Journal of the Serbian Chemical Society
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J. Serb. Chem. Soc. 86 (7–8) S125–S130 (2021) *Supplementary material*

SUPPLEMENTARY MATERIAL TO

Synthesis and biological profiling of novel isocoumarin derivatives and related compounds

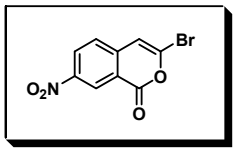
MILENA R. SIMIĆ[1]*, SLAVICA ERIĆ[2], IVAN BORIĆ[3], ANNAMARIA LUBELSKA[4], GNIEWOMIR LATACZ[4], KATARZYNA KIEC-KONONOWICZ[4], SANDRA VOJNOVIĆ[5], JASMINA NIKODINOVIĆ-RUNIĆ[5] and VLADIMIR M. SAVIC[1]

[1]University of Belgrade, Faculty of Pharmacy, Department of Organic Chemistry, Vojvode Stepe 450, 11221 Belgrade, Serbia; [2]University of Belgrade, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Vojvode Stepe 450, 11221 Belgrade, Serbia, [3]IQVIA, Clinical Department, Rudnička 2, 11000 Belgrade, Serbia, [4]Jagiellonian University, Medical College, Department of Technology and Biotechnology of Drugs, Medyczna 9, 30-688 Kraków, Poland and [5]University of Belgrade, Institute for Molecular Genetics and Genetic Engineering, Laboratory for Microbial Molecular Genetics and Ecology, Vojvode Stepe 444a, 11042 Belgrade, Serbia

J. Serb. Chem. Soc. 85 (7–8) (2021) 639–649

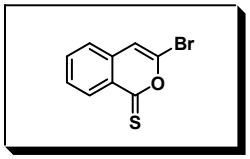
SYNTHETIC PROCEDURES AND CHARACTERIZATION DATA OF SYNTHESISED COMPOUNDS

*3-Bromo-7-nitro-1*H*-isochromen-1-one (**2b**)*



Compound as synthesised from 4-nitro homophthalic anhydride following the modified literature procedure.[1,2] Flash chromatography (SiO_2, 7:3 v/v petroleum ether-diethyl ether, Rf = 0.30) afforded **2b** (20 %) as a pale yellow amorphous solid, mp = 143-145 ºC. IR (ATR) cm^{-1}: 1743, 1617, 1511, 1344, 1056, 741, 680; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 (s, 1H), 8.54 (d, 1H, *J* = 8.8 Hz), 7.54 (d, 1H, *J* = 8.8 Hz), 6.83 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.9, 147.2, 141.9, 136.3, 129.7, 126.3, 126.2, 119.9, 108.7; MS (EI): *m/z* 268.9 $[M]^+$, 224.9, 189.9, 174.0, 134.0.

*3-Bromo-1*H*-isochromene-1-thione (**2c**)*

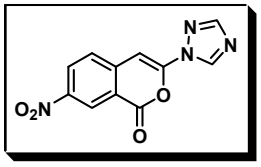


Compound as synthesised from **2a** following the general procedure for synthesis of thioisocoumarins. Flash chromatography (SiO_2, 9:0.5:0.5 v/v petroleum ether-diethyl ether-dichloromethane, Rf = 0.35) afforded the product **2c** (7 mg, 27 %) as a yellow amorphous solid,

* Corresponding author. E-mail: milena@pharmacy.bg.ac.rs

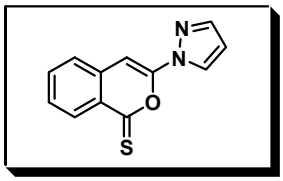
mp = 111-113 ºC; IR (ATR) cm^{-1}: 1613, 1546, 1468, 1327, 1298, 835, 879, 766; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, 1H, J = 8.4 Hz), 7.71 (t, 1H, J = 7.6 Hz), 7.50 (t, 1H, J = 7.6 Hz), 7.32 (d, 1H, J = 7.6 Hz), 6.85 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 135.4, 133.9, 133.1, 132.2, 129.7, 129.6, 125.2, 112.2; MS (EI): *m/z* 239.8 $[M]^+$, 225.9, 213.9, 160.9, 133.0, 105.9, 89.0; HRMS (ESI/Q-TOF) *m/z*calcd for $[C_9H_5BrOS + H^+]$: 240.9323, found 240.9322.

