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SYNTHESIS AND CHARACTERIZATION OF BISCOUMARIN AND BENZOPYRANO DICOUMARIN DERIVATIVES

(Sintesis dan Pencirian Terbitan Biskumarin dan Benzopirano Dikumarin)

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Abstract

The wide-ranging biological activities of 4-hydroxycoumarin have stimulated considerable interest in this class of compounds, and various biscoumarin derivatives have been synthesized. Recently, a number of methods have been reported for the synthesis of biscoumarin by the reaction of 4-hydroxycoumarin and various aldehydes in the presence of catalysts. In the present study, a new series of biscoumarin and benzopyrano dicoumarin were synthesized and physically characterized by nuclear magnetic resonane (^{1}H and ^{13}C NMR), fourier transform infrared spectroscopy (FTIR), mass spectrometry (MS) and melting point.

Keywords: synthesis, 4-hydroxycoumarin, biscoumarin, benzopyrano, nuclear magnetic resonane

Abstrak

Aktiviti biologi yang meluas daripada 4-hydroksikumarin telah merangsang minat yang besar di dalam kelas sebatian ini dan pelbagai terbitan biskumarin telah disintesis. Baru-baru ini, beberapa kaedah telah dilaporkan bagi sintesis biskumarin melalui tindak balas 4-hidroksikumarin dan pelbagai aldehid dengan kehadiran pemangkin. Dalam kajian ini, satu siri baru biskumarin dan benzopyrano dikumarin telah disintesis dan telah dicirikan secara fizikal oleh resonans magnet nukleus (^{1}H dan ^{13}C NMR), spektroskopi infra merah transformasi Fourier (FTIR), spektrometri jisim (MS) dan pengukuran takat lebur .

Kata kunci: sintesis, 4-hidroksikumarin, biskumarin, benzopirano, resonans magnet nukleus

Introduction

Significant properties and wide-ranging biological activities of 4-hydroxycoumarin have stimulated considerable interest in this class of compounds, and various biscoumarin derivatives have been synthesized. Biscoumarin, the bridge substituted dimers of 4-hydroxycoumarin, have enormous potential as anticoagulants [1, 2], antidiabetic [3], urease inhibitors [4], anticancer [5], antibacterial [6]. A number of biscoumarin have also been found to significantly inhibit c-Met phosphorylation in BaF3/TPR-Met and EBC-1 NSCLC cell lines [7]. Recently, a number of methods have been reported for the synthesis of biscoumarin by reaction of 4-hydroxycoumarin and various aldehydes in the presence of various catalysts such as tetrabutylammonium bromide [8], molecular iodine [9], [bmin] BF4 [10], SO_3H-functionalized ionic liquid [11], sodium dodecyl sulfate [12], piperidine [4], n-dodecylbenzene sulfonic acid (DBSA) [13], nano silica chloride [14], ruthenium (III) chloride hydrate [15] and Zn (proline)2 [16]. Benzopyrano dicoumarin are a derivative of biscoumarin resulting from the removal of a water

molecule. Both compounds are reported to possess versatile activities through chemical modifications (different substituents on the aromatic ring) [4,17].

Therefore, in the present study a new series of biscoumarin and benzopyrano dicoumarin were synthesized and physically characterized by Nuclear Magnetic Resonane (^{1}H and ^{13}C NMR), Fourier Transform Infrared Spectroscopy (FTIR), Mass Spectrometry (MS) and measurement of melting point.

Materials and Methods

Instrumentation

Infrared spectra were recorded on a Spectrum One FTIR Spectrometer (Perkin Elmer), using KBr discs and values were signified in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were measured on Bruker 500 Ultrashield Plus NMR (500 MHz) in DMSO-*d*6 as solvent, using tetramethylsilane (TMS) as an internal standard, and chemical shifts are expressed as ppm. HR-ESI-MS were determined on Agilent 6224 TOF-LC/MS using negative mode at Faculty of Pharmacy, UiTM Puncak Alam, Malaysia.

