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Preliminary Communication

Synthesis of novel chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline derivatives

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Abstract

New coumarin heteroanalogs were synthesized by condensation of 2-amino-4-aryl-3-cyano-5-oxo-4*H*,5*H*-pyrano-[3,2-*c*] chromenes and 1,3-cyclohexanedione in 35–78% yield.

Keywords: chromeno-pyranoquinolines; coumarin heteroanalogs; malononitrile.

Introduction

Dihydropyrano[*c*]chromenes containing coumarin system exhibit spasmolytic, diuretic, anti-coagulant, anti-cancer, and anti-anaphylactic properties (Thaisrivongs et al., 1996; Yang et al., 1999; Rappa et al., 2001). Coumarins fused to pyridines have been reported to possess antiallergic (Ukawa et al., 1986), antidiabetic (Heber, 1987; Thapa et al., 2011) and analgesic (Heber and Berghaus, 1994) properties. Tacrine, a potent acetylcholinesterase (AChE) inhibitor is the first approved drug in the USA for palliative treatment of Alzheimer's disease. Similar drugs with a 4-aminopyridine moiety (Summers et al., 1986; Sakakian et al., 1993), including highly potent tetracyclic tacrines **1** (Figure 1) have been synthesized (Marco et al., 2001, 2006). In general, the fusion of a cyclohexanone and a 4*H*-pyran to pyridine moiety results in remarkable changes in pharmacological effects. These findings together with our interest in novel coumarin derivatives (Miri et al., 2011; Shafiee et al., 2011) prompted us to synthesize new tetracyclic tacrines heteroanalogs, namely chromeno[4′,3′-*b*] pyrano[6,5-*b*]quinoline-6,9-diones **4a–l**.

Results and discussion

Our synthesis of compounds **4a–l** is related to the chemistry reported previously (Marco and Martinez-Grau, 1997; Marco et al., 2001, 2006). The key starting materials are: 2-amino-4-aryl-3-cyano-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromenes **3a–l** (Abdolmohammadi and Balalaie, 2007), which were synthesized as shown in Scheme 1. Condensation of these intermediate products with 1,3-cyclohexadione in boiling acetic acid for 12 h yielded the desired products **4a–l**. The ^{1}H-^{1}H shift COSY, HSQC, and HMBC experiments were conducted with the selected compound **4h** to establish the inter-fragment relationship and to assign the proton signals. The mass spectra displayed molecular ion peaks at appropriate values.

In summary, we have prepared new chromeno [4′,3′-*b*] pyrano[6,5-*b*]quinolines of potential biological interest. Being structurally similar to compounds **1** and tacrine, the biological evaluation of compounds is the next step on our projected structure activity relationship (SAR) analysis, directed to define the key structural and functional elements that might improve the pharmacological profile of these molecules.

Experimental

^{1}H-NMR spectra were taken in $CDCl_3$ on a Bruker 500 MHz spectrometer (Bruker, Rheinstetten, Germany). The IR spectra were acquired in KBr disks on a Nicollet FT-IR magna 550 instrument (Nicollet, Madison, WI, USA). Electron-impact mass spectra were obtained using a Finnegan MAT TSQ-70 spectrometer (Finnegan Mat, Bremen, Germany). The purity of compounds was confirmed by thin layer chromatography (TLC) using different mobile phases.

Synthesis of 8-amino-7-aryl-10,11-dihydro-7*H*, 12*H*-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-diones 4a–l

A solution of **3a–l** (5.4 mmol), 1,3-cyclohexanedione (0.6 g, 5.4 mmol) in acetic acid (50 mL) was heated under reflux for 12 h, then cooled to room temperature and concentrated under reduced pressure. The residue of the crude product was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (20:80) to give **4a–l**.

8-Amino-7-(2-chlorophenyl)-10,11-dihydro-7H,12H-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4a) Yield 46%; mp 243°C; IR: ν 3444, 3055, 2955, 1726, 1675 cm^{-1}; ^{1}H NMR: δ 1.82–1.88 (m, 2H, H_{11}), 2.10–2.29 (m, 2H, H_{12}), 2.34–2.42 (m, 2H, H_{10}), 5.21 (s, 1H, H_7), 7.12 (t, 1H, *J*=8.0 Hz, H_{18}), 7.21 (t, 1H, *J*=8.0 Hz, H_{19}), 7.29 (d, 1H, *J*=8.0, H_{20}), 7.31–7.37 (m, 2H, H_2, H_4), 7.39 (d, 1H, *J*=8.0, H_{17}), 7.61 (t, 1H, *J*=7.5 Hz, H_3), 8.13 (d, 1H, *J*=7.5 Hz, H_1); MS: *m/z* 444 (10) [M$^+$], 409 (15), 334 (25), 263 (100), 199 (85), 171 (78). Anal. Calcd. for $C_{25}H_{17}ClN_2O_4$: C, 67.50, H, 3.85, N, 6.30. Found: C, 67.30, H, 3.79, N, 6.24.

