

Supplementary material

Synthesis, *in vitro* and *in vivo* anticancer activities of novel 4-substituted 1,2-bis(4-chlorophenyl)-pyrazolidine-3,5-dione derivatives

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1. General Experimental

Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel (Qingdao Haiyang Chemical Co., G60F-254) and visualized by UV light (254 nm). ¹H NMR and ¹³C NMR spectra were recorded on a Bruker 400 MHz and 100 MHz spectrometer respectively. High-resolution mass spectra (HRMS) were recorded on a Waters Micromass Q-T of Micromass spectrometer by electrospray ionization (ESI).

2. Experimental Procedures and Analytical Data

Preparation of 1,2-bis(4-chlorophenyl)diazene (**1**)

Manganese dioxide (8.69 g) was added to a stirred solution of p-chloroaniline (2.551 g, 20 mmol) in toluene (50 mL). The mixture was heated at reflux for 8 h under the action of water segregator and TLC analysis indicated that the reaction was complete. The mixture was filtered through a buchner funnel and the filtrate was concentrated under reduced pressure. **1** (1.23 g, 48.9 %) was obtained as a deep yellow solid.

Preparation of 1,2-bis(4-chlorophenyl)hydrazine (**2**)

Saturated ammonium chloride solution (3 mL) and zinc powder (11.30 g, 172.3 mmol) were added to a stirred solution of compound **1** (5.64, 22.46 mmol) in acetone (15 mL). The reaction mixture was stirred for 5 h at 25 °C and TLC analysis indicated that the reaction was complete. The mixture was filtered through a buchner funnel, then

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small amount of acetone was used to wash the filter cake. All of the filtrate was concentrated to the half of its original volume. After this, ice water was added to the concentrated filter and precipitate was separated out at the same time. The precipitate was stirred for 1 h lower in nitrogen protection, concentrated under reduced pressure. Then the precipitate was washed with H₂O until neutral and dried in a vacuum. **2** (5.49 g, 96.6 %) was obtained as a light yellow solid.

Preparation of 1,2-bis(4-chlorophenyl)pyrazolidine-3,5-dione (**3**)

Sodium (0.574 g, 23.9 mmol) was added to anhydrous ethanol (25 mL), then added the compound **2** lower in nitrogen protection. The mixture was heated to 50 °C to form a solution. Diethyl malonate (3.5 ml, 3.67 g, 23.1 mmol) was added to the solution. The mixture was stirred 15 minutes, pulled out the plug and raised temperatures up to 150 °C slowly then keep 3 h. The reaction mixture was cooled to room temperature and added water (200 mL). The mixture was extracted with aether (3 × 100 mL), then combined water phases were extracted with aether (3 × 100 mL) again. The water phases were acidized twice that amount of 5 % HCl at 0 °C. Then, the precipitate was extracted with CH₂Cl₂ then washed successively with 5 % HCl and dried in a vacuum. **3** (2.37 g, 44.5 %) was obtained as a yellow solid.

General procedure for synthesis of **4** (**4a-4w**)

To a solution of compound **3** (0.32 g, 1 mmol) in methanol (10 mL), substituted aldehydes or ketones (1.5 mmol) was added in one portion. The mixture was stirred under reflux for 30 minutes. The solid was precipitated from the solution, filtered off and washed with ethanol to give the desired product.

1,2-bis(4-chlorophenyl)-4-(propan-2-ylidene)pyrazolidine-3,5-dione (4a)

Following general procedure for synthesis of **4**, acetone was added as the substituted ketone, and then yielded **4a** as a yellow solid. Yield 84%, Mp: 205-207°C; ¹H NMR (400 MHz, CDCl₃) δ 7.34 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.34 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.25 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 8.9 Hz, 2H) 2.68 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 180.45, 163.08, 135.12, 131.90, 129.09, 123.42, 115.09, 24.39. HR-MS (ESI): Calcd. C₁₈H₁₄Cl₂N₂O₂, [M+Na]⁺ m/z: 361.0511, found: 361.0512.

