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SHORT COMMUNICATIONS

Synthesis and Biological Activity of Substituted Spiro[chromene-4,3′-indoles] and Spiro[indole-3,4′-quinolines]

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Abstract—New substituted spiro[chromene-4,3′-indoles] and spiro[indole-3,4′-quinolines] have been synthesized in 35–65% yields by one-pot regioselective three-component condensation of N-substituted isatins with two active methylene compounds.

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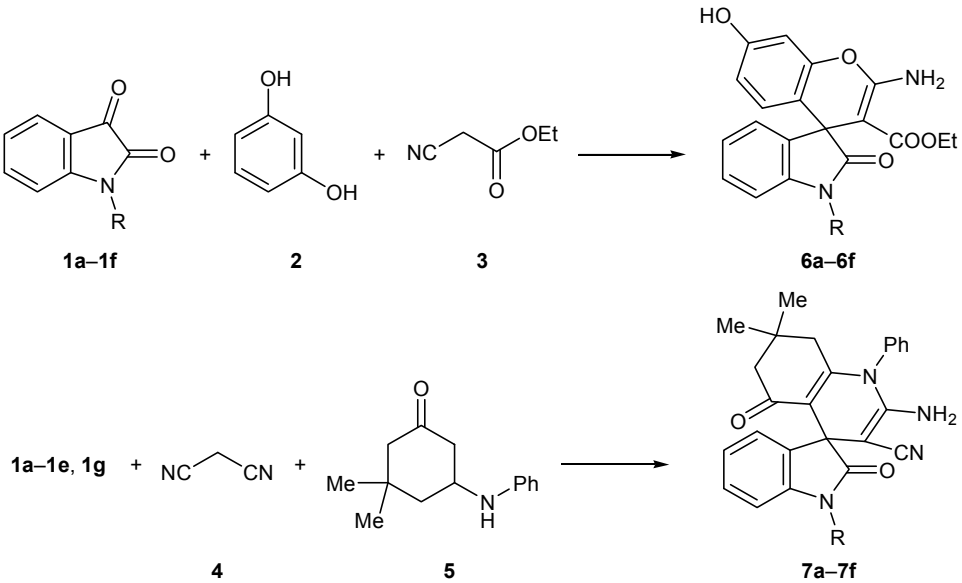
We previously synthesized a series of spiro heterocycles containing an oxodihydroindole fragment [1, 2]. Interest in these compounds is determined by the possibility of extending their synthetic potential. The synthesis of some spiro[indole-3,4′-quinolines] under microwave irradiation has been reported [3, 4]. In continuation of these studies, we have developed a new procedure for the synthesis of analogous spiro compounds by domino reaction of isatins with two CH acids in the presence of a catalytic amount of a base. In order to estimate the scope of the new preparative procedure, we used as starting compounds N-substituted isatins **1a**–**1g** and resorcinol (**2**) and ethyl cyanoacetate (**3**) or malononitrile (**4**) and 3,3-dimethyl-5-anilinocyclohexan-1-one (**5**). The condensation of isatin with two other components containing an active methylene group followed the cascade cyclization path, leading to regioselective formation of spiro-fused oxoindole derivatives **6a**–**6f** and **7a**–**7f**.

The antibacterial activity of compounds **6a**–**6f** and **7a**–**7f** was assayed by the agar diffusion method [5] at a bacterial load of 20×10^6 CFU/mL. The test cultures



1, **6**, R = H (**a**), Me (**b**), Et (**c**), Pr (**d**), $PhCH_2$ (**e**), CH_2=$CHCH_2$ (**f**), Bu (**g**); **7**, R = H (**a**), Me (**b**), Et (**c**), Pr (**d**), Bu (**e**), $PhCH_2$ (**f**).

were gram-positive *S. aureus* and gram-negative *Sh. flexneri* and *E. coli*. The compounds to be tested and reference drug were dissolved in DMSO at a dilution of 1:20. Petri dishes containing an agar nutrient medium were inoculated with the test cultures, and a 0.1-mL sample of a solution of **6a**–**6f** or **7a**–**7f** or reference drug was applied thereonto. The results were evaluated as the diameter (*d*, mm) of the inhibition zone after incubation for 24 h in a thermostat. The reference drug was furazolidone [6].