8-Amino-7-(3-chlorophenyl)-10,11-dihydro-7*H*,12*H*-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4b) Yield 76%; mp 220°C; IR: ν 3450, 3040, 2965, 1726, 1670 cm^{-1}; ^{1}H NMR: δ 2.10–2.15 (m, 2H, H_{11}), 2.38–2.49 (m, 2H, H_{12}), 2.76–2.8 (m, 1H, H_{10}), 2.87–2.91 (m, 1H, H_{10}), 4.97(s, 1H, H_7), 7.14 (d, 1H, *J*=7.5 Hz, H_{20}), 7.18 (t, 1H, *J*=7.5 Hz, H_{19}), 7.26 (s, 1H, H_{16}), 7.31 (m, 3H, H_2, H_4, H_{18}), 7.58 (t, 1H, *J*=7.5, H_3), 7.87 (d, 1H, *J*=7.5 Hz, H_1); MS:

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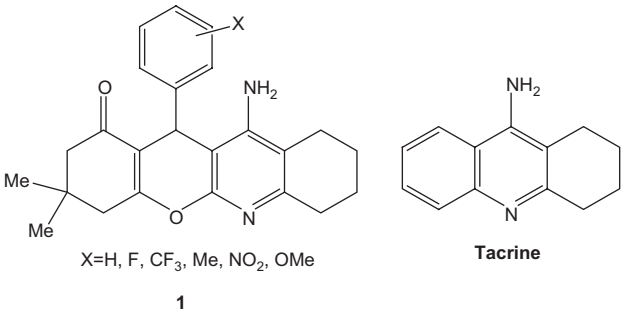


Figure 1 Structure of compound **1** and tacrine.

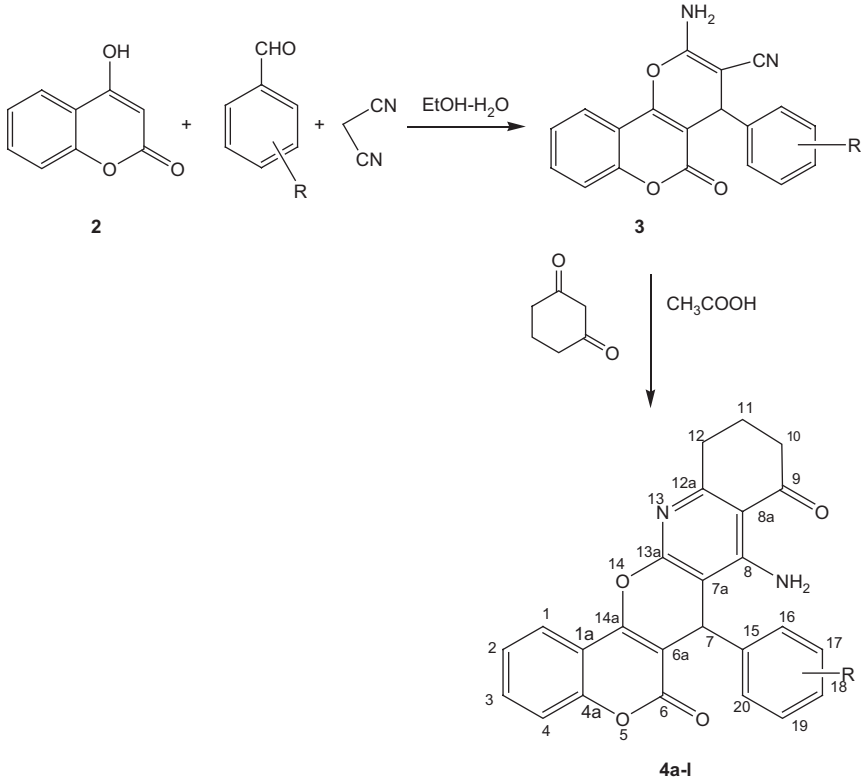
m/z 446 (8) [M$^+$+2], 444 (25) [M$^+$], 409 (15), 333 (55), 263 (100), 56 (35). Anal. Calcd. for $C_{25}H_{17}ClN_2O_4$: C, 67.50, H, 3.85, N, 6.30. Found: C, 67.44, H, 3.75, N, 6.19.