General procedure for the synthesis of compounds 1 – 18

Biscoumarin analogs 1 – 16 and benzopyrano dicoumarin 17 – 18 were synthesized by stirring the mixture of 6-Cl-4-hydroxycoumarin (1 mmol) and substituted aromatic aldehyde (0.5 mmol) in water and 10 mmol triethyl ammonium bromide (TEAB) [3]. The reaction mixture was refluxed for 24 hours. Completion of reaction was monitored by periodic TLC. After completion of reaction, the product was filtered and then washed with distilled water affording a pure product in high yields. The structures of compounds 1 – 18 were characterized by using different spectroscopic techniques namely Nuclear Magnetic Resonanes (^{1}H and ^{13}C NMR), Fourier Transform Infrared Spectroscopy (FTIR), Mass Spectrometry (MS) and melting point.

Results and Discussion

Characterization study: 3,3'-(o-tolylmethylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (1)

Yield; 0.23g (84%). m.p. 227 °C. IR(KBr) (ν_{max}, cm^{-1}): 3076, 1668, 1610, 1560, 1115, 1175. ^{1}H NMR (500 MHz, DMSO) δ 7.77 (d, *J* = 2.5 Hz, 2H), 7.54 (dd, *J* = 8.8, 2.5 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 4.0 Hz, 1H), 7.19 (t, *J* = 5.5 Hz, 1H), 7.02 (s, 2H), 6.08 (s, 1H, Ar_3CH), 2.08 (s, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO) δ 166.5, 164.0, 151.4, 140.6, 136.1, 131.1, 130.6, 128.6, 127.7, 125.9, 125.4, 123.6, 121.4, 118.2, 104.4, 36.12. EI-MS: 493.0255 (M^-, 1).

3,3'-((2-chlorophenyl)methylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (2)

Yield; 0.24g (86%). m.p. 225 °C. IR(KBr) (ν_{max}, cm^{-1}): 3277, 1668, 1618, 1567, 1176, 1116. ^{1}H NMR (500 MHz, DMSO) δ 7.77 (d, *J* = 2.5 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 8.7, 2.6 Hz, 2H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.27 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.25 – 7.09 (m, 2H), 6.13 (s, 1H, Ar_3CH). ^{13}C NMR (126 MHz, DMSO) δ 166.3, 163.8, 151.4, 139.9, 133.1, 131.2, 130.7, 129.9, 127.8, 127.8, 126.6, 123.6, 121.4, 118.2, 104.0, 36.7. EI-MS: 512.9706 (M^-, 1).

3,3'-(p-tolylmethylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (3)

Yield; 0.23g (84%). m.p. 280°C. IR(KBr) (ν_{max}, cm^{-1}): 3026, 1671, 1619, 1567, 1177. ^{1}H NMR (500 MHz, DMSO) δ 7.76 (d, *J* = 2.6 Hz, 2H), 7.56 (dd, *J* = 8.7, 2.6 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 6.98 (s, 4H), 6.21 (s, 1H, Ar_3CH), 2.23 (s, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO) δ 166.3, 164.6, 151.5, 138.5, 134.4, 131.3, 128.9, 127.7, 127.0, 123.6, 121.4, 118.2, 104.8, 36.3, 21.0. EI-MS: 493.0252 (M^-, 1).

3,3'-((3-hydroxyphenyl)methylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (4)

Yield (0.24 g) 86%. m.p. 292 °C. IR(KBr) (ν_{max}, cm^{-1}): 3077, 1657, 1618, 1564, 1169. ^{1}H NMR (500 MHz, DMSO) δ 7.77 (d, *J* = 2.4 Hz, 2H), 7.55 (dd, *J* = 8.7, 2.4 Hz, 2H), 7.41 (dd, *J* = 13.1, 5.3 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.25 (t, *J* = 7.9 Hz, 1H), 7.17 (dd, *J* = 12.8, 6.4 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.98 (dd, *J* = 10.6, 8.6 Hz, 1H), 6.30 (s, 1H, Ar_3CH). ^{13}C NMR (126 MHz, DMSO) δ 166.5, 163.9, 151.4, 131.2, 130.3, 127.7, 123.8, 123.7, 121.5, 118.2, 115.5, 115.3, 103.8, 32.5. HR-EI-MS: 495.0043 (M^-, 1).