*7-Nitro-3-(1*H*-1,2,4-triazol-1-yl)-1*H*-isochromen-1-one (**3c**)*



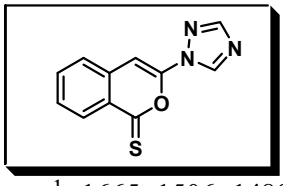
Compound was synthesised from 3-bromo-7-nitro-isocoumarine (**2b**) and 1, 2, 4-triazole following the general procedure for Buchwald-Hartwig reaction.[3] Flash chromatography (SiO_2, 9:1 v/v diethyl ether-petroleum ether, Rf = 0.29) afforded the product **3c** (10 mg, 48 %) as a pale yellow amorphous solid, mp = 208-211 ºC. IR (ATR) cm^{-1}: 1755, 1652, 1611, 1341, 1218, 985, 869, 665; ^1H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1H), 8.88 (s, 1H), 8.58 (d, 1H, J = 8.8 Hz), 8.18 (s, 1H), 7.73 (d, 1H, J = 8.8 Hz), 7.15 (s, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 157.3, 154.0, 147.0, 146.6, 142.3, 141.9, 129.9, 127.9, 126.3, 119.8, 90.9; MS (EI): *m/z* 258.0 $[M]^+$,230.0, 188.9, 149.0, 134.0, 88.0; HRMS (ESI/Q-TOF) *m/z* calcd for $[C_{11}H_6N_4O_4 + H^+]$: 259.1467, found 259.0468.

*3-(1*H*-pyrazol-1-yl)-1*H*-isochromene-1-thione (**4a**)*



Compound was synthesised from **3a** following the general procedure for synthesis of thioisocoumarins. Flash chromatography (SiO_2, 8:1:1 v/v petroleum ether-diethyl ether-dichloromethane, Rf = 0.28) afforded the product **4a** (18 mg, 67 %) as a yellow needles, mp = 107-109 ºC. IR (ATR) cm^{-1}: 1657, 1551, 1480, 1457, 1288, 1160, 823, 760; ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, 1H, J = 8.0 Hz), 8.30 (s, 1H), 7.78 (s, 1H), 7.71 (t, 1H, J = 7.6 Hz), 7.48-7.42 (m, 2H), 7.15 (s, 1H), 6.52 (d, 1H, J = 1.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 149.3, 143.4, 135.6, 133.2, 133.1, 129.3, 128.5, 127.8, 126.5, 108.5, 92.9; MS (EI): *m/z* 228.0 $[M]^+$, 199.0, 168.0, 146.0, 133.0, 89.0; HRMS (ESI/Q-TOF) *m/z* calcd for $[C_{12}H_8N_2OS + H^+]$: 229.0436, found 229.0435.

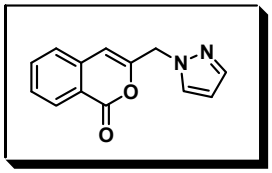
*3-(1*H*-1,2,4-triazol-1-yl)-1*H*-isochromene-1-thione (**4b**)*



Compound was synthesised from **3b** following the general procedure for synthesis of thioisocoumarins. Flash chromatography (SiO_2, 7:3 v/v petroleum ether-ethyl acetate, Rf = 0.35) afforded the product **4b** (50 %) as a yellow amorphous solid, mp = 60-63 ºC.IR (ATR) cm^{-1}: 1665, 1506, 1480, 1286, 1163, 1100, 1055, 996, 742, 685; ^1H NMR (400

