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Different positions of amide side chains on the benzimidazo[1,2-*a*]quinoline skeleton strongly influenced biological activity

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Solution of equimolar amounts of 2-cyanomethylbenzimidazole, corresponding aromatic aldehydes (**3** or **4**) and a few drops of piperidine in absolute ethanol, was refluxed for 2 h. Following reaction, the mixture was cooled to room temperature; the crude product was filtered off and recrystallized from ethanol.

(*E*)-2-(1*H*-benzimidazol-2-yl)-3-(2-chlorophenyl)acrylonitrile 5

Compound **5** was prepared using above described method, from 2-cyanomethylbenzimidazole **1** (2.000 g, 12.74 mmol) and 2-chlorobenzaldehyde **3** (1.790 g, 12.74 mmol) in absolute ethanol (15 mL) to yield 3.380 g (95%) of light brown crystals; mp 243–245 °C;

^{1}H NMR (600 MHz, DMSO-d_6): δ = 13.33 (s, 1H, $NH_{benzimid.}$), 8.52 (s, 1H, $H_{arom.}$), 8.14 (dd, 1H, J_1 = 2.34 Hz, J_2 = 6.84 Hz, $H_{arom.}$), 7.72 (bs, 1H, $H_{arom.}$), 7.70 (dd, 1H, J_1 = 1.74 Hz, J_2 = 7.50 Hz, $H_{arom.}$), 7.64–7.55 (m, 3H, H_{arom}), 7.30 (bs, 2H, $H_{arom.}$); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 176.27, 147.10, 141.84, 134.28, 133.15, 131.70, 130.51, 130.21, 128.24, 115.82, 107.23; Found: C, 68.70; H, 3.60; N, 15.02. Calc. for $C_{16}H_{10}ClN_3$: C, 68.60; H, 3.70; N, 15.09%.

(*E*)-2-(1*H*-benzimidazol-2-yl)-3-(4-cyanophenyl)acrylonitrile 6

Compound **6** was prepared using above described method, from 2-cyanomethylbenzimidazole **1** (2.000 g, 12.74 mmol) and 4-cyanobenzaldehyde **4** (1.670 g, 12.74 mmol) in absolute ethanol (15 mL) to yield 2.873 g (84%) of light brown powder; mp 290–291 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.21 (s, 1H, $H_{benzimid.}$), 8.40 (s, 1H, $H_{arom.}$), 8.11 (d, 2H, J = 8.64 Hz, $H_{arom.}$), 8.04 (d, 2H, J = 8.52 Hz, $H_{arom.}$), 7.68 (bs, 1H, $H_{arom.}$), 7.63 (d, 1H, J = 7.70 Hz, $H_{arom.}$), 7.27 (bs, 2H, $H_{arom.}$); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 147.28, 147.27, 143.68, 137.48, 133.48 (2C), 130.42 (2C), 118.79, 124.55, 123.18, 119.20, 118.79, 116.07, 135.58, 112.09, 105.99; Found: C, 75.54; H, 3.73; N, 20.73. Calc. for $C_{17}H_{10}N_4$: C, 75.62; H, 3.70; N, 20.68%.

(*E*)-4-(2-(1*H*-benzimidazol-2-yl)vinyl)benzonitrile 7

Heating a mixture of equimolar amounts (37.81 mmol) of 4-cyanobenzaldehyde **4** and 2-methylbenzimidazole **2** in a sealed tube at 200 °C and recrystallization from methanol gave 6.60 g (71%) of yellow powder; mp 220–221 ºC;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.72 (s, 1H, NH), 7.85 (bs, 4H, $H_{arom.}$), 7.69 (d, 1H, J = 16.47 Hz, H_{etenil}), 7.54 (d, 1H, J = 6.99 Hz, $H_{arom.}$), 7.49 (d, 1H, J = 6.90 Hz, $H_{arom.}$), 7.39 (d, 1H, J = 16.50 Hz, H_{etenil}), 7.26–7.11 (m, 2H, $H_{arom.}$);

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.43, 150.66, 140.90, 133.28 (2C), 132.82, 131.15, 130.45, 128.17 (2C), 123.42, 122.29, 121.71, 119.38, 119.32, 114.71; Found: C, 78.35; H, 4.52; N, 17.13. Calc. for $C_{16}H_{11}N_3$: C, 78.25; H, 4.60; N, 17.15%.