3,3'-(m-tolylmethylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (5)
Yield (0.23 g) 84%. m.p. 243 °C. IR(KBr) (ν_{max}, cm^{-1}): 3014, 1668, 1618, 1565, 1181. ^{1}H NMR (500 MHz, DMSO) δ 7.76 (d, *J* = 2.4 Hz, 2H), 7.55 (dd, *J* = 8.7, 2.5 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.90 (m, 3H), 6.22 (s, 1H, Ar_3CH), 2.19 (s, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO) δ 166.5, 164.6, 151.5, 141.8, 137.1, 131.2, 128.2, 127.7, 127.7, 126.3, 124.3, 123.7, 121.6, 118.2, 104.7, 36.6, 21.7. EI-MS: 493.0257 (M^-, 1).

3,3'-((2-nitrophenyl)methylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (6)
Yield (0.20 g) 78%. m.p. 244°C. IR(KBr) (ν_{max}, cm^{-1}): 3084, 1676, 1616, 1563, 1479, 1440, 1367, 1257, 1176, 1119, 1070. ^{1}H NMR (500 MHz, DMSO) δ 7.71 (d, *J* = 2.5 Hz, 2H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.55 (dd, *J* = 8.8, 2.6 Hz, 2H), 7.51 (td, *J* = 8.0, 1.0 Hz, 1H), 7.37 (dd, *J* = 15.2, 7.8 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.45 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 166.7, 163.5, 151.5, 150.0, 135.0, 132.1, 131.3, 130.0, 127.7, 127.3, 124.4, 123.6, 121.2, 118.3, 103.3, 34.5. HR-EI-MS: 523.9945 (M^-, 1).

3,3'-((2-fluorophenyl)methylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (7)
Yield (0.24 g) 86%. m.p. 201°C. IR(KBr) (ν_{max}, cm^{-1}): 3080, 1660, 1615, 1565, 1489, 1452, 1253, 1116, 977, 760. ^{1}H NMR (500 MHz, DMSO) δ 7.77 (d, *J* = 2.4 Hz, 2H), 7.55 (dd, *J* = 8.7, 2.4 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.25 (t, *J* = 7.9 Hz, 1H), 7.17 (dd, *J* = 12.8, 6.4 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.98 (dd, *J* = 10.6, 8.6 Hz, 1H), 6.30 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 166.5, 163.9, 151.4, 131.2, 130.3, 127.7, 123.8, 123.6, 121.5, 118.2, 115.5, 115.3, 103.8, 32.5. HR-EI-MS: 497.0005 (M^-, 1).

3,3'-(pyridin-2-ylmethylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (8)
Yield (0.21 g) 80%. m.p. 309°C. IR(KBr) (ν_{max}, cm^{-1}): 3155, 2837, 1648, 1606, 1534, 1455, 1349, 1205, 1168, 1032, 947, 765. ^{1}H NMR (500 MHz, DMSO) δ 8.62 (d, *J* = 5.4 Hz, 1H), 8.42 (t, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.85 (dd, *J* = 6.6, 5.0 Hz, 1H), 7.74 (d, *J* = 2.5 Hz, 2H), 7.61 (dd, *J* = 8.8, 2.5 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 6.48 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 167.7, 163.9, 151.8, 131.9, 127.9, 123.9, 121.3, 118.5, 101.6, 37.2. HR-EI-MS: 480.0047 (M^-, 1).

3,3'-((3-chlorophenyl)methylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (9)
Yield (0.24 g) 86%. m.p. 222°C. IR(KBr) (ν_{max}, cm^{-1}): 3079, 1654, 1614, 1563, 1475, 1440, 1341, 1298, 1253, 1181, 1071, 978, 785. ^{1}H NMR (500 MHz, DMSO) δ 7.78 (s, 2H), 7.56 (dd, *J* = 8.7, 2.5 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.20 (dd, *J* = 21.6, 7.9 Hz, 2H), 7.08 (d, *J* = 5.3 Hz, 2H), 6.25 (s, 1H).^{13}C NMR (126 MHz, DMSO) δ 166.6, 164.5, 151.5, 134.6, 133.3, 131.4, 130.2, 127.8, 126.8, 126.0, 125.7, 123.7, 121.3, 118.3, 104.1, 36.6. HR-EI-MS: 512.9709 (M^-, 1).