8-Amino-7-(4-chlorophenyl)-10,11-dihydro-7*H*,12*H*-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4c) Yield 43%; mp 172°C; IR: ν 3456, 3030, 2968, 1710, 1680 cm^{-1}; ^{1}H NMR: δ 2.09–1.98 (m, 2H, H_{11}), 2.36–2.39 (m, 2H, H_{12}), 2.72–2.92 (m, 2H, H_{10}), 4.71 (s, 1H, H_7), 7.20 (d, 2H, *J*=8.5 Hz, H_{20}, H_{16}), 7.34 (d, 2H, *J*=8.5 Hz, H_{17}, H_{19}), 7.45–7.50 (m, 2H, H_2, H_4), 7.71 (t, 1H, *J*=7.5 Hz, H_3), 7.96 (d, 1H, *J*=7.5 Hz, H_1); MS: *m/z* 446 (5) [M$^+$+2], 444 (18) [M$^+$], 409 (35), 374 (20), 333 (25), 263 (100), 120 (42), 92 (28). Anal. Calcd. for $C_{25}H_{17}ClN_2O_4$: C, 67.50, H, 3.85, N, 6.30. Found: C, 67.39, H, 3.80, N, 6.20.

8-Amino-7-(3-bromophenyl)-10,11-dihydro-7*H*,12*H*-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4d) Yield 56%; mp 260°C; IR: ν 3550, 3050, 2950, 1731, 1674 cm^{-1}; ^{1}H NMR: δ 2.11–2.18 (m, 2H, H_{11}), 2.39–2.50 (m, 2H, H_{12}), 2.76–2.80 (m, 1H, H_{10}), 2.88–2.93 (m, 1H, H_{10}), 4.96 (s, 1H, H_7), 7.14 (t, H, *J*=7.5 Hz, H_{19}), 7.30 (d, 1H, *J*=7.5 Hz, H_{20}), 7.33 (d, 1H, *J*=7.5 Hz, H_4), 7.38 (t, 1H, *J*=7.5 Hz, H_2), 7.41–7.43 (m, 2H, H_{18}, H_{16}), 7.58 (t, 1H, *J*=7.5 Hz, H_3), 7.89 (d, 1H, *J*=7.5 Hz, H_1); MS: *m/z* 490 (10) [M$^+$+2], 488 (10) [M$^+$], 420 (25), 353 (32), 333 (45), 263 (100), 120 (70), 76 (60). Anal. Calcd. for $C_{25}H_{17}BrN_2O_4$: C, 61.36, H, 3.50, N, 5.72. Found: C, 61.22, H, 3.43, N, 5.60.

8-Amino-7-(4-bromophenyl)-10,11-dihydro-7*H*,12*H*-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4e) Yield 50%; mp 254°C; IR: ν 3530, 3080, 2939, 1716, 1667 cm^{-1}; ^{1}H NMR: δ 2.00–2.11 (m, 2H, H_{11}), 2.22–2.39 (m, 2H, H_{12}), 2.50–2.66 (m, 2H, H_{10}), 4.85 (s, 1H, H_7), 7.21 (d, 2H, *J*=8.0 Hz, H_{20}, H_{16}), 7.44 (d, 2H, *J*=8.0 Hz, H_{17}, H_{19}), 7.35–7.39 (m, 2H, H_2, H_4), 7.62 (t, 1H, *J*=7.5 Hz, H_3), 7.81 (d, 1H, *J*=7.5 Hz, H_1); MS: *m/z* 490 (18) [M$^+$+2], 488 (16) [M$^+$], 409 (40), 418 (30), 420 (20), 353 (45), 333 (23), 263 (100), 120 (18), 92 (38), 66 (42). Anal. Calcd. for $C_{25}H_{17}BrN_2O_4$: C, 61.36, H, 3.50, N, 5.72. Found: C, 61.27, H, 3.40, N, 5.69.

8-Amino-7-(2-methylphenyl)-10,11-dihydro-7*H*,12*H*-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4f) Yield 35%; mp 270°C; IR: ν 3462, 3078, 2965, 1731, 1677 cm^{-1}; ^{1}H NMR: δ 2.06–2.20 (m, 2H, H_{11}), 2.41–2.44 (m, 2H, H_{12}), 2.75 (m, 1H, H_{10}), 2.88 (m, 1H, H_{10}), 2.88 (s, 3H, CH_3), 5.11 (s, 1H, H_7), 6.97 (m, 1H, H_{20}), 7.02–7.04 (m, 2H, H_{18}, H_{19}), 7.12 (m, 1H, H_{17}), 7.30 (d, 1H, *J*=7.5 Hz, H_4), 7.36 (t, 1H, *J*=7.5 Hz, H_2), 7.56 (t, 1H, *J*=7.5 Hz, H_3),



Scheme 1 **4a**: R=2-chloro, **4b**: R=3-chloro, **4c**: R=4-chloro, **4d**: R=3-bromo, **4e**: R=4-bromo, **4f**: R=2-methyl, **4g**: R=3-methyl, **4h**: R=4-methyl, **4i**: R=2-methoxy, **4j**: R=3-methoxy, **4k**: R=4-methoxy, **4l**: R=2-nitro.

