS-SPIDER IP diffractometer at 50 kV and 20 mA and data collection was performed at 273(2) K by using graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å).

2-Amino-*N*-methylbenzamide (**1b**)

To a solution of 2-nitrobenzoic acid (1.0 g, 6 mmol) in MeOH (15 mL) was slowly added concd H₂SO₄ (2 mL) at r.t. over 15 min. Then, the mixture was refluxed, and the end of the reaction was monitored by TLC (eluent: PE–EtOAc, 5:1, v/v). The reaction mixture was cooled to r.t. Brine (50 mL) was added and the mixture was extracted with CH₂Cl₂ (2 × 30 mL). The combined organic phases were dried (MgSO₄). The solvent was removed under vacuum to afford a residue. A mixture of the residue and aq MeNH₂ (20 mL) was refluxed for 2 h. After cooling, brine (50 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried (MgSO₄) and the solvent was removed un-

der vacuum to afford an orange solid. The solid was stirred with 12 M HCl (20 mL) at 55 °C. SnCl₂ (2.84 g, 15 mmol) was slowly added to the mixture and the resulting solution was stirred at 100 °C for 15 min. After cooling to r.t., white crystals separated out. The crude product was washed with aq 1 M NaOH (30 mL) and extracted with CH₂Cl₂ (2 × 30 mL). The combined organic phases were dried (MgSO₄) and concentrated. The crude product was purified by recrystallization from EtOAc (20 mL) to afford the desired product **1b** as a white solid (0.62 g, 69%); mp 75.0–76.3 °C (Lit.²³ mp 76–78 °C).

11-Oxo-10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepine-6-carbonitrile (**3d**); Typical Procedure

To a solution of 2-aminobenzamide (**1a**; 100 mg, 0.74 mmol) in anhyd DMF (10 mL) were added 2,3-difluorobenzonitrile (**2e**; 124 mg, 0.89 mmol) and Cs₂CO₃ (723 mg, 2.22 mmol) at r.t. under a dry N₂ atmosphere. The resulting solution was stirred at 150 °C, and the progress of the reaction was monitored by TLC (eluent: PE–EtOAc, 5:1, v/v). The mixture was diluted with brine (100 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (PE–EtOAc, 8:1, v/v) afforded the desired product **3d**; yield: 94 mg (54%); pale yellow crystals; mp 191.8–193.2 °C.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 8.14–8.11 (dd, *J* = 0.9, 8.4 Hz, 1 H), 7.96–7.93 (dd, *J* = 1.5, 8.1 Hz, 1 H), 7.89–7.86 (dd, *J* = 0.9, 8.7 Hz, 1 H), 7.58–7.52 (m, 1 H), 7.37–7.32 (m, 1 H), 7.20 (s, 2 H), 6.97–6.94 (dd, *J* = 0.6, 8.4 Hz, 1 H), 6.75–6.70 (m, 1 H).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 165.60, 150.02, 149.16, 143.64, 134.15, 129.29, 128.91, 125.78, 116.86, 116.44, 116.21, 116.16, 105.56, 101.36.

HRMS (ESI): *m/z* [M + H⁺] calcd for C₁₄H₉N₃O: 236.0818; found: 236.0814.

8-Fluoro-5H-dibenzo[*b,e*][1,4]diazepin-11(10H)-one (**3a**)^{21c}

Yield: 115 mg (68%); orange crystals; mp 219.6–222.3 °C (Lit.^{21c} mp 222–223 °C).

¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.90–7.87 (dd, *J* = 1.2, 9.3 Hz, 1 H), 7.81–7.73 (m, 2 H), 7.31–7.23 (m, 2 H), 7.08 (s, 2 H), 6.92–6.90 (d, *J* = 7.5 Hz, 1 H), 6.72–6.66 (m, 1 H).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 163.46, 159.74 (d, ¹*J*_{C,F} = 239.2 Hz), 148.63, 148.62 (d, ³*J*_{C,F} = 15.8 Hz), 137.73, 132.60, 127.89, 119.50 (d, ³*J*_{C,F} = 10.5 Hz), 116.06, 115.41, 112.18 (d, ²*J*_{C,F} = 24.0 Hz), 106.08 (d, ⁴*J*_{C,F} = 2.2 Hz), 98.79 (d, ²*J*_{C,F} = 28.5 Hz).

¹⁹F NMR (282 MHz, DMSO-*d*₆): δ = –115.77.

HRMS (ESI): *m/z* [M + H⁺] calcd for C₁₃H₉FN₂O: 229.0772; found: 229.0764.