Benzimidazo[1,2-*a*]quinoline-6-carbonitrile 8

Compound **5** (3.000 g, 10.74 mmol) was dissolved in sulfolane (8 mL) and reaction mixture was heated for 30 min at 280 °C. The cooled mixture was poured into water (20 mL) and the resulting product was filtered off and recrystallized from ethanol to obtain a brown powder (1.682 g, 64%); mp 256–258 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.77 (d, 1H, J = 8.640 Hz, $H_{arom.}$), 8.74 (s, 1H, $H_{arom.}$), 8.66 (d, 1H, J = 8.10 Hz, $H_{arom.}$), 8.06 (d, 1H, J = 7.44 Hz, $H_{arom.}$), 7.95 (d, 1H, J = 8.00 Hz, $H_{arom.}$), 7.93 (t, 1H, J = 8.10 Hz, $H_{arom.}$), 7.59 (t, 1H, J = 7.44 Hz, $H_{arom.}$), 7.55–7.51 (m, 2H, H_{arom}), ^{13}C NMR (75 MHz, DMSO-d_6): δ = 144.44, 143.74, 140.67, 135.80, 133.65, 131.21, 125.19, 123.64, 121.20, 120.26, 115.97, 115.38, 114.86; Found: C, 79.00; H, 3.73; N, 17.27. Calc. for $C_{16}H_9N_3$: C, 79.10; H, 3.65; N, 17.25%.

General method for the synthesis of compounds 9 and 10

Solutions of respectively (*E*)-2-(1*H*-benzimidazol-2-yl)-3-(4-cyanophenyl)acrylonitrile **6** in ethanol (c = 2.22×10^{-3} moldm^{-3}) and (*E*)-4-(2-(1*H*-benzimidazol-2-yl)vinyl)benzonitrile **7** in ethanol (c = 4.08×10^{-3} moldm^{-3}) were irradiated at room temperature with 400 W, high-pressure mercury lamp using a Pyrex filter for 12–20 h, until the UV spectra showed that the reaction of photochemical dehydrocyclization was completed. The solutions were concentrated under reduced pressure and resulting product was filtered off.

Benzimidazo[1,2-*a*]quinoline-2,6-dicarbonitrile 9

Yield 0.146 g (31%) of light brown crystals; mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.99 (s, 1H, $H_{arom.}$), 8.75 (d, 1H, J = 8.34 Hz, $H_{arom.}$), 8.73 (s, 1H, $H_{arom.}$), 8.17 (d, 1H, J = 8.10 Hz, $H_{arom.}$), 7.93 (d, 1H, J = 8.10 Hz, $H_{arom.}$), 7.89 (d, 1H, J = 7.86 Hz, $H_{arom.}$), 7.53–7.47 (m, 2H, $H_{arom.}$); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 144.10, 143.97, 139.97, 135.80, 132.50, 130.83, 128.47, 126.03, 124.82, 124.78, 120.85, 119.96, 118.44, 115.74, 115.35, 115.28, 104.62; Found: C, 76.11; H, 3.01; N, 20.88. Calc. for $C_{17}H_8N_3$: C, 76.08; H, 3.10; N, 20.82%.

Benzimidazo[1,2-*a*]quinoline-2-carbonitrile 10

Yield 0.123g (31%) of yellow powder; mp 210–212 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.13 (s, 1H, $H_{arom.}$), 8.86 (d, 1H, J = 8.88, $H_{arom.}$), 8.27 (d,1H, J = 8.13, $H_{arom.}$), 8.01–7.94 (m,

3H, $H_{arom.}$), 7.82 (d, 1H, *J* = 9.51, $H_{arom.}$), 7.60–7.53 (m, 2H, $H_{arom.}$); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.26, 145.59, 132.38, 131.09, 129.43, 127.93, 126.83, 125.20, 123.87, 120.52, 119.68, 119.22, 118.98, 115.52, 112.40, 109.52; Found: C, 79.00; H, 3.73; N, 17.27. Calc. for $C_{16}H_9N_3$: C, 78.70; H, 3.80; N, 17.50%.

