Synthesis of some novel *N*-substituted
phthalazinone and pyridopyridazinone derivatives

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Supplementary Information

Section A General Information

Section B Experimental procedures and spectral data

Section C ¹H, ¹³C NMR , IR Spectra of compounds **3**, **4**, **5**, **9**

Section A General Information

The melting points were determined on a Boetius hot stage apparatus and are uncorrected. ^1H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra at 50 MHz on a Varian Gemini 200 BB spectrometer with TMS as an internal reference. IR spectra were recorded on a Nexus FT-IR spectrometer. Mass spectra analyses were performed on a Mass Spectrometer MAT95 - Finnigan. The analytical thin layer chromatography tests (TLC) were carried out on Merck silica gel plates (Kieselgel 60 F₂₅₄, layer thickness 0.2 mm) and the spots were visualised using UV lamp.

3-Hydroxy-1*H*-isoindolin-1-ones **1**, pyrrolopyridinones **6**, 2*H*-phthalazin-1-ones **2**, pyridopyridazinones **8**, *N*-(2-bromoethyl) phthalimide, 2-chloro-*N,N*-dimethylethanamine, 1- *N*-tosylaziridine, toluene-4-sulfonic acid 2-[methyl-(toluene-4-sulfonyl)-amino]-ethyl ester were prepared according to an already reported procedure.^[8-13] Reagents were purchased from Sigma-Aldrich / Fluka and used without further purification. Solvents were purified by conventional methods.

Section B Experimental procedures and spectral data

General Procedure for Preparation of 2-[2-(1-Oxo-1*H*-phthalazin-2-yl)-ethyl]-isoindole-1,3-diones **3**

The reaction was carried out under argon. To a stirred suspension of sodium hydride (4.25 mol) in dry DMF (10 cm³) was added slowly a solution of 2*H*-phthalazin-1-one **2** (3.95×10^{-3} mol) in dry DMF (50 cm³). The reaction mixture was stirred at room temperature for 45 minutes. Next, the whole lot was cooled to 0 °C and the solution of *N*-(2-bromoethyl)phthalimide (5.92×10^{-3} mol) in dry DMF (10 cm³) was added in portions. At first the mixture was kept for 5 hours in 0 °C and later for 16 hours in ambient temperature. After this time the reaction mixture was poured into ice-water mixture (100 cm³) and next extracted with CHCl₃ (3×50 cm³). The combined extracts were dried over MgSO₄ and concentrated under vacuum. The isoindole-1,3-dione **3** was isolated by column chromatography or crystallization.

2-[2-(1-Oxo-1*H*-phthalazin-2-yl)-ethyl]-isoindole-1,3-dione (**3a**):^[8]

Yield 35%; mp 205-208 °C (AcOEt–hexane) (Ref.^[8] 205-208 °C); IR (KBr, cm⁻¹): ν = 1719, 1656 (C=O); ¹H NMR (200 MHz, DMSO-*d*₆, ppm): δ = 8.29 (s, 1H, 4-pyridH), 8.18 (d, 1H, 5-ArH, *J* = 7.7 Hz), 7.95-7.80 (m, 7H, ArH), 4.39 (t, 2H, CH₂, *J* = 5.1 Hz), 4.02 (t, (2H, CH₂, *J* = 5.1 Hz) ppm; ¹³C NMR (50 MHz, CDCl₃, ppm): δ = 167.9, 159.5, 137.7, 133.7, 132.9, 131.5, 126.5, 125.9, 123.1 49.5, 36.6. Anal. calcd for C₁₈H₁₃N₃O₃: C 67.71, H 4.10, N 13.16%. Found: C 67.65, H 4.15, N 13.19%.

2-[2-(1-Oxo-4-phenyl-1*H*-phthalazin-2-yl)-ethyl]-isoindole-1,3-dione (3b):

Yield 47%; mp 203-205 °C; R_f = 0.84 (AcOEt–CH₂Cl₂ 1:3); IR (KBr, cm⁻¹): ν = 1712, 1660, 1653 (C=O); ¹H NMR (200 MHz, CDCl₃, ppm): δ = 8.49-8.44 (m, 1H, ArH), 7.78-7.60 (m, 7H, ArH), 7.40-7.22 (m, 5H, ArH), 4.62 (t, 2H, CH₂, J = 5.0 Hz), 4.23 (t, 2H, CH₂, J = 5.0 Hz) ppm; ¹³C NMR (50MHz, CDCl₃, ppm): δ = 168.1, 159.4, 147.2, 134.9, 133.7, 132.8, 132.1, 131.3, 129.2, 128.8, 128.3, 128.0, 127.1, 126.7, 123.1, 49.1, 36.7. Anal. calcd. for (C₂₄H₁₇N₃O₃): C 72.90, H 4.33, N 10.63%. Found: C 72.85, H 4.68, N 10.71%.

