Supporting Information

An Efficient and Convenient Synthesis of 1H-Pyrazolo [1, 2-b] Phthalazine-5, 10- Dione Derivatives Mediated by L-Proline

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1. General Methods and Experimental Procedures:

All of the reagents and solvents are commercially available and were used as purchased without any further purification. Some solvents except laboratory reagent grade were dried and purified, when necessary. Reactions were monitored by thin layer chromatographic (TLC) plates over silica gel (60 GF₂₅₄, E. Merck). The melting points of the compounds were recorded on electro thermal melting point apparatus (Gallenkamp). NMR (¹H & ¹³C) spectra were recorded in d- CDCl₃ & d₆-DMSO using an AC-Bruker 500 MHz spectrometer. Chemical shift (δ) and coupling constant (J) are given in ppm and Hz units with respect to TMS as an internal standard.

General procedure for the preparation of phthalazine derivatives (9)

A mixture of phthalimide / phthalic anhydride (1.0 mmol), hydrazine hydrate (1.2 mmol), L-proline (0.1 mmol) and LiCl as a co-catalyst in ethanol: water (1:1) was stirred at 80⁰C for 4h with an efficient CaCl₂ guard tube over the reaction vessel. Then aromatic aldehyde (1.0 mmol), ethyl cyanoacetate (1.0 mmol) were added sequentially to the mixture and it was again heated (80⁰C) till completion (monitored by TLC). After completion, the reaction mixture was allowed to cool to room temperature. A pale yellow colored product was appeared over the solvent mixture and it was separated by filtration. Finally, the product was washed with ethanol and for a few cases, recrystallization were done by MeOH to obtain sufficiently pure product **9**.

2. Spectral data of products (9) are given below:

(9a). Ethyl-3-amino-1-(4-nitrophenyl)-5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate

Pale yellow powder (90 %); mp. 242-244 ⁰C; [α]_D²⁵ = -0.71 (c=0.14, pyridine). ¹H NMR (500 MHz, CDCl₃): δ = 1.02 (3H, brs, -CH₃), 4.06-4.04 (2H, m, -OCH₂), 6.32 (1H, s, -CH), 7.61 (2H, d, J = 8 Hz, H-Ar), 7.87-7.89 (2H, m, H-Ar), 8.18 (2H, d, J = 8 Hz, H-Ar), 8.20-8.23(1H, m, H-Ar), 8.35-8.36 (1H, m, H-Ar) ppm. ¹³C NMR (500 MHz, CDCl₃): δ = 14.1, 59.8, 63.2, 123.6, 127.7, 127.9, 128.5,

128.7, 133.9, 135.0, 145.7, 147.7, 154.1, 157.2 ppm. HRMS calcd for C₂₀H₁₆N₄O₆: 408.3642, found: 408.3640.

(9b). Ethyl-3-amino-1-(2-nitrophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo [1,2-b]phthalazine-2-carboxylate

Pale yellow powder (87 %); mp. 238-241 °C. ¹H NMR (500 MHz, CDCl₃): δ = 0.95 (3H, t, *J* = 7 Hz, -CH₃), 3.92-4.00 (2H, m, -OCH₂), 7.00 (1H, s, -CH), 7.50 (1H, m, H-Ar), 7.53 (1H, m, H-Ar), 7.62 (1H, m, H-Ar), 7.94 (3H, m, H-Ar), 8.0 (1H, m, H-Ar), 8.28-8.30 (1H, m, H-Ar) ppm. ¹³C NMR (500 MHz, CDCl₃): δ = 19.3, 60.1, 62.6, 63.9, 85.7, 129.2, 132.0, 132.5, 133.8, 134.1, 138.7, 139.0, 139.9, 154.2, 155.6, 158.5, 162.1, 169.0 ppm. HRMS calcd for C₂₀H₁₆N₄O₆: 408.3642, found: 408.3641.

(9c). Ethyl-3-amino-1-(3-nitrophenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo [1,2-b]phthalazine-2-carboxylate

Pale yellow powder (85 %); mp. 236-238 °C. ¹H NMR (500 MHz, CDCl₃): δ = 1.01 (3H, t, *J* = 7 Hz, -CH₃), 3.62-4.00 (2H, m, -OCH₂), 6.24 (1H, s, -CH), 7.59-7.62 (1H, m, H-Ar), 7.90-7.98 (3H, m, H-Ar), 8.09-8.13 (2H, m, H-Ar), 8.63 (2H, m, H-Ar) ppm. ¹³C NMR (500 MHz, CDCl₃): δ = 19.3, 64.0, 67.9, 85.9, 127.6, 127.6, 127.9, 131.9, 139.0, 139.8, 147.4, 152.8, 158.7, 162.2, 169.1 ppm. HRMS calcd for C₂₀H₁₆N₄O₆: 408.3642, found: 408.3640.