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7.89 (d, 1H, *J*=7.5 Hz, H_1); MS: *m/z* 424 (16) [M^+], 354 (18), 333 (45), 263 (100), 91 (20), 64 (35). Anal. Calcd for $C_{26}H_{20}N_2O_4$: C, 73.57, H, 4.75, N, 6.60. Found: C, 73.45, H, 4.50, N, 6.49.

8-Amino-7-(3-methylphenyl)-10,11 dihydro-7*H*,12*H*-chromeno [4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4g) Yield 35%; mp >300°C; IR: ν 3425, 3100, 2955, 1726, 1681 cm^{-1}; ^1H NMR: δ 2.04–2.17 (m, 2H, H_{11}), 2.29 (s, 3H, CH_3), 2.37–2.48 (m, 2H, H_{12}), 2.72–2.79 (m, 1H, H_{10}), 2.86–2.91 (m, 1H, H_{10}), 4.96 (s, 1H, H_7), 6.97 (d, 1H, *J*=5.5 Hz, H_{18}), 7.13–7.14 (m, 2H, H_{20}, H_{19}), 7.19 (s, 1H, H_{16}), 7.31 (d, 1H, *J*=7.5 Hz, H_4), 7.35 (t, 1H, *J*=7.5 Hz, H_2), 7.56 (t, 1H, *J*=7.5 Hz, H_3), 7.88 (d, 1H, *J*=7.5 Hz, H_1); MS: *m/z* 424 (15) [M^+], 409 (16), 354 (18), 333 (35), 263 (100), 91 (30), 65 (20). Anal. Calcd. for $C_{26}H_{20}N_2O_4$: C, 73.57, H, 4.75, N, 6.60. Found: C, 73.52, H, 4.66, N, 6.53.

8-Amino-7-(4-methylphenyl)-10,11-dihydro-7*H*,12*H*-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4h) Yield 57%; mp 220°C; IR: ν 3443, 3068, 2955, 1733, 1680 cm^{-1}; ^1H NMR: δ 2.13 (m, 2H, H_{11}), 2.26 (s, 3H, CH_3), 2.45 (m, 2H, H_{12}), 2.78 (m, 1H, H_{10}), 2.86 (m, 1H, H_{10}), 4.97 (s, 1H, H_7), 7.06 (d, 2H, *J*=7.5 Hz, H_{17}, H_{19}), 7.28 (d, 2H, *J*=7.5 Hz, H_{16}, H_{20}), 7.32–7.37 (m, 2H, H_2, H_4), 7.56 (t, 1H, *J*=7.5 Hz, H_3), 7.88 (d, 1H, *J*=7.5 Hz, H_1); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.2, 21.1, 27.1, 32.9, 36.9, 106.92, 113.7, 116.5, 116.8, 122.4, 124.2, 128.5, 129.0, 130.0, 130.9, 132.1, 136.6, 139.8, 152.5, 153.7, 160.6, 163.4, 196.1; MS: *m/z* 425 (20) [M^++1], 409 (20), 354 (18), 333 (40), 263 (100), 91 (30), 64 (20). Anal. Calcd. for $C_{26}H_{20}N_2O_4$: C, 73.57, H, 4.75, N, 6.60. Found: C, 73.55, H, 4.68, N, 6.51.

8-Amino-7-(2-methoxyphenyl)-10,11-dihydro-7H,12H-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4i) Yield 67%; mp >300°C; IR: ν 3520, 3067, 2945, 1721, 1675 cm^{-1}; ^1H NMR: δ 2.03–2.17 (m, 2H, H_{11}), 2.37–2.40 (m, 2H, H_{12}), 2.75–2.82 (m, 2H, H_{10}), 3.70 (s, 3H, CH_3), 5.05 (s, 1H, H_7), 6.77 (d, 1H, *J*=8.00, Hz, H_{17}), 6.89 (t, 1H, *J*=8.00 Hz, H_{19}), 7.14–7.17 (m, 2H, H_{18}, H_{20}), 7.29 (d, 1H, *J*=7.5 Hz, H_4), 7.34 (t, 1H, *J*=7.5 Hz, H_2), 7.54 (t, 1H, *J*=7.5 Hz, H_3), 7.88 (d, 1H, *J*=7.5 Hz, H_1); MS: *m/z* 440 (55) [M^+], 425 (30), 409 (18), 333 (10), 263 (100), 197 (25), 76 (12). Anal. Calcd. for $C_{26}H_{20}N_2O_5$: C, 70.90, H, 4.58, N, 6.36. Found: C, 70.79, H, 4.48, N, 6.29.