3,3'-((3-fluorophenyl)methylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (10)
Yield (0.26 g) 90%. m.p. 238°C. IR(KBr) (ν_{max}, cm^{-1}): 3079, 1654, 1615, 1563, 1485, 1440, 1256, 1183, 1104, 1072, 813, 789. ^{1}H NMR (500 MHz, DMSO) δ 7.77 (d, *J* = 2.0 Hz, 2H), 7.56 (dd, *J* = 8.7, 1.9 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.22 (dd, *J* = 14.6, 7.5 Hz, 1H), 6.91 (dd, *J* = 28.3, 17.6 Hz, 2H), 6.83 (s, 1H), 6.25 (s, 1H).^{13}C NMR (126 MHz, DMSO) δ 166.7, 164.4, 151.5, 131.3, 127.7, 123.7, 123.2, 121.5, 118.3, 104.2, 36.7. HR-EI-MS: 497.0006 (M^-, 1).

3,3'-((3-nitrophenyl)methylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (11)
Yield (0.25 g) 88%. m.p. 248°C. IR(KBr) (ν_{max}, cm^{-1}): 3075, 1657, 1611, 1563, 1529, 1348, 1104, 977, 818, 793. ^{1}H NMR (500 MHz, DMSO) δ 8.01 (d, *J* = 7.5 Hz, 1H), 7.88 (s, 1H), 7.76 (d, *J* = 2.4 Hz, 2H), 7.65 – 7.53 (m, 3H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 2H), 6.33 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 167.0, 164.3, 151.6, 134.2, 131.5, 129.9, 127.8, 123.7, 121.5, 121.5, 121.0, 118.3, 103.7, 36.9. HR-EI-MS: 523.9949 (M^-, 1).

3,3'-(pyridin-3-ylmethylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (12)
Yield (0.21 g) 80%. m.p. 376°C. IR(KBr) (ν_{max}, cm^{-1}): 3446, 3062, 2594, 2147, 1685, 1610, 1537, 1389, 1179, 1123, 1012, 815. ^{1}H NMR (500 MHz, DMSO) δ 8.78 – 8.61 (m, 2H), 8.37 (d, *J* = 8.1 Hz, 1H), 7.93 (dd, *J* = 7.9, 5.9 Hz, 1H), 7.74 (d, *J* = 2.5 Hz, 2H), 7.59 (dd, *J* = 8.7, 2.6 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.38 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 167.2, 164.0, 151.7, 145.1, 142.5, 140.9, 139.8, 131.6, 127.8, 127.1, 123.7, 121.4, 118.4, 102.7, 35.2. HR-EI-MS: 480.0049 (M^-, 1).

3,3'-((4-chlorophenyl)methylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (13)
Yield (0.22 g) 82%. m.p. 277°C. IR(KBr) (ν_{max}, cm^{-1}): 2929, 1668, 1566, 1492, 1340, 1302, 1252, 1179, 1117, 1097, 1071, 821, 789, 758. ^{1}H NMR (500 MHz, DMSO) δ 7.75 (d, *J* = 2.1 Hz, 2H), 7.55 (dd, *J* = 8.7, 2.3 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.21 (s, 1H).
^{13}C NMR (126 MHz, DMSO) δ 166.7, 164.5, 151.5, 140.9, 131.3, 130.2, 129.0, 128.2, 127.8, 123.7, 121.5, 118.2, 104.3, 36.3. HR-EI-MS: 512.9709 (M^-, 1).

3,3'-((4-nitrophenyl)methylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (14)
Yield (0.24 g) 86%. m.p. 285°C. IR(KBr) (ν_{max}, cm^{-1}): 3067, 1644, 1570, 1512, 1483, 1440, 1331, 1252, 1118.^{1}H NMR (500 MHz, DMSO) δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 2.5 Hz, 2H), 7.57 (dd, *J* = 8.8, 2.6 Hz, 2H), 7.36 (dd, *J* = 10.9, 8.9 Hz, 4H), 6.32 (s, 1H).^{13}C NMR (126 MHz, DMSO) δ 167.0, 164.3, 151.6, 151.0, 145.9, 131.4, 128.4, 127.8, 123.7, 123.6, 121.5, 118.3, 103.8, 37.3. HR-EI-MS: 523.9953 (M^-, 1).