4-(butan-2-ylidene)-1,2-bis(4-chlorophenyl)pyrazolidine-3,5-dione (4b)

Following general procedure for synthesis of **4**, 2-butanone was added as the substituted ketone, and then yielded **4b** as a yellow solid. Yield 85%, Mp: 185-186°C; ¹H NMR (400 MHz, CDCl₃) δ 7.33 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.33 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.25 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 8.9 Hz, 2H), 3.11 (q, *J* = 7.6 Hz, 2H), 2.67 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 183.43, 163.12, 135.23, 131.91, 129.13, 123.51, 115.02, 25.23, 23.32, 12.43. HR-MS (ESI): Calcd. C₁₉H₁₆Cl₂N₂O₂, [M+Na]⁺ m/z: 375.0667, found: 375.0664.

1,2-bis(4-chlorophenyl)-4-(4-hydroxybenzylidene)pyrazolidine-3,5-dione (4c)

Following general procedure for synthesis of **4**, p-hydroxy benzaldehyde was added as the substituted aldehyde, and then yielded **4c** as a yellow solid. Yield 82%, Mp:

260-262°C; ¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, *J* = 8.8 Hz, 2H), 8.10 (s, 1H), 7.33 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.33 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.25 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 179.79, 173.24, 168.28, 166.09, 161.97, 145.72, 140.71, 140.64, 135.79, 135.69, 134.22, 134.02, 133.90, 129.71, 129.63, 129.60, 129.48, 123.56, 122.28, 120.11, 119.73. HR-MS (ESI): Calcd. C₂₂H₁₄Cl₂N₂O₂, [M+Na]⁺ m/z: 425.0460, found: 425.0462.

1,2-bis(4-chlorophenyl)-4-(4-(dimethylamino)benzylidene)pyrazolidine-3,5-dione (4d)

Following general procedure for synthesis of **4**, 4-(dimethylamino)benzaldehyde was added as the substituted aldehyde, then yielded **4d** as a yellow solid. Yield 85.5%, Mp:

273-275°C; ¹H NMR (400 MHz, CDCl₃) δ 8.57 (d, *J* = 6.4 Hz, 2H), 7.97 (s, 1H), 7.42 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.42 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 2H), 6.74 (d, *J* = 9.2 Hz, 2H), 3.19 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 178.65, 172.21, 167.26, 165.11, 161.95, 145.73, 140.61, 140.34, 135.45, 135.32, 134.24, 134.14, 133.34, 129.61, 129.33, 129.42, 129.21, 123.02, 122.12, 117.14, 116.23, 41.33. HR-MS (ESI): Calcd. C₂₄H₁₉Cl₂N₃O₂, [M+Na]⁺ m/z: 452.0933, found: 452.0931.

1,2-bis(4-chlorophenyl)-4-(4-fluorobenzylidene)pyrazolidine-3,5-dione (4e)

Following general procedure for synthesis of **4**, 4-fluorobenzaldehyde was added as the substituted aldehyde, and then yielded **4e** as a deep yellow solid. Yield 82.1%, Mp:

169-171°C; ¹H NMR (400 MHz, CDCl₃) δ 8.66 – 8.59 (m, 2H), 8.13 (s, 1H), 7.37 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.37 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.33 (d, *J* = 8.9 Hz, 2H), 7.33 (d, *J* = 8.9 Hz, 2H), 7.22 (t, *J* = 8.6 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 167.72, 165.13, 163.74, 162.05, 153.29, 138.09, 138.00, 134.96, 134.85, 132.41, 132.14, 129.25, 129.23, 128.90, 128.87, 123.73, 123.25, 116.62, 116.40, 115.94. HR-MS (ESI): Calcd. C₂₂H₁₃Cl₂N₂O₂F, [M+Na]⁺ m/z: 427.0416, found: 427.0415.

4-(4-chlorobenzylidene)-1,2-bis(4-chlorophenyl)pyrazolidine-3,5-dione (4f)

Following general procedure for synthesis of **4**, 4-chlorobenzaldehyde was added as the substituted aldehyde, and then yielded **4f** as a yellow solid. Yield 93.9%, Mp: 204-

206°C; ¹H NMR (400 MHz, CDCl₃) δ 8.51 (d, *J* = 8.5 Hz, 2H), 8.11 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.40 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.37 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 163.51, 161.84, 153.06, 141.23, 136.22, 134.87, 134.77, 132.47, 132.20, 130.73, 129.46, 129.26, 129.24, 123.74, 123.26, 116.89. HR-MS (ESI): Calcd. C₂₂H₁₃Cl₃N₂O₂, [M+Na]⁺ m/z: 443.0121, found: 445.0076.