2-{2-[6-Methoxy-4-(2-methoxyphenyl)-1-oxo-1*H*-phthalazin-2-yl]-ethyl}-isoindole-1,3-dione (3c):

Yield: 50%; mp 180-184 °C; R_f = 0.72 (AcOEt–toluene 1:1); IR (KBr, cm⁻¹): ν = 1710, 1653 (C=O); ¹H NMR (200 MHz, DMSO-*d*₆, ppm): δ = 8.21 (d, 1H, 8-ArH, J = 8.9 Hz), 7.88-7.79 (m, 4H, ArH), 7.47-7.37 (m, 2H, ArH), 7.10 (d, 1H, ArH, J = 8.4 Hz), 6.77 (m, 1H, ArH), 6.58 (dd, 1H, ArH, J = 7.4, 1.7 Hz), 6.47 (d, 1H, 5-ArH, J = 2.4 Hz), 4.72-4.63 (m, 1H, CH₂), 4.14-4.03 (m, 3H, CH₂), 3.73 (s, 3H, OMe), 3.63 (s, 3H, OMe); ¹³C NMR (50 MHz, DMSO-*d*₆, ppm): δ = 167.6, 162.5, 158.1, 156.8, 144.3, 134.4, 131.4, 131.1, 130.8, 130.2, 128.3, 123.1, 120.3, 120.0, 111.3, 108.1, 55.5, 55.2, 48.4, 36.1. Anal. calcd. for (C₂₆H₂₁N₃O₅): C 68.56, H 4.65, N 9.23%. Found: C 68.54, H 4.76, N 9.21%.

2-{2-[6-Methoxy-1-oxo-4-(pyridin-2-yl)-1*H*-phthalazin-2-yl]-ethyl}-isoindole-1,3-dione (3d):

Yield: 45%; mp 189-193 °C; R_f = 0.62 (AcOEt–toluene 1:1); IR (KBr, cm⁻¹): ν = 1712, 1653 (C=O); ¹H NMR (200 MHz, CDCl₃, ppm): δ = 8.64-8.62 (m, 1H, 6-PyH), 8.36 (d, 1H, 8-ArH, J = 8.9 Hz), 7.91 (d, 1H, 5-ArH, J = 2.5 Hz), 7.74-7.43 (m, 5H, ArH, PyH), 7.32-7.23 (m, 3H,

ArH, PyH), 4.64-4.59 (m, 2H, CH₂), 4.26-4.21 (m, 2H, CH₂), 3.87 (s, 3H, OMe); ¹³C NMR (50 MHz, CDCl₃, ppm): δ = 168.0, 163.0, 159.3, 154.7, 148.2, 143.5, 136.7, 133.7, 131.9, 130.4, 128.9, 123.8, 123.2, 123.1, 121.8, 120.2, 108.9, 55.5, 48.7, 36.8. Anal. calcd. for (C₂₄H₁₈N₄O₄): C 67.60, H 4.25, N 13.14%. Found: C 67.72, H 4.33, N 13.08%.

Synthesis of Amines **4**

To a solution of phthalimido- derivative of phthalazinone **3** (1.49×10^{-3} mol) in dry EtOH (15 cm³) was added hydrazine monohydrate (98%, 4.04×10^{-3} mol, 0.2 cm³). The mixture was heated to boiling until TLC analysis (CHCl₃–MeOH 19:1) indicated the absence of a starting lactam. After the reaction was completed mixture was cooled to ambient temperature and acidified by addition of a hydrochloric acid and next all was again heated to boiling for 30 minutes. After this time, the mixture was again cooled to ambient temperature and the separated product was filtrated off. The filtrate was alkalized by a solution of 40% KOH. In next step the solution was extracted with CH₂Cl₂ (3×50 cm³). The combined extracts were dried over MgSO₄ and concentrated under vacuum. The amine was isolated by column chromatography.