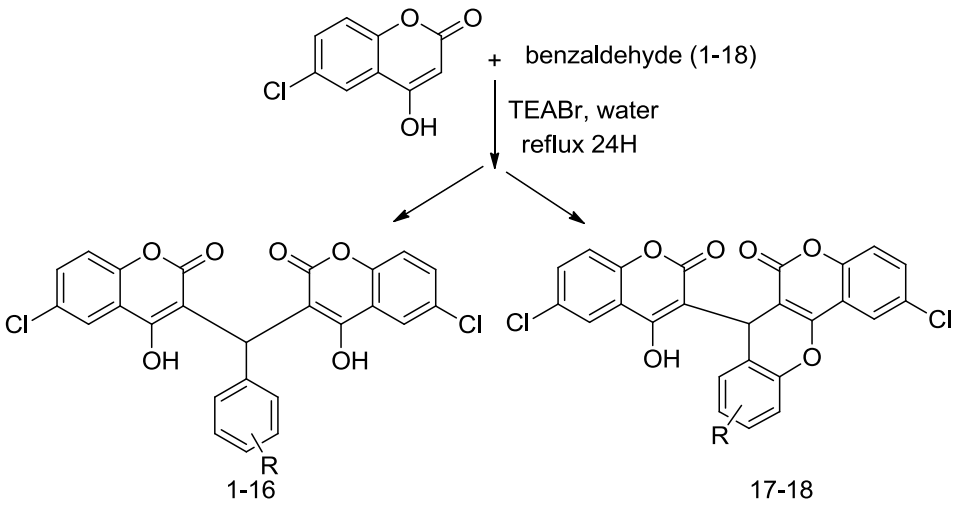
3,3'-((4-hydroxyphenyl)methylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (15)
Yield (0.21 g) 80%. m.p. 358°C. IR(KBr) (ν_{max}, cm^{-1}): 3083, 1717, 1663, 1614, 1564, 1299, 1241, 1177, 1118. ^{1}H NMR (500 MHz, DMSO) δ 7.76 (d, *J* = 2.5 Hz, 2H), 7.54 (dd, *J* = 8.7, 2.5 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.57 (d, *J* = 8.5 Hz, 2H), 6.15 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 166.3, 164.6, 155.3, 151.4, 131.6, 131.1, 128.0, 127.7, 123.6, 121.6, 118.2, 115.1, 105.0, 35.9. HR-EI-MS: 495.0046 (M^-, 1).

3,3'-(pyridin-4-ylmethylene)bis(6-chloro-4-hydroxy-2H-chromen-2-one) (16)
Yield (0.25 g) 88%. m.p. 349°C. IR(KBr) (ν_{max}, cm^{-1}): 3446, 1673, 1608, 1390, 1246, 1205, 1124, 1052. ^{1}H NMR (500 MHz, DMSO) δ 8.66 (d, *J* = 4.7 Hz, 2H), 7.80 (d, *J* = 4.7 Hz, 2H), 7.74 (s, 2H), 7.60 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 6.41 (s, 1H).^{13}C NMR (126 MHz, DMSO) δ 167.32, 164.08, 151.75, 141.88, 131.75, 127.87, 125.57, 123.78, 121.33, 118.44, 102.51, 38.15. HR-EI-MS: 480.0050 (M^-, 1).

2-chloro-7-(6-chloro-4-hydroxy-2-oxo-2H-chromen-3-yl)-10,11-dihydroxychromeno[4,3-b]chromen-6(7H) -one (17)
Yield (0.24 g) 86%. m.p. 375°C. IR(KBr) (ν_{max}, cm^{-1}): 3291, 1676, 1608, 1568, 1488, 1422, 1371, 1199. ^{1}H NMR (500 MHz, DMSO) δ 9.32 (s, 1H), 9.14 (s, 1H), 8.58 (d, *J* = 2.4 Hz, 1H), 8.03 (s, 1H), 7.73 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.63 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 6.57 (d, *J* = 8.3 Hz, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 5.64 (bs, 1H). ^{13}C NMR (126 MHz, DMSO) δ 160.6, 151.3, 151.2, 146.2, 133.5, 132.5, 132.1, 130.4, 129.1, 128.7, 128.5, 123.3, 118.9, 118.8, 118.4, 117.9, 116.0, 113.0, 27.3. HR-EI-MS: 508.9840 (M^-, 1).