4-(4-bromobenzylidene)-1,2-bis(4-chlorophenyl)pyrazolidine-3,5-dione (4g)

Following general procedure for synthesis of **4**, 4-bromobenzaldehyde was added as the substituted aldehyde, and then yielded **4g** as a yellow solid. Yield 84.2%, Mp: 191-192°C; ¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, *J* = 8.6 Hz, 2H), 8.07 (s, 1H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.35 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.35 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.30 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 8.9 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 161.41, 160.65, 152.11, 140.32, 135.13, 133.76, 133.24, 131.34, 131.11, 129.66, 128.44, 128.23, 128.16, 122.65, 122.14, 115.23. HR-MS (ESI): Calcd. C₂₂H₁₃Cl₂N₂O₂Br, [M+Na]⁺ m/z: 486.9616, found: 487.0012.

1,2-bis(4-chlorophenyl)-4-(3,4,5-trimethoxybenzylidene)pyrazolidine-3,5-dione (4h)

Following general procedure for synthesis of **4**, 3,4,5-trimethoxybenzaldehyde was added as the substituted aldehyde, and then yielded **4h** as a yellow solid. Yield 85%, Mp: 168-170°C; ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 1H), 8.01 (s, 2H), 7.40 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.37 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.30 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 8.9 Hz, 2H), 4.03 (s, 3H), 3.97 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 164.86, 163.13, 156.23, 155.81, 155.63, 147.32, 135.21, 133.54, 132.24, 131.78, 129.34, 129.21, 125.87, 123.68, 123.42, 116.11, 114.79, 112.54, 56.33, 60.81. HR-MS (ESI): Calcd. C₂₅H₂₀Cl₂N₂O₅, [M+Na]⁺ m/z: 499.0828, found: 499.0825.

1,2-bis(4-chlorophenyl)-4-(4-hydroxy-3-methoxybenzylidene)pyrazolidine-3,5-dione (4i)

Following general procedure for synthesis of **4**, vanillin was added as the substituted aldehyde, and then yielded **4i** as a yellow solid. Yield 82.1%, Mp: 120-122°C; ¹H NMR (400 MHz, CDCl₃) δ 8.91 (d, *J* = 1.8 Hz, 1H), 8.04 (s, 1H), 7.71 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.38 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.38 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.27 (d, *J* = 8.9 Hz, 2H), 7.27 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.71 (s, 1H), 4.02 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.75, 163.08, 155.07, 152.76, 146.63, 135.48, 135.23, 133.62, 132.19, 131.82, 129.20, 129.15, 125.99, 123.98, 123.26, 116.02, 114.89, 112.36, 56.36. HR-MS (ESI): Calcd. C₂₃H₁₆Cl₂N₂O₄, [M+Na]⁺ m/z: 455.0565, found: 455.0569.

1,2-bis(4-chlorophenyl)-4-(2-hydroxy-3-methoxybenzylidene)pyrazolidine-3,5-dione (4j)

Following general procedure for synthesis of **4**, o-vanillin was added as the substituted aldehyde, and then yielded **4j** as a yellow solid. Yield 80.7%, Mp: 201-203°C; ¹H NMR (400 MHz, CDCl₃) δ 8.79 (s, 1H), 8.64 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.40 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.40 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 7.09 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.96 (t, *J* = 8.1 Hz, 1H), 6.82 (s, 1H), 3.95 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.56, 163.13, 153.21, 150.22, 145.56, 134.44, 134.21, 132.56, 131.24, 130.67, 128.26, 128.07, 125.12, 122.77, 122.16, 115.16, 113.21, 111.19, 56.67. HR-MS (ESI): Calcd. C₂₃H₁₆Cl₂N₂O₄, [M+Na]⁺ m/z: 455.0565, found: 455.0569.