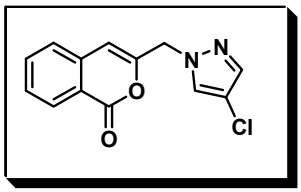
MHz, $CDCl_3$): δ 8.99 (*s*, 1H), 8.65 (*d*, 1H, J = 8.4 Hz), 8.19 (s, 1H), 7.77 (t, 1H, J = 7.6 Hz), 7.54-7.51 (m, 2H) 7.16 (s, 1H) ppm; ^{13}C (100 MHz, $CDCl_3$) δ 196.3, 153.1, 146.4, 141.7, 135.8, 133.3, 131.8, 129.9, 129.6, 126.9, 95.1 ppm;MS (EI): *m/z* 229.0 $[M]^+$, 200.9, 185.0, 146.9, 132.9, 120.0, 89.0; HRMS (ESI/Q-TOF) *m/z* calcd for $[C_{11}H_7N_3OS + H^+]$: 230.0388, found 230.0388.

*3-Pyrazol-1-ylmethyl-isochromen-1-one (**6a**)*



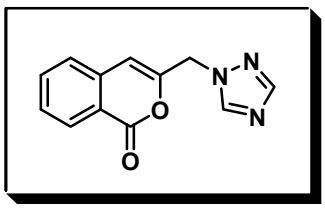
Compound **6a** was synthesised from 3-brom-methylisocoumarin and pyrazole following the general procedure. Flash chromatography (SiO_2, 7:3 v/v diethyl ether-petroleum ether, Rf = 0.29) afforded the product **6a** (45 %) as a colourless solid, mp = 110-111 °C. IR(ATR) cm^{-1}: 1721, 1283, 1051, 1021, 755, 687; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, 1H, J = 7.9 Hz), 7.70 – 7.64 (m, 1H), 7.59 (dd, 2H, J = 10.7, 1.7 Hz), 7.50 - 7.46 (m, 1H), 7.34 (d, 1H, J = 7.8 Hz), 6.33 (t, 1H, J = 2.0 Hz), 6.27 (s, 1H), 5.14 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 151.6, 140.4, 136.4, 134.9, 130.4, 129.6, 128.7, 125.9, 120.6, 106.5, 104.8, 52.9; MS (EI): *m/z* 226.0 $[M]^+$, 198.0, 184.0, 169.0, 143.0, 130.0, 117.0, 89.0; HRMS (ESI/Q-TOF) *m/z* calcd for $[C_{13}H_{10}N_2O_2 + H^+]$: 227.0821, found 227.0821.

*3-(4-Chloro-pyrazol-1-ylmethyl)-isochromen-1-one (**6b**)*



Compound **6b** was synthesised from 3-brom-methylisocoumarin and 4-chloropyrazole following the general procedure. Flash chromatography (SiO_2, 6:4 v/v diethyl ether-petroleum ether, Rf = 0.28) afforded the product **6b** (81 %) as a colourless solid, mp = 160-163 °C. IR (ATR) cm^{-1}: 1722, 1400, 1378, 938, 833, 757, 688; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, 1H, J = 4.0 Hz), 7.72 (t, 1H, J = 8.0 Hz), 7.61-7.50 (m, 3H), 7.40, d, 1H, J = 8.0 Hz), 6.37 (s, 1H), 5.08 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 150.5, 138.9, 136.1, 135.1, 129.8, 129.0, 128.2, 126.0, 120.7, 111.0, 105.4, 53.7; MS (EI): *m/z* 260.0 $[M]^+$, 232.0, 218.0, 169.0, 89.0; HRMS (ESI/Q-TOF) *m/z* calcd for $[C_{13}H_9ClN_2O_2 + H^+]$: 261.0431, found 261.0432.

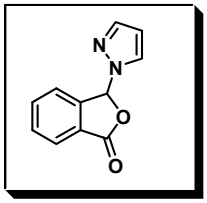
*3-[1,2,4]Triazol-1-ylmethyl-isochromen-1-one (**6c**)*



Compound **6c** was synthesised from 3-brom-methylisocoumarin and 1,2,4-triazole following the general procedure. Flash chromatography (SiO_2, 1:1 v/v ethyl acetate/diethyl ether, Rf = 0.21) afforded the product **6c** (61 %) as a colourless solid, mp = 153-157°C.IR (ATR) cm^{-1}: 1720, 1504, 1267, 1058, 1015, 768, 677; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.27 (d, 1H, J