Amines **4b** and **4c** were unstable and their full analysis was difficult. For this compounds were only recorded IR, NMR and MS spectra.

2-(2-Aminoethyl)-2H-phthalazin-1-one (4a): ^[14]

Yield: 50% (oil); (mp 84-88°C Ref.^[14]); R_f = 0.04 (AcOEt–MeOH 3:1, next MeOH); IR (KBr, cm^{-1}): ν = 3330, 3290 (NH), 1656 (C=O); ^1H NMR (200 MHz, CDCl_3 , ppm): δ = 8.50-8.40 (m, 1H, ArH), 8.20 (s, 1H, 4-pyridH), 7.90-7.70 (m, 3H, ArH), 4.33 (t, 2H, CH_2 , J = 6.2 Hz), 3.19 (t, 1H, CH_2 , J = 6.2 Hz), 1.40 (s, 2H, NH_2) ppm; ^{13}C NMR (50 MHz, CDCl_3 , ppm): δ = 160.0, 138.1, 133.3, 131.9, 129.8, 128.0, 126.9, 126.2, 53.8, 41.0.

2-(2-Aminoethyl)-6-methoxy-4-(2-methoxyphenyl)-2H-phthalazin-1-one (4b):

Yield: 39% (oil); R_f = 0.00 (CHCl_3 –MeOH 19:1, next MeOH); IR (KBr, cm^{-1}): ν = 3374, 3300 (NH), 1652 (C=O); ^1H NMR (200 MHz, CDCl_3 , ppm): δ = 8.41 (d, 1H, 8-ArH, J = 8.8 Hz), 7.54-7.45 (m, 1H, ArH), 7.38-7.27 (m, 2H, ArH), 7.15-7.03 (m, 2H, ArH), 6.68 (d, 1H, 5-ArH, J = 2.3 Hz), 4.35 (t, 2H, CH_2 , J = 6.1 Hz), 3.78 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.19 (t, 2H, CH_2 , J = 6.1 Hz), 1.75 (brs, 2H, NH_2); ^{13}C NMR (50 MHz, CDCl_3 , ppm): δ = 162.9, 159.6, 157.5, 145.0, 131.9, 131.2, 130.9, 128.6, 124.1, 121.6, 121.0, 119.9, 111.2, 108.3, 55.5, 55.4, 53.7, 41.2; MS: m/z = 326.4 (M+1), 283.4 (100%).

Amine **4b** was unstable and its full analysis was difficult. For this compound was only recorded IR, NMR and MS spectra.

2-(2-Aminoethyl)-6-methoxy-4-(pyridin-2-yl)-2H-phthalazin-1-one (4c):

Yield: 93% (oil); R_f = 0.04 (CHCl_3 –MeOH 19:1, next MeOH); IR (KBr, cm^{-1}): ν = 3359, 3297(NH), 1656 (C=O); ^1H NMR (200 MHz, CDCl_3 , ppm): δ = 8.78-8.74 (m, 1H, 6-PyH), 8.43 (d, 1H, 8-ArH, J = 8.9 Hz), 7.94 (d, 1H, 5-ArH, J = 2.5 Hz), 7.90-7.84 (m, 2H, PyH), 7.43-7.31 (m

2H, PyH, 7-ArH), 4.38 (t, 2H, CH₂, $J = 6.2$ Hz), 3.89 (s, 3H, OMe), 3.22 (t, 2H, CH₂, $J = 6.2$ Hz), 1.40 (brs, 2H, NH₂); ¹³C NMR (50 MHz, CDCl₃, ppm): δ = 162.9, 159.4, 154.9, 148.5, 143.4, 137.1, 130.4, 128.9, 124.2, 123.5, 121.9, 120.3, 108.6, 55.6, 53.9, 41.2; MS: (M⁺): calcd for C₁₆H₁₆N₄O₂: 296.1273, m/z = 297,3 (M+1), 254.3 (100%).

Amine **4c** was unstable and its full analysis was difficult. For this compound was only recorded IR, NMR and MS spectra.