1,2-bis(4-chlorophenyl)-4-(4-methoxybenzylidene)pyrazolidine-3,5-dione (4k)

Following general procedure for synthesis of **4**, 4-methoxybenzaldehyde was added as the substituted aldehyde, and then yielded **4k** as a yellow solid. Yield 85.2%, Mp:

234-236°C; ¹H NMR (400 MHz, CDCl₃) δ 8.62 (d, *J* = 9.0 Hz, 2H), 8.10 (s, 1H), 7.37 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.37 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 3.94 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.56, 163.16, 155.46, 154.89, 135.73, 135.45, 133.76, 132.32, 131.91, 129.34, 129.09, 125.86, 123.72, 123.34, 116.13, 114.95, 112.25, 111.43, 55.48. HR-MS (ESI): Calcd. C₂₃H₁₆Cl₂N₂O₃, [M+Na]⁺ *m/z*: 439.0616, found: 439.0621.

4-(3-chlorobenzylidene)-1,2-bis(4-chlorophenyl)pyrazolidine-3,5-dione (4l)

Following general procedure for synthesis of **4**, 3-chlorobenzaldehyde was added as the substituted aldehyde, and then yielded **4l** as a yellow solid. Yield 87.7%, Mp: 198-

200°C; ¹H NMR (400 MHz, CDCl₃) δ 8.64 (t, *J* = 1.7 Hz, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.09 (s, 1H), 7.64–7.56 (m, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.40 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.40 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.43, 163.89, 153.17, 141.46, 136.34, 135.76, 134.34, 132.56, 132.34, 130.23, 129.58, 128.25, 128.24, 123.56, 123.47, 116.21. HR-MS (ESI): Calcd. C₂₂H₁₃Cl₃N₂O₂, [M+Na]⁺ *m/z*: 443.0121, found: 443.0124.

1,2-bis(4-chlorophenyl)-4-(3-methoxybenzylidene)pyrazolidine-3,5-dione (4m)

Following general procedure for synthesis of **4**, 3-methoxybenzaldehyde was added as the substituted aldehyde, and then yielded **4m** as a yellow solid. Yield 80.1%, Mp:

196-198°C; ¹H NMR (400 MHz, CDCl₃) δ 8.49 – 8.46 (m, 1H), 8.15 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.40 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.20 (dd, *J* = 8.1, 2.4 Hz, 1H), 3.93 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.68, 163.06, 161.45, 154.46, 135.34, 135.21, 133.78, 132.34, 131.78, 129.43, 129.09, 125.87, 123.96, 123.56, 116.31, 114.36, 113.42, 112.33, 55.78. HR-MS (ESI): Calcd. C₂₃H₁₆Cl₂N₂O₃, [M+Na]⁺ *m/z*: 439.0616, found: 439.0633.

1,2-bis(4-chlorophenyl)-4-(1-(4-hydroxyphenyl)ethylidene)pyrazolidine-3,5-dione (4n)

Following general procedure for synthesis of **4**, 1-(4-hydroxyphenyl)ethanone was added as the substituted ketone, and then yielded **4n** as a yellow solid. Yield 75.7%,

Mp: 266-268°C; ¹H NMR (400 MHz, CDCl₃) δ 9.57 (s, 1H), 7.49 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.49 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.30 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 8.9 Hz, 2H), 7.22 (dd, *J* = 10.6, 5.8 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.86 (dd, *J* = 4.0, 2.0 Hz, 2H), 2.81 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 178.45, 164.11, 163.32, 158.55, 135.74, 135.18, 133.68, 132.23, 131.67, 129.12, 129.32, 127.29, 123.78, 123.45, 116.22, 114.56, 113.45, 112.31, 21.42. HR-MS (ESI): Calcd. C₂₃H₁₆Cl₂N₂O₃, [M+Na]⁺ *m/z*: 461.0436, found: 461.0437.

1,2-bis(4-chlorophenyl)-4-(3,4-dimethoxybenzylidene)pyrazolidine-3,5-dione (4o)

Following general procedure for synthesis of **4**, 3,4-dimethoxybenzaldehyde was added as the substituted aldehyde, and then yielded **4o** as a yellow solid. Yield 81.2%, Mp: 241-242°C; ¹H NMR (400 MHz, CDCl₃) δ 8.86 (d, *J* = 1.8 Hz, 1H), 8.08 (s, 1H), 7.82 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.40 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.40 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 1H), 4.02 (t, *J* = 7.0 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 164.68, 162.98, 155.27, 154.74, 149.07, 135.51, 135.27, 132.84, 132.17, 131.81, 129.19, 129.14, 126.32, 123.94, 123.24, 116.17, 112.80, 110.75, 56.27, 56.26. HR-MS (ESI): Calcd. C₂₄H₁₈Cl₂N₂O₄, [M+Na]⁺ m/z: 491.0541, found: 491.0540.