Compounds **6a**–**6d** showed no antibacterial activity, and the activity of **6e** and **6f** was low (inhibition zone 10–13 mm against 24–25 mm for the reference drug). We also examined the antiradical activity of compounds **6a**–**6f** by the DPPH assay (reaction with 2,2′-diphenyl-1-picrylhydrazyl) at ratios of 1:1, 1:2, and 1:4 in methanol. The measurements were performed by spectrophotometry over a period of 20 min [7]. The tested compounds displayed almost no antiradical activity. Increase of the **6**–DPPH ratio from 1:1 to 4:1 did not change their ability to trap the stable radical to an appreciable extent.

Compounds 6 and 7 (*general procedure***).** Isatin **1a**–**1g**, 20 mmol, was dissolved in 80 mL of ethanol, 20 mmol of resorcinol (**2**), 20 mmol of ethyl cyanoacetate (**3**) [or 20 mmol of 5-anilino-3,3-dimethylcyclohexan-1-one (**5**) and 20 mmol of malononitrile (**4**)], and 2 mL of triethylamine were added, and the mixture was refluxed for 2 h with stirring. The solvent was partially distilled off (40 mL), the residue was cooled, and the precipitate was filtered off and recrystallized from ethanol.

Ethyl 2-amino-7-hydroxy-2′-oxo-1′,2′-dihydrospiro[chromene-4,3′-indole]-3-carboxylate (6a). Yield 4.5 g (64%), mp 306–308°C, R_f 0.6. IR spectrum, ν, cm^{-1}: 3410 (OH), 3310 (NH_2), 3170 (NH), 1699 (C=O), 1660 (C=O), 1630 (C=C), 1616 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.78 t.d (3H, CH_3, J = 7.1 Hz), 3.75 m (2H, OCH_2), 6.35 d.d (1H, 6-H, J = 8.6, 2.4 Hz), 6.41 d (1H, 8-H, J = 2.4 Hz), 6.44 d (1H, 7-H, J = 8.6 Hz), 6.75–6.84 m (3H) and 7.04 t (1H, J = 7.4, 1.6 Hz) (4′-H, 5′-H, 6′-H, 7′-H), 7.64 br.s (2H, NH_2), 9.28 s (1H, OH), 10.08 s (1H, NH). Found, %: C 64.72; H 4.52; N 7.97. $C_{19}H_{16}N_2O_5$. Calculated, %: C 64.74; H 4.54; N 7.95.

Ethyl 2-amino-7-hydroxy-1′-methyl-2′-oxo-1′,2′-dihydrospiro[chromene-4,3′-indole]-3-carboxylate (6b). Yield 4.1 g (54%), mp 312–314°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 3396 (OH), 3288, 3144 (NH_2), 1699 (C=O), 1660 (C=O), 1630 (C=C), 1626 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.72 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 3.20 s (3H, NCH_3), 3.69 q (2H, OCH_2, J = 7.1 Hz), 6.28 d (1H, 5-H, J = 8.6 Hz), 6.33 d.d (1H, 6-H, J = 8.6, 2.4 Hz), 6.42 d (1H, 8-H, J = 2.4 Hz), 6.83–6.91 m (3H) and 7.11–7.20 m (1H) (4′-H, 5′-H, 6′-H, 7′-H), 7.70 br.s (2H, NH_2), 9.33 s (1H, OH). Found, %: C 65.56; H 4.47; N 7.65. $C_{20}H_{18}N_2O_5$. Calculated, %: C 65.57; H 4.37; N 7.65.