Preparation of 4-Methyl-*N*-[2-(1-oxo-1*H*-phthalazin-2-yl)-ethyl]-benzenesulfonamide (**5**):

To a solution of sodium methoxide (1.52×10^{-2} mol) in dry MeOH (40 cm³) was added 2*H*-phthalazin-1-one **2** (0.0137 mol). The mixture was heated under reflux for 30 minutes. Afterwards, *N*-tosylaziridine (1.64×10^{-2} mol) was added and heating was continued for next 10 h. Then the mixture was cooled to ambient temperature and neutralized by solution of hydrochloric acid (1:1). The separated product was filtrated, washed with dry MeOH and purified by recrystallization from AcOEt.

Yield 55%; mp 209-212 °C (AcOEt); IR (KBr, cm⁻¹): ν = 3162 (NH), 1636 (C=O); ¹H NMR (200 MHz, DMSO-*d*₆, ppm): δ = 8.39 (s, 1H, 4-pyridH), 8.23 (d, 1H, 5-ArH, $J = 7.2$ Hz), 7.82-7.74 (m, 3H, 6,7,8-ArH), 7.77 (t, 1H, NH, $J = 6.3$ Hz), 7.61 (d, 2H, TsH, $J = 8.0$ Hz), 7.28 (d, 2H, TsH, $J = 8.0$ Hz), 4.17 (t, 2H, CH₂, $J = 6.3$ Hz), 3.18 (m, 2H, CH₂), 2.30 (s, 3H, Me); ¹³C NMR (50 MHz, DMSO-*d*₆, ppm): δ = 158.3, 142.2, 137.7, 137.3, 133.1, 131.6, 129.2, 129.1, 126.8, 126.5, 126.1, 125.4, 49.8, 20.8. Anal. calcd. for (C₁₇H₁₇N₃O₃S): C 59.46, H 4.99, N 12.24, S 9.34%. Found: C 59.52, H 4.97, N 12.31, S 9.19%.

General Procedure for Preparation of Benzenesulfonamides 9

To a solution of sodium methoxide (1.65×10^{-2} mol) in dry MeOH (70 cm³) was added pyridopyridazinone **8** (1.53×10^{-2} mol). The mixture was heated to boiling for 30 minutes. Afterwards, toluene-4-sulfonic acid 2-[methyl-(toluene-4-sulfonyl)-amino]-ethyl ester (0.0230 mol) was added and heating was continued for next 7 h. After this time, the mixture was cooled to ambient temperature. The separated product was filtrated off, washed with dry MeOH and purified by crystallization or column chromatography.

4,*N*-Dimethyl-*N*-[2-(8-oxo-8*H*-pyrido[2,3-*d*]pyridazin-7-yl)-ethyl]-benzenesulfonamide (9a):

Yield: 60%; mp 189-191 °C (MeOH); IR (KBr, cm⁻¹): ν = 1668 (C=O); ¹H NMR (200 MHz, CDCl₃, ppm): δ = 9.11(dd, 1H, ArH, *J* = 4.4, 1.7 Hz), 8.18 (s, 1H, ArH), 8.07 (dd, 1H, ArH, *J* = 8.1, 1.7Hz), 7.74 (dd, 1H, ArH, *J* = 8.1, 4.5 Hz), 7.66-7.56 (m, 2H, ArH), 7.25-7.16 (m, 2H, ArH), 4.47 (t, 2H, CH₂, *J* = 6.1 Hz), 3.52 (t, 2H, CH₂, *J* = 6.1 Hz), 2.90 (s, 3H, NMe), 2.36 (s, 3H, TsMe). Anal. calcd. for (C₁₇H₁₈N₄O₃S): C 56.97, H 5.06, N 15.63, S 8.95%. Found: C 56.78, H 5.11, N 15.61, S 8.83%.