(9d). Ethyl-3-amino-5,10-dioxo-1-phenyl-5,10-dihydro-1H-pyrazolo [1,2-b]phthalazine-2-carboxylate

Pale yellow powder (88 %); mp. 245-247 °C. ¹H NMR (500 MHz, CDCl₃): δ = 1.09 (3H, brs, -CH₃), 4.07 (2H, q, *J* = 7 Hz, -OCH₂), 6.30 (1H, s, -CH), 7.29-7.30 (1H, m, H-Ar), 7.32-7.35 (2H, m, H-Ar), 7.45-7.46 (2H, m, H-Ar), 7.86-7.87 (2H, m, H-Ar), 8.28-8.30 (1H, m, H-Ar), 8.36-8.38 (1H, m, H-Ar) ppm. ¹³C NMR (500 MHz, CDCl₃): δ = 14.2, 59.5, 64.1, 127.5, 127.7, 127.7, 128.3, 128.3, 128.6, 129.3, 133.4, 134.6, 138.5, 153.8, 157.23 ppm. HRMS calcd for C₂₀H₁₇N₃O₄: 363.3667, found: 363.3666.

(9e). Ethyl-3-amino-1-naphthyl-5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate

Pale yellow powder (87 %); mp. 136-138 °C. ¹H NMR (500 MHz CDCl₃): δ = 0.73 (3H, brs, -CH₃), 3.86-3.91 (2H, m, -OCH₂), 7.12 (1H, brs, -CH), 7.41-7.44 (1H, m, H-Ar), 7.46-7.54 (1H, m, H-Ar), 7.59-7.63 (1H, m, H-Ar), 7.80-7.88 (3H, m, H-Ar), 8.20 (1H, d, *J* = 8.5, H-Ar) 8.40 (1H, d, *J* = 8.5, H-Ar) ppm. ¹³C NMR (500 MHz CDCl₃): δ = 13.8, 59.4, 123.0, 125.2, 125.6, 126.2, 127.9, 128.7, 128.8, 129.0, 129.0, 129.3, 133.4, 134.7, 149.9, 153.8, 157.4 ppm. HRMS calcd for C₂₄H₁₉N₃O₄: 413.4354, found: 413.4353.

(9f). Ethyl-3-amino-1-(4-chlorophenyl)-5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate

Pale yellow powder (89 %); mp. 275-277 °C; [α]_D²⁵ = -2.40 (c = 0.12, pyridine). ¹H NMR (500 MHz, CDCl₃): δ = 1.11 (3H, brs, -CH₃), 4.08 (2H, q, *J* = 7 Hz, -OCH₂), 6.26 (1H, s, CH), 7.30 (2H, t, *J* = 8 Hz, H-Ar), 7.40 (2H, d, *J* = 8 Hz, H-Ar), 7.86-7.90 (2H, m, H-Ar), 8.27-8.30 (1H, m, H-Ar), 8.35-8.37 (1H, m, H-Ar) ppm. ¹³C NMR (500 MHz, CDCl₃): δ = 14.2, 59.7, 63.4, 127.7, 127.7, 128.5, 128.6, 129.0, 129.1, 133.6, 134.07, 134.7, 137.1, 153.7, 157.2 ppm. HRMS calcd for C₂₀H₁₆ClN₃O₄: 397.8176, found: 397.8174.

(9g). Ethyl-3-amino-1-(2-chlorophenyl)-5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate

Pale yellow powder (88 %); mp. 238-240 °C. ¹H NMR (500 MHz, DMSO- d₆): δ = 1.03 (3H, t, *J* = 7 Hz, -CH₃), 4.00 (2H, q, *J* = 7 Hz, -OCH₂), 6.58 (1H, brs, -CH), 7.16-7.21 (2H, m, H-Ar), 7.28-7.33 (2H, m, H-Ar), 7.82-7.84 (2H, m, H-Ar), 8.19-8.21 (1H, m, H-Ar), 8.32-8.33 (1H, m, H-Ar) ppm. ¹³C NMR (500 MHz, DMSO- d₆): δ = 9.2, 54.9, 122.1, 122.8, 122.9, 123.8, 124.0, 124.6, 125.2, 128.9, 130.0, 149.0, 152.5, 203.3 ppm. HRMS calcd for C₂₀H₁₆ClN₃O₄: 397.8176, found: 397.8175.