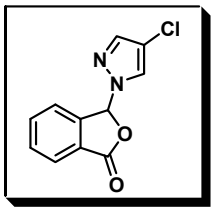
= 8.0 Hz), 8.01 (s, 1H), 7.73 (d, 1H, *J* = 8.0 Hz), 7.55 (t, 1H, *J* = 8.0Hz), 7.42 (d, 1H, *J* = 8.0 Hz), 6.46 (s, 1H), 5.20 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 152.6, 149.4, 144.0, 135.9, 135.2, 129.9, 129.2, 126.0, 120.8, 106.0, 50.6; MS (EI): *m/z* 227.0 $[M]^+$, 198.9, 185.0, 169.9, 144.9, 117.0, 89.0; HRMS (ESI/Q-TOF) *m/z* calcd for $[C_{12}H_9N_3O_2 + H^+]$: 228.0773, found 228.0773.

*3-Pyrazol-1-yl-3*H-*isobenzofuran-1-one* (***8a***)



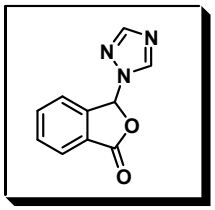
Compound **8a** was synthesised from 3-bromophthalide and pyrazole following the general procedure. Flash chromatography (SiO_2, 6:4 v/v diethyl ether-petroleum ether, Rf = 0.28) afforded the product **8a** (78 %) as a colourless solid, mp = 58-59 ºC. IR (ATR) cm^{-1}: 1768, 1437, 1283, 1061, 947, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,02 (d, 1H, *J* = 7.6 Hz), 7.85 (dt, 1H, *J* = 7.6 and 1.2 Hz), 7.71 (t, 1H, J = 7.6 Hz), 7.66 (d, 1H, 1.6 Hz), 7.54 (s, 1H), 7.51 (d, 1H, *J* = 0.4 Hz), 7.36 (d, 1H, *J* = 2.4 Hz), 7.35 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 143.7, 141.9, 134.9, 131.3, 128.9, 126.9, 126.0, 123.7, 108.0, 87.5; MS (EI): *m/z* 200.0 $[M]^+$, 171.0, 166.0, 133.0, 105.0, 77.0; HRMS (ESI/Q-TOF) *m/z* calcd for $[C_{11}H_8N_2O_2 + H^+]$: 201.0659, found 201.0659.

*3-(4-Chloro-pyrazol-1-yl)-3*H-*isobenzofuran-1-one* (***8b***)



Compound **8b** was synthesised from 3-bromophthalide and 4-chloropyrazole following the general procedure. Flash chromatography (SiO_2, 6:4 v/v petroleum ether-diethyl ether, Rf = 0.29) afforded the product **8b** (61 %) as a colourless solid, mp = 104-106 ºC. IR (ATR) cm^{-1}: 1773, 1430, 1284, 1060, 950, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 1H, *J* = 7.2 Hz), 7.80 (t, 1H, *J* = 7.2 Hz), 7.73 (t, 1H, *J* = 7.2 Hz), 7.58 (s, 1H), 7.54 (d, 1H, *J* = 7.6 Hz), 7.31 (s, 1H), 7.25 (d, 1H, *J* = 6.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 142.9, 140.4, 135.2, 131.6, 126.8, 126.6, 126.1, 123.8, 112.8, 87.7; MS (EI): *m/z* 234.0 $[M]^+$, 190.0, 133.0, 105.0, 77.0; HRMS (ESI/Q-TOF) *m/z* calcd for $[C_{11}H_7ClN_2O_2 + H^+]$: 235.0274, found 235.0271.