General method for the synthesis of compounds 11–13

2 N solution of sulfuric acid and benzimidazo[1,2-*a*]quinolines **8–10** was refluxed for 24 h. Cooled reaction mixture was poured into ice, and resulting product was filtered off.

Benzimidazo[1,2-*a*]quinoline-6-carboxylic acid 11

Compound **11** was prepared using above described method, from benzimidazo[1,2-*a*]quinoline-6-carbonitrile **8** (2.000 g, 8.22 mmol) and 2 N aqueaus solution of sulfuric acid (11.8 mL) to yield 1.466 g (84%) of yellow powder; mp 290–293 °C;

^1H NMR (300 MHz, DMSO-d_6): δ = 9.23 (s, 1H, $H_{arom.}$), 9.14 (d, 1H, *J* = 8.61 Hz, $H_{arom.}$), 9.04 (d, 1H, *J* = 8.13 Hz, $H_{arom.}$), 8.53 (d, 1H, *J* = 7.38 Hz, $H_{arom.}$), 8.23–8.16 (m, 2H, H_{arom}), 7.89 (t, 1H, *J* = 7.70 Hz, H_{arom}), 7.84–7.74 (m, 2H, H_{arom}); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.70 (2C), 135.48 (2C), 135.29, 132.92 (2C), 129.26, 127.87, 127.36, 125.85, 123.08 (2C), 117.36, 117.29, 116.60; Found: C, 73.27; H, 3.84; N, 10.68. Calc. for $C_{16}H_{10}N_2O_2$: C, 73.37; H, 3.80; N, 10.72%.

Benzimidazo[1,2-*a*]quinoline-2,6-dicarboxylic acid 12

Compound **12** was prepared using above described method, from benzimidazo[1,2-*a*]quinoline-2,6-dicarbonitrile **9** (0.200 g, 0.75 mmol) and 2 N aqueous solution of sulfuric acid (4.3 mL) to yield 0.171 g (75%) of yellow powder; mp 297–299 °C;

^1H NMR (300 MHz, DMSO-d_6): δ = 13.93 (bs, 2H, COOH), 9.11(s, 1H, $H_{arom.}$), 8.77(s, 1H, $H_{arom.}$), 8.47–8.44 (m, 1H, $H_{arom.}$), 8.39 (d, 1H, *J* = 8.22 Hz, $H_{arom.}$), 8.12 (d, 1H, *J* = 8.21 Hz, $H_{arom.}$), 8.07–8.04 (m, 1H, $H_{arom.}$), 7.70–7.64 (m, 2H, $H_{arom.}$); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.67, 165.21, 146.84, 143.37, 136.85, 136.60, 135.13, 133.47, 131.27, 126.82, 126.34, 126.21, 125.62, 121.28, 121.04, 117.16, 115.34; Found: C, 66.67; H, 3.29; N, 9.15. Calc. for $C_{17}H_{10}N_2O_4$: C, 66.75; H, 3.33; N, 9.10%.

Benzimidazo[1,2-*a*]quinoline-2-carboxylic acid 13

Compound **13** was prepared using above described method, from benzimidazo[1,2-*a*]quinoline-2-carbonitrile **10** (0.158 g, 0.65 mmol) and 2 N aqueous solution of sulfuric acid (1.8 mL) to yield 0.166 g (98%) of light brown powder; mp >300 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.20 (s, 1H, $H_{arom.}$), 8.52 (d, 1H, J = 7.14 Hz, $H_{aromat.}$), 8.27–8.22 (m, 2H, $H_{arom.}$), 8.15 (d, 1H, J = 8.10 Hz, $H_{arom.}$), 8.04–8.00 (m, 1H, $H_{arom.}$), 7.89 (d, 1H, J = 9.51 Hz, $H_{arom.}$), 7.73–7.65 (m, 2H, $H_{arom.}$); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.78, 147.72, 142.31, 135.54, 134.22, 133.63, 131.63, 131.17, 127.63, 126.83, 126.46, 125.47, 120.21, 119.08, 117.56, 115.72; Found: C, 73.27; H, 3.84; N, 10.68. Calc. for $C_{16}H_{10}N_2O_2$: C, 73.20; H, 3.90; N, 10.72%.

General method for the synthesis of compounds 14–16

A mixture of corresponding carboxylic acids **11**–**13** and thionyl chloride in absolute toluene was refluxed for 19 h. Toluene and excess of thionyl chloride was removed under reduce pressure. The crude product was washed 3 times with absolute toluene to obtained powdered product.