1,2-bis(4-chlorophenyl)-4-(2,3-dimethoxybenzylidene)pyrazolidine-3,5-dione (4p)

Following general procedure for synthesis of **4**, 2,3-dimethoxybenzaldehyde was added as the substituted aldehyde, and then yielded **4p** as a yellow solid. Yield 70.5%, Mp: 104-106°C; ¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H), 8.67 (dd, *J* = 6.7, 2.8 Hz, 1H), 7.41 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.41 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.21 – 7.14 (m, 2H), 3.99 (s, 3H), 3.93 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 163.95, 162.00, 152.47, 151.78, 149.62, 135.20, 135.07, 132.18, 131.92, 129.16, 129.13, 126.29, 125.55, 123.78, 123.63, 123.09, 119.08, 116.63, 62.31, 56.06. HR-MS (ESI): Calcd. C₂₄H₁₈Cl₂N₂O₄, [M+Na]⁺ m/z: 491.0541, found: 491.0539.

1,2-bis(4-chlorophenyl)-4-(2-methoxybenzylidene)pyrazolidine-3,5-dione (4q)

Following general procedure for synthesis of **4**, 2-methoxybenzaldehyde was added as the substituted aldehyde, and then yielded **4q** as a yellow solid. Yield 73.7%, Mp: 184-186°C; ¹H NMR (400 MHz, CDCl₃) δ 8.92 – 8.84 (m, 1H), 8.65 (s, 1H), 7.50 (dd, *J* = 5.2, 2.0 Hz, 2H), 7.39 (ddd, *J* = 8.4, 6.1, 2.6 Hz, 1H), 7.34 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.34 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 1.57 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 163.04, 161.34, 150.20, 138.20, 134.95, 134.80, 134.73, 134.26, 132.47, 132.22, 130.10, 129.80, 129.31, 129.25, 129.22, 126.86, 123.66, 123.18, 118.40, 58.51. HR-MS (ESI): Calcd. C₂₃H₁₆Cl₂N₂O₃, [M+Na]⁺ m/z: 439.0616, found: 439.0544.

1,2-bis(4-chlorophenyl)-4-(2,4-dichlorobenzylidene)pyrazolidine-3,5-dione (4r)

Following general procedure for synthesis of **4**, 2,4-dichlorobenzaldehyde was added as the substituted aldehyde, and then yielded **4r** as a yellow solid. Yield 84.6%, Mp: 240-241°C; ¹H NMR (400 MHz, CDCl₃) δ 8.91–8.84 (m, 1H), 8.65 (s, 1H), 7.54–7.47 (m, 2H), 7.34 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.34 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 1.57 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 164.69, 162.98, 155.28, 154.76, 149.07, 135.50, 135.26, 132.85, 132.18, 131.82, 129.19, 129.15, 126.32, 123.94, 123.25, 116.17, 112.80, 110.75, 56.26. HR-MS (ESI): Calcd. C₂₂H₁₂Cl₄N₂O₂, [M+Na]⁺ m/z: 478.9721, found: 477.0035.

1,2-bis(4-chlorophenyl)-4-(2,4-difluorobenzylidene)pyrazolidine-3,5-dione (4s)

Following general procedure for synthesis of **4**, 2,4-difluorobenzaldehyde was added as the substituted aldehyde, and then yielded **4s** as a yellow solid. Yield 83.5%, Mp: 200-202°C; ¹H NMR (400 MHz, CDCl₃) δ 8.83 (ddd, *J* = 11.3, 7.8, 2.0 Hz, 1H), 8.16 – 8.08 (m, 1H), 8.05 (s, 1H), 7.37 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.37 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.33 (d, *J* = 8.9 Hz, 2H), 7.33 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 9.3 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 167.62, 165.17, 163.75, 157.15, 154.30, 138.12, 138.07, 134.89, 134.72, 132.35, 132.15, 129.23, 129.13, 128.89, 128.56, 123.79, 123.54, 116.96, 116.36, 115.77. HRMS (ESI): Calcd. C₂₂H₁₂Cl₂F₂N₂O₂, [M+Na]⁺ m/z: 445.0322, found: 445.0320.