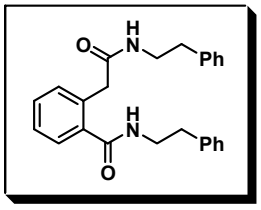
*3-[1,2,4]Triazol-1-yl-3*H-*isobenzofuran-1-one* (***8c***)



Compound **8c** was synthesised from3-bromophthalide and 1,2,4-triazole following the general procedure. Flash chromatography (SiO_2, 1:1 v/v diethyl ether-ethylacetate, Rf = 0.42) afforded the product **8c** (50 %) as a colourless solid, mp = 133-136 ºC. IR (ATR) cm^{-1}: 1769, 1432, 1301, 1139, 965, 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.98 (d, 1H, *J* = 7.6 Hz), 7.96 (s, 1H), 7.75 (dt, 1H, *J* = 7.6 and 1.2 Hz), 7.68 (t, 1H, *J* = 7.6 Hz), 7.48 (dd, 1H, *J* = 7.6 and 0.8 Hz), 7.30 (s, 1H); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 167.1, 153.1, 143.4, 142.6, 135.3, 131.8, 126.4, 126.3, 123.6, 84.7; MS (EI): *m/z* 201.0 $[M]^+$, 172.0, 133.0, 105.0, 77.0; HRMS (ESI/Q-TOF) *m/z* calcd for $[C_{10}H_7\ N_3O_2 + H^+]$: 202.0608, found 202.0608.

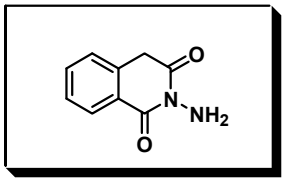
N-*Phenethyl-2-(phenethylcarbamoyl-methyl)-benzamide (**9**)*



To a solution of 3-bromoisocoumarin (23 mg, 0.10 mmol) in dichloromethane (2 mL) 2-phenylethylamine (44 mg, 0.36 mmol) was added at r.t. The mixture was stirred at r.t. overnight. Solvent was removed under reduced pressure and crude mixture was purified by flash chro00matography (SiO_2, diethyl ether, Rf = 0.35) to afford the product **9** (50 %) as a colourless solid, mp = 197-198 ºC. IR (ATR) cm^{-1}: 1637, 1535, 1319, 744, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.16 (m, 15 H), 7.04 (d, 2H, *J* = 7.2 Hz), 6.59 (s, 1H), 3.70 (q, 2H, *J* = 6.8 Hz), 3.47 (s, 2H), 3.42 (q, 2H, *J* = 6.8 Hz), 2.94 (t, 2H, *J* = 6.8 Hz), 2.75 (t, 2H, *J* = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 169.9, 139.1, 138.6, 135.9, 134.5, 130.8, 130.7, 128.8, 128.7 (2C), 128.4, 127.4, 127.1, 126.7, 126.2, 41.6, 41.1, 40.9, 35.6, 35.5; HRMS (ESI/Q-TOF) *m/z* calcd for $[C_9H_{26}N_2O_2 + H^+]$: 387.2072, found 387.2072.

Reaction of compound **3b** with phenylethylamine also gave **9**, confirmed only by ^1H NMR spectrum of crude product.

*2-Amino-4*H*-isoquinoline-1,3-dione (**10**)*



To a solution of 3-bromoisocoumarin (26 mg, 0.12 mmol) in dichloromethane (2 mL) hydrazine hydrate (6.5 mg, 0.13 mmol) and K_2CO_3 (16 mg, 0.12 mmol) were added at room temperature. The mixture was stirred at r.t. for 1h. After completion of the reaction indicated by TLC, the mixture was diluted with DCM, washed with water and dried over $MgSO_4$. Solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography (SiO_2, diethyl ether, Rf = 0.33) to afford the product **10** (56 %) as a colourless solid, mp = 48-150 ºC. IR (ATR) cm^{-1}: 1719, 1637, 1548, 1387, 1194, 919, 746; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, 1H, *J* = 8.0 Hz), 7.61 (t, 1H, *J* = 7.6 Hz), 7.47 (t, 1H, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 7.6 Hz), 5.29 (s, 2H), 4.13 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 161.8, 133.7, 133.3, 128.9, 127.9, 127.3, 124.6, 36.0; MS (EI): *m/z* 176.0 $[M]^+$, 161.0, 145.0, 132.0, 118.0, 104.0, 90.0, 77.0, 63.0; HRMS (ESI/Q-TOF) *m/z* calcd for $[C_9H_8\ N_2O_2 + H^+]$: 177.0664, found 177.0659.

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