Benzimidazo[1,2-*a*]quinoline-6-carbonyl chloride 14

Compound **14** was prepared using above described method, from benzimidazo[1,2-*a*]quinoline-6-carboxylic acid **11** (0.500 g, 1.91 mmol), absolute toluene (20 mL) and 2.70 mL thionyl chloride to yield 0.530 g (99%) of yellow powder; mp 242–245 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.40 (s, 1H, $H_{arom.}$), 9.23 (d, 1H, J = 8.67 Hz, $H_{arom.}$), 9.13 (d, 1H, J = 8.22 Hz, $H_{arom.}$), 8.60 (dd, 1H, J_1 = 1.02 Hz, J_2 = 7.89 Hz, $H_{arom.}$), 8.29–8.22 (m, 2H, $H_{arom.}$), 7.96 (t, 1H, J = 7.58 Hz, H_{arom}), 7.90 (t, 1H, J = 7.92 Hz, H_{arom}), 7.84 (t, 1H, J = 7.13 Hz, H_{arom}); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.66, 143.12, 142.09, 135.99, 135.15, 133.13, 132.61, 128.71, 128.67, 127.97, 126.61, 123.41, 117.92, 117.08, 116.19, 114.31; Found: C, 68.46; H, 3.23; N, 9.98. Calc. for $C_{16}H_{10}ClN_2O$: C, 68.40; H, 3.19; N, 10.03%.

Benzimidazo[1,2-*a*]quinoline-2,6-dicarbonyl chloride 15

Compound **15** was prepared using above described method, from benzimidazo[1,2-*a*]quinoline-2,6-dicarboxylic acid **12** (0.295 g, 0.96 mmol), absolute toluene (20 mL) and 1.40 mL thionyl chloride to yield 0.306 g (93%) of yellow powder; mp >300 °C;

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.39 (d, 1H, J = 6.90 Hz, $H_{arom.}$), 9.38 (s, 1H, $H_{arom.}$), 8.80–8.75 (m, 1H, $H_{arom.}$), 8.68 (d, 1H, J = 8.31 Hz, $H_{arom.}$), 8.36 (d, 1H, J = 8.31 Hz, $H_{arom.}$), 8.26–8.23 (m, 1H, $H_{arom.}$), 7.95–7.87 (m, 1H, $H_{arom.}$);

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.56, 164.44, 142.65, 141.53, 136.27, 135.08, 133.49, 128.93, 128.60, 127.31, 127.07, 126.03, 117.82, 116.92, 116.77, 116.27; Found: C, 59.50; H, 2.35; N, 8.16. Calc. for $C_{17}H_8Cl_2N_2O_2$: C, 59.40; H, 2.39; N, 8.12%.

Benzimidazo[1,2-*a*]quinoline-2-carbonyl chloride 16

Compound **16** was prepared using above described method, from benzimidazo[1,2-*a*]quinoline-2-carboxylic acid **13** (0.300 g, 1.14 mmol), absolute toluene (20 mL) and 0.82 mL thionyl chloride to yield 0.284 g (88%) of light brown powder; mp > 300 °C;
^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.33 (s, 1H, $H_{arom.}$), 8.70 (d, 1H, J = 8.16 Hz, $H_{arom.}$), 8.60 (d, 1H, J = 9.42 Hz, $H_{arom.}$), 8.43 (d, 1H, J = 8.22 Hz, $H_{arom.}$), 8.28 (dd, 1H, J_1 = 1.02 Hz, J_2 = 8.16 Hz, $H_{arom.}$), 8.12–8.10 (m, 2H, $H_{arom.}$), 7.86 (t, 1H, J = 7.05 Hz, $H_{arom.}$), 7.83 (t, 1H, J = 7.80 Hz, $H_{arom.}$); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.28, 144.65, 136.40, 133.61, 133.31, 130.97, 129.40, 129.02, 128.15, 127.22, 126.59, 126.17, 117.10, 116.47, 115.47, 114.78; Found: C, 68.46; H, 3.23; N, 9.98. Calc. for $C_{16}H_9ClN_2O$: C, 68.50; H, 3.21; N, 10.01%.