Ethyl 2-amino-1′-ethyl-7-hydroxy-2′-oxo-1′,2′-dihydrospiro[chromene-4,3′-indole]-3-carboxylate (6c). Yield 4.5 g (64%), mp 262–263°C, R_f 0.6. IR spectrum, ν, cm^{-1}: 3399 (OH), 3297 (NH_2), 1682 (C=O), 1642 (C=O), 1609 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.68 t (3H, $OCH_2C\mathbf{H}_3$, J = 7.1 Hz), 1.31 t (3H, $NCH_2C\mathbf{H}_3$, J = 7.1 Hz), 3.58–3.71 m and 3.75–3.89 m (2H each, NCH_2, OCH_2), 6.27 d (1H, 5-H, J = 8.6 Hz), 6.34 d.d (1H, 6-H, J = 8.6, 2.3 Hz), 6.43 d (1H, 8-H, J = 2.3 Hz), 6.84–6.92 m (3H) and 7.12–7.18 m (1H) (4′-H, 5′-H, 6′-H, 7′-H), 7.70 br.s (2H, NH_2), 9.34 s (1H, OH). Found, %: C 66.32; H 5.37; N 7.39. $C_{21}H_{20}N_2O_5$. Calculated, %: C 66.31; H 5.27; N 7.36.

Ethyl 2-amino-7-hydroxy-2′-oxo-1′-propyl-1′,2′-dihydrospiro[chromene-4,3′-indole]-3-carboxylate (6d). Yield 4.3 g (55%), mp 260–262°C, R_f 0.6. IR spectrum, ν, cm^{-1}: 3410 (OH), 3303 (NH_2), 1685 (C=O), 1642 (C=O), 1610 (C=C), 1608 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.68 t (3H, $OCH_2C\mathbf{H}_3$, J = 7.1 Hz), 1.04 t (3H, $CH_2CH_2C\mathbf{H}_3$, J = 7.4 Hz), 1.69–1.82 m (2H, $NCH_2C\mathbf{H}_2$); 3.44–3.53 m (1H), 3.58–3.69 m (1H), and 3.72–3.84 m (2H) (NCH_2, OCH_2); 6.27 d (1H, 5-H, J = 8.6 Hz), 6.33 d.d (1H, 6-H, J = 8.6, 2.3 Hz), 6.43 d (1H, 8-H, J = 2.3 Hz), 6.83–6.92 m (3H) and 7.12–7.18 m (1H) (4′-H, 5′-H, 6′-H, 7′-H), 7.70 br.s (2H, NH_2), 9.32 s (1H, OH). Found, %: C 67.02; H 5.57; N 7.11. $C_{22}H_{22}N_2O_5$. Calculated, %: C 67.00; H 5.58; N 7.11.

Ethyl 2-amino-1′-benzyl-7-hydroxy-2′-oxo-1′,2′-dihydrospiro[chromene-4,3′-indole]-3-carboxylate (6e). Yield 4.7 g (60%), mp 273–275°C, R_f 0.62. IR spectrum, ν, cm^{-1}: 3398 (OH), 3202 (NH_2), 1692 (C=O), 1677 (C=C), 1625 (C=C), 1608 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.54 t (3H, CH_3, J = 7.1 Hz), 3.42–3.53 m and 3.74–3.83 m (1H each, OCH_2), 4.68 d and 5.03 d (1H each, NCH_2, J = 15.2 Hz), 6.24 d (1H, 5-H, J = 8.6 Hz), 6.32 d.d (1H, 6-H, J = 8.6, 2.3 Hz), 6.45 d (1H, 8-H, J = 2.3 Hz); 6.81–6.93 m (3H) and 7.05–7.11 m (1H) (4′-H, 5′-H, 6′-H, 7′-H), 7.23–7.46 m (5H, Ph), 7.73 br.s (2H, NH_2), 9.35 s (1H, OH). Found, %: C 70.60; H 4.97; N 6.36. $C_{26}H_{22}N_2O_5$. Calculated, %: C 70.59; H 4.98; N 6.34.