(9h). Ethyl-3-amino-1-(4-methoxyphenyl)-5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate

Pale yellow powder (90 %); mp. 262-264 °C. ¹H NMR (500 MHz, CDCl₃): δ = 1.11 (3H, t, *J* = 7 Hz, -CH₃), 3.79 (3H, s, -OMe), 4.09 (2H, q, *J* = 7 Hz, -OCH₂), 6.28 (1H, s, -CH), 6.86 (2H, d, *J* = 8 Hz, H-Ar), 7.39 (2H, d, *J* = 9 Hz, H-Ar), 7.85-7.87 (2H, m, H-Ar), 8.28- 8.30 (1H, m, H-Ar) 8.35-8.36 (1H, m, H-Ar) ppm. ¹³C NMR (500 MHz, CDCl₃): δ = 13.7, 59.4, 63.6, 123.0, 125.2, 125.6, 126.2, 127.7, 128.7, 128.8, 129.0, 129.3, 133.4, 134.63, 149.7, 157.4 ppm. HRMS calcd for C₂₁H₁₉N₃O₅: 393.3963, found: 393.3960.

(9i). Ethyl-3-amino-1-(3-methoxyphenyl)-5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate

Pale yellow powder (87 %); mp. 256-258 °C; [α]_D²⁵ = -1.89 (c = 0.18, pyridine). ¹H NMR (500 MHz, CDCl₃): δ = 1.12 (3H, t, *J* = 7 Hz, -CH₃), 3.80 (3H, s, -OMe), 4.09 (2H, q, *J* = 7 Hz, -OCH₂), 6.26 (1H, s, -CH), 6.83 (1H, dd, *J* = 2, 8, Hz, H-Ar), 6.98 (1H, t, *J* = 1.8 Hz, H-Ar), 7.05 (1H, d, *J* = 8 Hz, H-Ar), 7.26 (1H, q, *J* = 8 Hz, H-Ar), 7.84-7.89 (2H, m, H-Ar), 8.27-8.30 (1H, m, H-Ar), 8.34-8.37

(1H, m, H-Ar) ppm. ^{13}C NMR (500 MHz, CDCl_3): δ = 14.2, 59.6, 63.9, 82.9, 113.4, 113.5, 120.0, 127.6, 127.7, 128.6, 129.3, 129.3, 133.4, 134.6, 140.3, 134.7, 137.1, 153.8, 157.2, 159.5 ppm. HRMS calcd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_5$, 393.3960, Found: 393.3959.

(9j). Ethyl-3-amino-1-(3-bromophenyl)-5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate

Pale yellow powder (88 %); mp. 199-200 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} = +3.87$ ($c = 0.16$, pyridine). ^1H NMR (500 MHz, CDCl_3): δ = 1.12 (3H, brs, $-\text{CH}_3$), 4.05-4.12 (2H, m, $-\text{OCH}_2$), 6.23 (1H, s, $-\text{CH}$), 7.20 (1H, t, $J = 8$ Hz, H-Ar), 7.41 (2H, dd, $J = 1.7$, 8 Hz, H-Ar), 7.55 (1H, t, $J = 1.7$ Hz, H-Ar), 7.84-7.89 (2H, m, H-Ar), 8.26-8.29 (1H, m, H-Ar), 8.34-8.37 (1H, m, H-Ar) ppm. ^{13}C NMR (500 MHz, CDCl_3): δ = 14.2, 59.6, 63.4, 82.3, 122.4, 126.5, 127.7, 127.7, 128.6, 129.1, 129.8, 130.3, 131.4, 133.6, 134.7, 141.0, 153.9, 157.2 ppm. HRMS calcd for $\text{C}_{20}\text{H}_{16}\text{BrN}_3\text{O}_4$, 442.2678, Found: 442.2676.

(9k). Ethyl 3-Amino-1-p-tolyl -5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate

Pale yellow powder (89 %); mp. 205-207 $^{\circ}\text{C}$. ^1H NMR (500 MHz, CDCl_3): δ = 1.11 (3H, t, $J = 7$ Hz, $-\text{CH}_3$), 2.32 (3H, s, Ar- CH_3), 4.08 (2H, q, $J = 7$ Hz, $-\text{OCH}_2$), 6.26 (1H, s, $-\text{CH}$), 7.13 (2H, d, $J = 8$ Hz, H-Ar), 7.34 (2H, d, $J = 8$ Hz, H-Ar), 7.82-7.85 (2H, m, H-Ar), 8.26-8.28 (1H, m, H-Ar), 8.32-8.34 (1H, m, H-Ar) ppm. ^{13}C NMR (500 MHz, CDCl_3): δ = 14.2, 59.5, 63.9, 83.0, 127.4, 127.6, 127.7, 128.6, 129.0, 129.4, 133.3, 134.5, 135.6, 138.0, 153.7, 157.2 ppm. HRMS calcd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_4$, 377.3947, Found: 377.3945