4,*N*-Dimethyl-*N*-[2-(1-oxo-1*H*-pyrido[3,4-*d*]pyridazin-2-yl)-ethyl]-benzenesulfonamide (9b):

Yield: 50%; mp 157-159 °C (MeOH); IR (KBr, cm^{-1}): $\nu = 1655$ (C=O); ^1H NMR (200 MHz, CDCl_3 , ppm): $\delta = 9.15$ (s, 1H, ArH), 8.98 (d, 1H, ArH, $J = 4.9$ Hz), 8.28 (s, 1H, ArH), 8.18 (d, 1H, ArH, $J = 5.5$ Hz), 7.60 (d, 2H, TsH, $J = 8.0$ Hz), 7.20 (d, 2H, TsH, $J = 8.0$ Hz), 4.42 (t, 2H, CH_2 , $J = 5.8$ Hz), 3.51 (t, 2H, CH_2 , $J = 5.8$ Hz), 2.91 (s, 3H, NMe), 2.36 (s, 3H, TsMe); ^{13}C NMR (50 MHz, CDCl_3 , ppm): $\delta = 157.9$, 150.6, 149.1, 143.1, 135.7, 134.8, 132.5, 129.4, 127.0, 123.9, 118.9, 48.7, 48.0, 35.1, 21.5. Anal. calcd. for ($\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$): C 56.97, H 5.06, N 15.63, S 8.95%. Found: C 57.01, H 5.09, N 15.68, S 8.95%.

***N*-{2-[1-(2-Methoxy-phenyl)-4-oxo-4*H*-pyrido[3,4-*d*]pyridazin-3-yl]-ethyl}-4,*N*-dimethyl-benzenesulfonamide (9c):^[8]**

Yield: 65%; mp 157-159 °C (*i*PrOH) (Ref.^[8] 157-159 °C); IR (KBr, cm^{-1}): $\nu = 1666$ (C=O); ^1H NMR (200 MHz, CDCl_3 , ppm): $\delta = 9.66$ (s, 1H, ArH), 8.84 (d, 1H, ArH, $J = 5.6$ Hz), 7.62-7.49 (m, 4H, ArH), 7.23-7.05 (m, 5H, ArH), 4.80-4.60 (m, 1H, CH_2), 4.32-4.05 (m, 1H, CH_2), 3.74 (s, 3H, OMe), 3.62-3.48 (m, 2H, CH_2), 2.90 (s, 3H, NMe), 2.32 (s, 3H, TsMe). Anal. calcd. for ($\text{C}_{24}\text{H}_{24}\text{N}_4\text{O}_4\text{S}$): C 62.05, H 5.21, N 12.06, S 6.90%. Found: C 61.83, H 5.18, N 12.07, S 6.95%.

***N*-{2-[8-(2-Methoxy-phenyl)-5-oxo-5*H*-pyrido[2,3-*d*]pyridazin-6-yl]-ethyl}-4,*N*-dimethyl-benzenesulfonamide (9d):**

Yield: 67%; mp 180-183 °C (*i*PrOH); IR (KBr, cm^{-1}): $\nu = 1659$ (C=O); ^1H NMR (CDCl_3 , ppm) δ : 8.85 (dd, 1H, ArH, $J = 4.6$, 1.8 Hz), 8.68 (dd, 1H, ArH, $J = 8.1$, 1.8 Hz), 7.66-7.45 (m, 6H, ArH), 7.16-7.03 (m, 3H, ArH), 4.46 (t, 2H, CH_2 , $J = 5.9$ Hz), 3.37 (s, 3H, OMe), 3.57 (t, 2H, CH_2 ,

$J = 6.7$ Hz), 2.91 (s, 3H, NMe), 2.32 (s, 3H, TsMe). Anal. calcd. for (C₂₄H₂₄N₄O₄S): C 62.05, H 5.21, N 12.06, S 6.90%. Found: C 61.92, H 5.22, N 12.17, S 7.10%.

Section C ^1H , ^{13}C NMR , IR Spectra of compounds 3, 4, 5, 9

3a

3b

Data: Wt Cze 12 12:22:22

Skanów: 16

KBr

Rozdzielczość: 4,000

3c

3d

Data: Wt Kwi 20 13:37:

Skanów: 16

KBr

Rozdzielczość: 4.000

5

Data: Śr Paź 11 13:52:56

Skanów: 16

KBr

Rozdzielczość: 4.000

5

5

5

9a

9a

9b

Data: Śr Paź 11 14:19:06

Skanów: 16

KBr

Rozdzielczość: 4.000

9b

9b

9b

9c

9c

9d

9d

4a

4a

4b

Data: Pt Maj 28 10:05:43

Skanów: 16

film

Rozdzielczość: 4.000

4b

4b

4c

Data: Pt Maj 28 10:31:37

Skanów: 16

KBr

Rozdzielczość: 4.000