Ethyl 2-amino-7-hydroxy-2′-oxo-1′-(prop-2-en-1-yl)-1′,2′-dihydrospiro[chromene-4,3′-indole]-3-carboxylate (6f). Yield 5.02 g (64%), mp 258–260°C, R_f 0.45. IR spectrum, ν, cm^{-1}: 3399 (OH), 3297 (NH_2), 1682 (C=O), 1650 (C=O), 1642 (C=C), 1609 (C=C). ^1H NMR spectrum, δ, ppm: 0.69 t (3H, CH_3, J = 7.1 Hz), 3.60–3.73 and 3.75–3.87 m (2H, OCH_2), 4.14 d.d.t and 4.47 d.d.t (2H, NCH_2, J = 15.8, 5.8, 1.2 Hz), 5.27 d.q (1H, =CH_2, J = 10.2, 1.4 Hz), 5.41 d.q (1H, =CH_2, J = 17.2, 1.4 Hz), 5.91 d.d.t (1H, C**H**=CH_2, J = 17.2, 1.4, 5.8 Hz), 6.30 d (1H, 5-H, J = 8.6 Hz), 6.35 d.d (1H, 6-H, J = 8.6, 2.3 Hz), 6.44 d (1H, 8-H, J = 2.3 Hz), 6.82–6.93 m (3H) and 7.09–7.15 m (1H) (4′-H, 5′-H, 6′-H, 7′-H), 7.70 br.s (2H, NH_2), 9.34 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 13.33, 42.08, 48.65, 57.73, 57.97, 73.10, 102.04, 107.47, 111.66, 112.30, 117.26, 121.85, 122.47, 126.52, 126.58, 126.82, 132.06, 138.60, 142.29, 148.11, 161.23, 178.53. Found, %: C 67.34; H 5.09; N 7.14. $C_{22}H_{20}N_2O_5$. Calculated, %: C 67.35; H 5.10; N 7.14.

2′-Amino-7′,7′-dimethyl-2,5′-dioxo-1′-phenyl-1,2,5′,6′,7′,8′-hexahydro-1′*H*-spiro[indole-3,4′-quinoline]-3-carbonitrile (7a). Yield 3.1 g (44%), mp 322–324°C, R_f 0.45. IR spectrum, ν, cm^{-1}: 3428, 3318 (NH_2), 3220 (NH), 2187 (C≡N), 1716 (C=O), 1696 (C=O), 1620 (C=C), 1590 (C=C). ^1H NMR spectrum, δ, ppm: 0.90 s and 0.96 s (3H each, 7′-CH_3), 1.84 d and 2.12 d (1H each, 6′-H or 8′-H, J = 17.2 Hz), 1.96 d and 2.12 d (1H each, 8′-H or 6′-H, J = 16.0 Hz), 5.06 br.s (2H, NH_2); 6.80 m, 6.98 m, 6.89 m, and 7.07–7.13 m (4H, 4-H, 5-H, 6-H, 7-H), 7.46 m and 7.57–7.64 m (5H, Ph), 10.12 s (1H, NH). Found, %: C 73.18; H 5.33; N 13.65. $C_{25}H_{22}N_4O_2$. Calculated, %: C 73.16; H 5.36; N 3.67.