(9l). Ethyl -3-amino-1-(benzo [d] [1, 3] dioxol-5-yl)-5, 10-dioxo-5, 10-dihydro-1H-pyrazolo [1, 2-b] phthalazine-2-carboxylate

Pale yellow powder (87 %); mp. 190-192 °C. ^1H NMR (500 MHz, CDCl_3): δ = 1.07 (3H, t, J = 7 Hz, - CH_3), 3.97-4.01 (2H, m, - OCH_2), 5.98 (2H, s, - $\text{O-CH}_2\text{-O}$), 6.02 (1H, s, H-Ar), 6.81-6.82 (1H, m, Ar-H), 6.90-6.92 (1H, m, H-Ar), 6.98 (1H, s, H-Ar), 7.95-7.99 (2H, m, H-Ar), 8.11 (1H, s, H-Ar) 8.26-8.28 (1H, m, H-Ar) ppm. ^{13}C NMR (500 MHz, CDCl_3): δ = 19.5, 63.8, 68.3, 86.7, 106.1, 112.7, 113.0, 126.4, 131.9, 138.8, 138.9, 139.8, 151.8, 152.2, 154.9, 158.36, 162.0, 169.3 ppm. HRMS calcd for $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_6$, 407.3855, Found: 407.3856.

3. Copies of NMR (^1H & ^{13}C) spectra of products (9):

^1H NMR: (9a). Ethyl-3-amino-1-(4-nitrophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-b] phthalazine-2-carboxylate

¹³C NMR: (9a). Ethyl-3-amino-1-(4-nitrophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2

b] phthalazine-2-carboxylate

¹H NMR: (9b). Ethyl-3-amino-1-(2-nitrophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-b] phthalazine-2-carboxylate

^{13}C NMR: (9b). Ethyl-3-amino-1-(2-nitrophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-b] phthalazine-2-carboxylate

¹H NMR: (9c). Ethyl-3-amino-1-(3-nitrophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-
b] phthalazine-2-carboxylate

¹³C NMR: (9c). Ethyl-3-amino-1-(3-nitrophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-
b] phthalazine-2-carboxylate

¹H NMR: (9d). Ethyl-3-amino-5, 10-dioxo-1-phenyl-5, 10-dihydro-1*H*-pyrazolo [1, 2-*b*]

phthalazine-2-carboxylate

¹³C NMR: (9d). Ethyl-3-amino-5, 10-dioxo-1-phenyl-5, 10-dihydro-1*H*-pyrazolo [1, 2-*b*]

phthalazine-2-carboxylate

¹H NMR: (9e). Ethyl-3-amino-1-naphthyl-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-*b*]phthalazine-2-carboxylate

¹³C NMR: (9e). Ethyl-3-amino-1-naphthayl-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-*b*] phthalazine-2-carboxylate

¹H NMR: (9f). Ethyl-3-amino-1-(4-chlorophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-
b] phthalazine-2-carboxylate

¹³C NMR: (9f). Ethyl-3-amino-1-(4-chlorophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-b] phthalazine-2-carboxylate

¹H NMR: (9g). Ethyl-3-amino-1-(2-chlorophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-b] phthalazine-2-carboxylate

¹³C NMR: (9g). Ethyl-3-amino-1-(2-chlorophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-b] phthalazine-2-carboxylate

¹H NMR: (9h). Ethyl-3-amino-1-(4-methoxyphenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo
[1, 2-b] phthalazine-2-carboxylate

¹³C NMR: (9h). Ethyl-3-amino-1-(4-methoxyphenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo
[1, 2-*b*] phthalazine-2-carboxylate

¹H NMR: (9i). Ethyl-3-amino-1-(3-methoxyphenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1,

2-*b*] phthalazine-2-carboxylate

¹³C NMR: (9i). Ethyl-3-amino-1-(3-methoxyphenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo

[1, 2-b] phthalazine-2-carboxylate

¹H NMR: (9j). Ethyl-3-amino-1-(3-bromophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-*b*] phthalazine-2-carboxylate

¹³C NMR: (9j). Ethyl-3-amino-1-(3-bromophenyl)-5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-*b*] phthalazine-2-carboxylate

¹H NMR: (9k). Ethyl 3-Amino-1-*p*-tolyl -5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-*b*]
phthalazine-2-carboxylate

^{13}C NMR: (9k). Ethyl 3-Amino-1-*p*-tolyl -5, 10-dioxo-5, 10-dihydro-1*H*-pyrazolo [1, 2-*b*] phthalazine-2-carboxylate

pyrazolo [1, 2-b] phthalazine-2-carboxylate

^{13}C NMR: (9I). Ethyl 3-amino-1-(benzo [d] [1, 3] dioxol-5-yl)-5, 10-dioxo-5, 10-dihydro-pyrazolo [1, 2-b] phthalazine-2-carboxylate

4. References

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