1,2-bis(4-chlorophenyl)-4-(furan-2-ylmethylene)pyrazolidine-3,5-dione (4t)

Following general procedure for synthesis of **4**, furfural was added as the substituted aldehyde, and then yielded **4t** as a yellow solid. Yield 87.2%, mp. 187-189°C; ¹H NMR (400 MHz, CDCl₃) δ 8.68 (d, *J* = 3.8 Hz, 1H), 8.02 (s, 1H), 7.88 (dd, *J* = 1.6, 0.5 Hz, 1H), 7.38 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.38 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 6.78 (ddd, *J* = 3.8, 1.6, 0.7 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 163.87, 162.50, 150.76, 150.70, 136.11, 135.28, 135.09, 132.11, 131.87, 129.19, 129.18, 128.02, 123.50, 123.12, 115.43, 111.02. HR-MS (ESI): Calcd. C₂₀H₁₂Cl₂N₂O₃, [M+Na]⁺ m/z: 399.0303, found: 99.0306.

(E)-1,2-bis(4-chlorophenyl)-4-(3-phenylallylidene)pyrazolidine-3,5-dione (4u)

Following general procedure for synthesis of **4**, cinnamic aldehyde was added as the substituted aldehyde, and then yielded **4u** as a yellow solid. Yield 87%, Mp: 220-222°C; ¹H NMR (400 MHz, CDCl₃) δ 8.41 (dd, *J* = 15.5, 12.0 Hz, 1H), 7.89 (d, *J* = 12.0 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.44 (dd, *J* = 11.0, 4.4 Hz, 4H), 7.36 – 7.28 (m, 8H). ¹³C NMR (101 MHz, CDCl₃) δ 163.48, 162.98, 153.80, 152.45, 135.18, 135.13, 135.02, 131.99, 131.89, 131.85, 129.21, 129.15, 129.13, 123.20, 123.16, 123.09, 115.03, 77.33, 77.02, 76.70. HR-MS (ESI): Calcd. C₂₄H₁₆Cl₂N₂O₂, [M+Na]⁺ m/z: 435.0667, found: 435.0666.

4-((1H-indol-3-yl)methylene)-1,2-bis(4-chlorophenyl)pyrazolidine-3,5-dione (4v)

Following general procedure for synthesis of **4**, 1H-indole-3-carbaldehyde was added as the substituted aldehyde, and then yielded **4v** as a yellow solid. Yield 83.5%, Mp: 238-240°C; ¹H NMR (400 MHz, CDCl₃) δ 9.84 (d, *J* = 3.4 Hz, 1H), 9.59 (s, 1H), 8.58 (s, 1H), 8.00 (d, *J* = 6.9 Hz, 1H), 7.38 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.38 (dd, *J* = 9.1, 2.2 Hz, 2H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.46 (dd, *J* = 7.8, 2H), 7.32 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 165.58, 164.71, 143.30, 139.67, 136.05, 131.43, 129.16, 129.08, 124.68, 123.68, 123.17, 118.70, 113.92, 112.44, 99.99, 58.53. HR-MS (ESI): Calcd. C₂₄H₁₅Cl₂N₃O₂, [M+Na]⁺ m/z: 448.0620, found: 448.0620.

4-benzylidene-1,2-bis(4-chlorophenyl)pyrazolidine-3,5-dione (4w)

Following general procedure for synthesis of **4**, benzaldehyde was added as the substituted aldehyde, and then yielded **4w** as a yellow solid. Yield 87%, Mp: 205-207°C; ¹H NMR (400 MHz, CDCl₃) δ 8.57–8.52 (m, 2H), 8.19 (s, 1H), 7.67–7.61 (m,

1H), 7.55 (t, $J = 7.6$ Hz, 2H), 7.40 (dd, $J = 9.1, 2.2$ Hz, 2H), 7.40 (dd, $J = 9.1, 2.2$ Hz, 2H), 7.32 (d, $J = 8.9$ Hz, 2H), 7.32 (d, $J = 8.9$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.79, 161.98, 155.01, 135.04, 134.92, 134.69, 132.33, 132.31, 132.08, 129.23, 129.19, 129.05, 123.72, 123.22, 116.51. HR-MS (ESI): Calcd. $\text{C}_{22}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_2$, $[\text{M}+\text{Na}]^+$ m/z : 409.0511, found: 409.0507.