2′-Amino-1,7′,7′-trimethyl-2,5′-dioxo-1′-phenyl-1,2,5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indole-3,4′-quinoline]-3-carbonitrile (7b). Yield 5.2 g (62%), mp 325–327°C, R_f 0.61. IR spectrum, ν, cm^{-1}: 3437, 3326 (NH_2), 2185 (C≡N), 1717 (C=O), 1642 (C=O), 1620 (C=C), 1590 (C=C). ^1H NMR spectrum, δ, ppm: 0.89 s and 0.96 s (3H each, 7′-CH_3), 1.84 d and 2.13 d (1H each, 6′-H or 8′-H, J = 17.1 Hz), 1.94 d and 2.09 d (1H each, 8′-H or 6′-H, J = 15.9 Hz), 3.22 s (3H, NCH_3), 5.11 br.s (2H, NH_2), 6.86 br.d (1H, 7-H, J = 7.6 Hz), 6.98 d.d.d (1H, 5-H, J = 7.33, 7.3, 0.8 Hz), 7.15 d.d (1H, 4-H, J = 7.3, 1.2 Hz), 7.22 t.d (1H, 6-H, J = 7.6, 1.2 Hz), 7.44–7.52 m and 7.54–7.65 m (5H, Ph). Found, %: C 73.56; H 5.65; N 13.25. $C_{26}H_{24}N_4O_2$. Calculated, %: C 73.58; H 5.66; N 13.21.

2′-Amino-1-ethyl-7′,7′-dimethyl-2,5′-dioxo-1′-phenyl-1,2,5′,6′,7′,8′-hexahydro-1′*H*-spiro[indole-3,4′-quinoline]-3-carbonitrile (7c). Yield 5.1 g (58%), mp 320–322°C, R_f 0.66. IR spectrum, ν, cm^{-1}: 3465, 3315, 3212 (NH_2), 2179 (C≡N), 1717, (C=O), 1653 (C=O), 1620 (C=C), 1590 (C=C). ^1H NMR spectrum, δ ppm: 0.89 s and 0.97 s (3H each, 7′-CH_3), 1.30 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 1.84 d and 2.14 d (1H each, 6′-H or 8′-H, J = 17.2 Hz), 1.93 d and 2.11 d (1H each, 8′-H or 6′-H, J = 15.9 Hz), 3.67–3.85 m (2H, NCH_2), 6.86 br.d (1H, 7-H, J = 7.6 Hz), 6.97 d.d.d (1H, 5-H, J = 7.6, 7.3, 0.7 Hz), 7.15 d.d (1H, 4-H, J = 7.3, 1.2 Hz), 7.21 t.d (1H, 6-H, J = 7.6, 1.2 Hz), 7.44–7.52 m and 7.53–7.64 m (5H, Ph). Found, %: C 73.96; H 5.95; N 12.78. $C_{27}H_{25}N_4O_2$. Calculated, %: C 73.97; H 5.94; N 12.79.

2′-Amino-7′,7′-dimethyl-2,5′-dioxo-1′-phenyl-1-propyl-1,2,5′,6′,7′,8′-hexahydro-1′*H*-spiro[indole-3,4′-quinoline]-3-carbonitrile (7d). Yield 4.8 g (53%), mp 313–316°C, R_f 0.53. IR spectrum, ν, cm^{-1}: 3415, 3153 (NH_2), 2179 (C≡N), 1707, (C=O), 1653 (C=O), 1620 (C=C), 1590 (C=C). ^1H NMR spectrum, δ, ppm: 0.89 s and 0.96 s (3H each, 7′-Me), 1.05 t (3H, $CH_2C\mathbf{H}_3$, J = 7.4 Hz), 1.70–1.83 m (2H, $NCH_2C\mathbf{H}_2$, J = 7.5 Hz), 1.84 d and 2.13 d (1H each, 6′-H or 8′-H, J = 17.2 Hz), 1.93 d and 2.11 d (1H each, 8′-H or 6′-H, J = 15.9 Hz), 3.55–3.75 m (2H, NCH_2), 5.08 s (2H, NH_2), 6.85 br.d (1H, 7-H), 6.96 d.d.d (1H, 5-H, J = 7.6, 7.3, 0.6 Hz), 7.14 d.d (1H, 4-H, J = 7.3, 1.2 Hz), 7.19 t.d (1H, 6-H, J = 7.6, 1.2 Hz), 7.44–7.52 m and 7.54–7.64 m (5H, Ph). Found, %: C 74.35; H 6.18; N 12.33. $C_{28}H_{28}N_4O_2$. Calculated, %: C 74.34; H 6.19; N 12.34.