8-Amino-7-(3-methoxyphenyl)-10,11-dihydro-7H,12H-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4j) Yield 70%; mp 162°C; IR: ν 3550, 3080, 2939, 1736, 1683 cm^{-1}; ^1H NMR: δ 2.10–2.15 (m, 2H, H_{11}), 2.39–2.50 (m, 2H, H_{12}), 2.73–2.79 (m, 1H, H_{10}), 2.85–2.90 (m, 1H, H_{10}), 3.79 (s, 3H, CH_3), 4.99 (s, 1H, H_7), 6.71 (d, 1H, *J*=7.5, 1.5 Hz, H_{20}), 6.95 (s, 1H, H_{16}), 6.98 (d, 1H, *J*=7.5 Hz, H_{18}), 7.18 (t, 1H, *J*=7.5 Hz, H_{19}), 7.32–7.37 (m, 1H, H_2, H_4), 7.56 (t, 1H, *J*=7.5 Hz, H_3), 7.88 (d, 1H, *J*=7.5 Hz, H_1); MS: *m/z* 440 (70) [M^+], 425 (10), 343 (65), 263 (100), 120 (90), 76 (95). Anal. Calcd. for $C_{26}H_{20}N_2O_5$: C, 70.90, H, 4.58, N, 6.36. Found: C, 70.82, H, 4.46, N, 6.31.

8-Amino-7-(4-methoxyphenyl)-10,11-dihydro-7*H*,12*H*-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4k) Yield 78%; mp 146°C; IR: ν 3510, 3180, 2950, 1726, 1677 cm^{-1}; ^1H NMR: δ 2.06–2.15 (m, 2H, H_{11}), 2.39–2.49 (m, 2H, H_{12}), 2.74 (m, 1H, H_{10}), 2.86 (m, 1H, H_{10}), 3.80 (s, 3H, CH_3), 4.96 (s, 1H, H_7), 6.7 (d, 2H, *J*=7.5 Hz, H_{17}, H_{19}), 7.29 (d, 2H, *J*=7.5 Hz, H_{16}, H_{20}), 7.34–7.37 (m, 2H, H_2, H_4), 7.56 (t, 1H, *J*=7.5 Hz, H_3), 7.88 (d, 1H, *J*=7.5 Hz, H_1); MS: *m/z* 440 (10) [M^+], 409 (23), 370 (18), 333 (10), 263 (100), 197 (40), 120 (60). Anal. Calcd. for $C_{26}H_{20}N_2O_5$: C, 70.90, H, 4.58, N, 6.36. Found: C, 70.85, H, 4.52, N, 6.28.

8-Amino-7-(2-nitrophenyl)-10,11-dihydro-7*H*,12*H*-chromeno[4′,3′-*b*]pyrano[6,5-*b*]quinoline-6,9-dione (4l) Yield 45%; mp 275°C; IR: ν 3525, 3062, 2955, 1726, 1668, 1526, 1352 cm^{-1}; ^1H NMR: δ 2.08–2.15 (m, 2H, H_{11}), 2.39–2.49 (m, 2H, H_{12}), 2.77–2.88 (m, 1H, H_{10}), 2.87–2.91 (m, 1H, H_{10}), 4.96 (s, 1H, H_7), 7.13 (d, 1H, *J*=7.5 Hz, H_{20}), 7.19 (t, 1H, *J*=7.5 Hz, H_{18}), 7.25 (d, 1H, *J*=7.5, H_{17}), 7.32–7.45 (m, 3H, H_2, H_4, H_{19}), 7.58 (t, 1H, *J*=7.0 Hz, H_3), 7.88 (d, 1H, *J*=7.0 Hz, H_1); MS: *m/z* 455 (11) [M^+], 385 (47), 333 (22), 263 (100), 143 (20), 122 (13), 83 (23), 55 (40). Anal. Calcd. for $C_{25}H_{17}N_3O_6$: C, 65.93, H, 3.76, N, 9.23. Found: C, 65.86, H, 3.79, N, 9.18.

Acknowledgments

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