6-Chloro-5H-dibenzo[*b,e*][1,4]diazepin-11(10H)-one (**3b**)^{3,22}

Yield: 101 mg (56%); orange crystals; mp 120.9–122.9 °C.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.94–7.91 (dd, *J* = 1.5, 8.1 Hz, 1 H), 7.77–7.74 (dd, *J* = 0.9, 8.1 Hz, 1 H), 7.51–7.48 (dd, *J* = 0.9, 8.1 Hz, 1 H), 7.43–7.41 (d, *J* = 7.8 Hz, 1 H), 7.38–7.28 (m, 1 H), 7.16 (s, 2 H), 6.94–6.92 (d, *J* = 7.5 Hz, 1 H), 6.73–6.68 (m, 1 H).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 164.02, 149.43, 140.78, 133.35, 132.25, 129.51, 128.51, 125.45, 120.38, 116.62, 115.94, 111.51, 106.30.

HRMS (ESI): *m/z* [M + H⁺] calcd for C₁₃H₉ClN₂O: 245.0476; found: 245.0476.

11-Oxo-10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepine-8-carbonitrile (**3c**)

From **2c**, yield: 89 mg (51%); from **2d**, yield: 104 mg (60%); pale yellow crystals; mp 186.1–188.2 °C.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 8.37–8.36 (d, *J* = 0.9 Hz, 1 H), 7.95–7.91 (m, 2 H), 7.86–7.82 (dd, *J* = 1.5, 8.4 Hz, 1 H), 7.36–7.30

(m, 1 H), 7.21 (s, 2 H), 6.95–6.92 (dd, *J* = 0.6, 8.4 Hz, 1 H), 6.74–6.68 (m, 1 H).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 166.12, 150.05, 148.48, 145.72, 134.10, 129.66, 128.85, 120.43, 119.42, 116.80, 116.07, 115.39, 107.03, 105.60.

HRMS (ESI): *m/z* [M + H⁺] calcd for C₁₄H₉N₃O: 236.0818; found: 236.0839.

8-(Trifluoromethyl)-5H-dibenzo[*b,e*][1,4]diazepin-11(10H)-one (**3e**)^{21c}

Yield: 97 mg (47%); white crystals; mp 205.1–207.0 °C (Lit.^{21c} mp 200–202 °C).

¹H NMR (300 MHz, DMSO-*d*₆): δ = 9.94 (s, 1 H), 7.96–7.94 (d, *J* = 2.7 Hz, 1 H), 7.92 (s, 1 H), 7.77–7.72 (m, 2 H), 7.27–7.22 (m, 1 H), 6.80–6.77 (d, *J* = 7.2 Hz, 1 H), 6.64–6.60 (m, 1 H), 6.46 (s, 1 H).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 167.56, 150.18, 139.28, 132.81, 128.85, 128.84, 127.52, 126.64 (q, ²*J*_{C,F} = 32.2 Hz), 126.50 (q, ³*J*_{C,F} = 3.75 Hz), 123.41 (q, ¹*J*_{C,F} = 270.8 Hz), 124.43 (q, ³*J*_{C,F} = 3.38 Hz), 116.81, 114.97, 113.52.

¹⁹F NMR (282 MHz, DMSO-*d*₆): δ = –60.75.

HRMS (ESI): *m/z* [M + H⁺] calcd for C₁₄H₉F₃N₂O: 279.0740; found: 279.1576.

6-Methyl-5H-dibenzo[*b,e*][1,4]diazepin-11(10H)-one (**3f**)

Yield: 111 mg (67%); orange crystals; mp 136.1–138.2 °C.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 11.26 (s, 1 H), 8.72 (s, 1 H), 8.19–8.16 (d, *J* = 8.7 Hz, 1 H), 7.66–7.63 (d, *J* = 8.1 Hz, 1 H), 7.33–7.26 (dd, *J* = 7.5, 15.6 Hz, 1 H), 7.01–6.98 (d, *J* = 8.4 Hz, 1 H), 6.79–6.73 (dd, *J* = 7.5, 11.7 Hz, 2 H), 5.78 (s, 1 H), 2.48 (s, 3 H).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 168.00, 149.94, 147.95, 135.49, 134.47, 133.59, 127.47, 125.97, 124.04, 122.01, 117.79, 117.19, 114.77, 22.22.

HRMS (ESI): *m/z* [M + H⁺] calcd for C₁₄H₁₂N₂O: 225.1022; found: 225.1032.

8-Chloro-5H-dibenzo[*b,e*][1,4]diazepin-11(10H)-one (**3g**)^{3,22}

Yield: 108 mg (60%); pale yellow crystals; mp 231.2–232.8 °C (Lit.³ mp 232–233 °C).

¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.95–7.94 (dd, *J* = 2.1, 8.4 Hz, 1 H), 7.91–7.88 (dd, *J* = 1.5, 8.1 Hz, 1 H), 7.80–7.77 (d, *J* = 8.4 Hz, 1 H), 7.46–7.42 (dd, *J* = 2.1, 8.4 Hz, 1 H), 7.33–7.27 (m, 1 H), 7.14 (s, 2 H), 6.94–6.91 (dd, *J* = 0.6, 8.4 Hz, 1 H), 6.72–6.67 (m, 1 H).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 164.02, 149.43, 140.78, 133.35, 132.25, 129.51, 128.51, 125.45, 120.38, 116.62, 115.94, 111.51, 106.30.

HRMS (ESI): *m/z* [M + H⁺] calcd for C₁₃H₉ClN₂O: 245.0476; found: 245.0480.

10-Methyl-11-oxo-10,11-dihydro-5H-dibenzo[*b,e*][1,4]diazepine-9-carbonitrile (**3i**)

Yield: 166 mg (90%); white crystals; mp 141.5–143.0 °C.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.92–7.89 (dd, *J* = 1.5, 7.8 Hz, 1 H), 7.42–7.35 (m, 3 H), 7.20–7.17 (dd, *J* = 8.1 Hz, 1 H), 7.14–7.08 (m, 1 H), 6.99–6.96 (dd, *J* = 0.9, 8.1 Hz, 1 H), 6.06 (s, 1 H), 3.53 (s, 3 H).

¹³C NMR (75 MHz, DMSO-*d*₆): δ = 169.39, 157.31, 153.99, 143.20, 131.41, 128.73, 126.62, 123.83, 120.62, 120.35, 119.24, 118.42, 115.01, 108.46, 26.16.

HRMS (ESI): *m/z* [M + H⁺] calcd for C₁₅H₁₁N₃O: 250.0975; found: 250.0993.

2-[(2-Nitrophenyl)amino]benzamide (**8**)

From **2i**, yield: 113 mg (60%); from **2j**, yield: 104 mg (55%); orange crystals; mp 201.3–203.2 °C.

^1H NMR (300 MHz, DMSO- d_6): δ = 11.22 (s, 1 H), 8.14–8.11 (dd, J = 1.2, 8.4 Hz, 2 H), 7.75–7.72 (dd, J = 1.2, 7.8 Hz, 1 H), 7.60–7.43 (m, 5 H), 7.15–7.10 (m, 1 H), 7.02–6.96 (m, 1 H).

^{13}C NMR (75 MHz, DMSO- d_6): δ = 170.00, 139.65, 139.26, 135.91, 135.53, 131.41, 129.13, 126.25, 124.39, 122.23, 120.05, 119.47, 117.88.

HRMS (ESI): m/z [$M + H^+$] calcd for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_3$; 258.0834; found: 258.0886.

2-(Tetrahydro-2H-pyran-2-yl)-5,11-dihydro-1H-benzo[e]pyridazino[4,5-b][1,4]diazepine-1,10(2H)-dione (5)

To a solution of 2-aminobenzamide (**1a**; 100 mg, 0.74 mmol) in anhyd DMF (10 mL) were added 4,5-dichloro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (**4**; 196 mg, 0.89 mmol) and NaH (60%, 89 mg, 2.22 mmol) at r.t. under a dry N_2 atmosphere: The mixture was stirred for 2 h at 80 °C and then quenched with brine (100 mL). The precipitated crude product was purified by recrystallization from EtOAc (20 mL) to afford the desired product **5** as an orange solid; yield: 194 mg (84%); orange crystals; mp 271.8–273.2 °C.

^1H NMR (300 MHz, DMSO- d_6): δ = 9.81 (s, 1 H), 7.72–7.69 (dd, J = 1.0, 9.2 Hz, 2 H), 7.61–7.66 (s, 1 H), 7.33–7.29 (m, 1 H), 7.11–7.09 (d, J = 8.0 Hz, 1 H), 6.87–6.83 (dd, J = 7.6, 15 Hz, 1 H), 5.84–5.81 (dd, J = 1.9, 10.8 Hz, 1 H), 3.96–3.93 (d, J = 11.0 Hz, 1 H), 3.61–3.54 (m, 1 H), 2.10–2.00 (m, 1 H), 1.94–1.91 (d, J = 12.0 Hz, 1 H), 1.71–1.60 (m, 2 H), 1.51–1.46 (m, 2 H).

^{13}C NMR (75 MHz, DMSO- d_6): δ = 167.11, 156.02, 146.05, 134.84, 133.64, 132.88, 128.67, 122.62, 121.68, 120.72, 120.50, 83.22, 67.92, 28.35, 25.12, 22.75.

HRMS (ESI): m/z [$M + H^+$] calcd for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_3$; 313.1295; found: 313.1291.

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