2′-Amino-1-butyl-7′,7′-dimethyl-2,5′-dioxo-1′-phenyl-1,2,5′,6′,7′,8′-hexahydro-1′*H*-spiro[indole-3,4′-quinoline]-3-carbonitrile (7e). Yield 4.3 g (36%), mp 310–312°C, R_f 0.62. IR spectrum, ν, cm^{-1}: 3415, 3193 (NH_2), 2181 (C≡N), 1697, (C=O), 1630 (C=O), 1620 (C=C), 1590 (C=C). ^1H NMR spectrum, δ, ppm: 0.89 s and 0.96 s (3H, 7′-CH_3), 1.01 t (3H, $CH_2C\mathbf{H}_3$, J = 7.3 Hz), 1.43–1.56 m (2H, $C\mathbf{H}_2CH_3$), 1.66–1.76 m (2H, $NCH_2C\mathbf{H}_2$), 1.84 d and 2.13 d (1H each, 6′-H or 8′-H, J = 17.2 Hz), 1.93 d and 2.11 d (1H each, 8′-H or 6′-H, J = 15.9 Hz), 3.57–3.77 m (2H, NCH_2), 5.07 s (2H, NH_2), 6.84 br.d (1H, 7-H), 6.96 d.d.d (1H, 5-H, J = 7.6, 7.3, 0.8 Hz), 7.14 d.d (1H, 4-H, J = 7.3, 1.2 Hz), 7.19 t.d (1H, 6-H, J = 7.6, 1.2 Hz), 7.44–7.52 m and 7.54–7.64 m (5H, Ph). Found, %: C 74.70; H 6.49; N 12.04. $C_{28}H_{28}N_4O_2$. Calculated, %: C 74.68; H 6.48; N 12.07.

2′-Amino-1-benzyl-7′,7′-dimethyl-2,5′-dioxo-1′-phenyl-1,2,5′,6′,7′,8′-hexahydro-1′*H*-spiro[indole-3,4′-quinoline]-3-carbonitrile (7f). Yield 3.9 g (39%), mp 326–328°C, R_f 0.60. IR spectrum, ν, cm^{-1}: 3466, 3303, 3200 (NH_2), 2194 (C≡N), 1708 (C=O), 1630 (C=O), 1620 (C=C), 1590 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.92 s and 0.99 s (3H, 7′-CH_3), 1.88 d (1H, 6′-H or 8′-H, J = 17.3 Hz), 2.00 d (1H, 8′-H or 6′-H, J = 15.5 Hz), 2.17 d (1H, 8′-H or 6′-H, J = 15.5 Hz), 2.17 d (1H, 6′-H or 8′-H, J = 17.2 Hz), 4.92 d and 4.97 d (1H each, NCH_2, J = 16.2 Hz), 5.15 br.s (2H, NH_2), 6.56 br.d (1H, C_6H_4, J = 7.5 Hz), 6.96 t.d (1H, C_6H_4, J = 7.6, 1.0 Hz), 7.07 t.d (1H, C_6H_4, J = 7.3, 1.3 Hz), 7.16–7.34 m (4H, H_{arom}), 7.46–7.65 m (7H, H_{arom}). Found, %: C 76.7; H 5.6; N 11.3. $C_{32}H_{28}N_4O_2$. Calculated, %: C 76.8; H 5.6; N 11.2.

The IR spectra were recorded in mineral oil on a Nicolet Avatar 330 FT-IR spectrometer. The ^{1}H NMR spectra were recorded on a Varian Mercury 300 spectrometer at 300 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal standard. Analytical TLC was performed on Silufol UV-254 plates (eluent benzene–ethanol, 5:2; spots were visualized by treatment with iodine vapor). The melting points were measured on a Boetius melting point apparatus.

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