2-chloro-7-(6-chloro-4-hydroxy-2-oxo-2H-chromen-3-yl)-9-hydroxychromeno[4,3-b]chromen-6(7H)-one (18)
Yield (0.23 g) 84%. m.p. 310°C. IR(KBr) (ν_{max}, cm^{-1}): 3306, 1695, 1614, 1568, 1473, 1423, 1386, 1206. ^{1}H NMR (500 MHz, DMSO) δ 9.79 (s, 1H), 8.12 (d, *J* = 2.4 Hz, 1H), 8.04 (d, *J* = 1.1 Hz, 1H), 7.74 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.64 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 2.2 Hz, 1H), 6.59 (dd, *J* = 8.4, 2.3 Hz, 1H), 5.62 (bs, 1H). ^{13}C NMR (126 MHz, DMSO) δ 160.51, 157.87, 155.73, 151.25, 151.03, 150.10, 132.58, 132.18, 129.56, 129.17, 128.51, 122.4, 119.0, 118.8, 118.3, 115.8, 113.6, 103.4, 28.7. HR-EI-MS: 492.9892 (M^-, 1).

In this work, a new series of biscoumarin and benzopyrano dicoumarincoumarin were synthesized (Scheme 1) in moderately good yields by Claisen condensation according to a previous report [3]. The formation of biscoumarin 1–16 were prompted with aldol condensation of 6-Cl-4-hydroxycoumarin (2 mmol) and substituted aromatic aldehydes linker (1 mmol) followed by dehydration of the aldol product to give a chromone. Subsequent *in situ* reaction of the chromone with another 6-Cl-4-hydroxycoumarin present in excess gave dimeric coumarin derivatives 1–16 bearing an aryl substituent in the central methylene linker [6]. In contrast, the chromone derivatives containing an *ortho*-substituted phenyl moiety gave fused benzopyrano dicoumarin 17-18 under spontaneous cyclization and removal of water. The structures of compounds 1 – 18 (Table 1) were characterized by using different spectroscopic techniques such as ^{1}H, ^{13}C NMR, FTIR, Mass Spectroscopy and melting point.



Scheme 1. Synthesis of biscoumarin (1-16) and benzopyrano dicoumarin derivatives (17-18)

Table 1. Aldehyde substituents of compound (1-18)

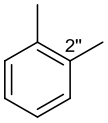
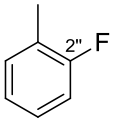
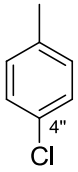
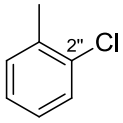
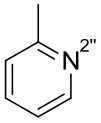
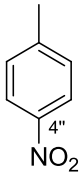
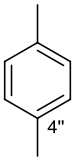
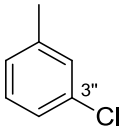
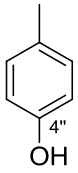
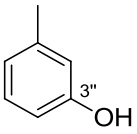
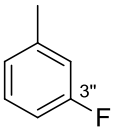
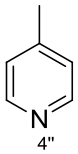
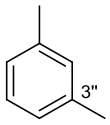
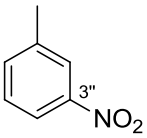
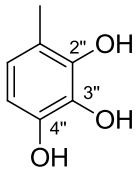
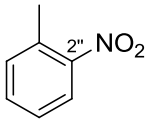
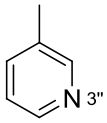
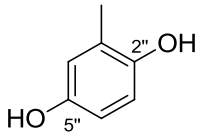
Comp. No	R	Comp. No	R	Comp. No	R
1		7		13	
2		8		14	
3		9		15	
4		10		16	

Table 1 (cont'd). Aldehyde substituents of compound (1-18)

Comp. No	R	Comp. No	R	Comp. No	R
5		11		17	
6		12		18	

The ^{1}H NMR spectra of biscoumarin derivatives 1 – 16 showed characteristic of sharp singlet peak at δ 6.08–6.48 assigned to a methine proton, a bridge substituted dimers of 4-hydroxycoumarin. In the ^{13}C NMR spectra, this methine carbon appeared at δ 38.2 – 32.5. The hydroxyl protons of 4-hydroxycoumarin were not observed in the ^{1}H NMR spectra. Benzopyrano dicoumarin of compound 17 – 18 were form when benzaldehyde having 2-hydroxy substituent was allowed to react with 4-hydroxycoumarin under the same reaction conditions. In the ^{1}H NMR spectra, the methine was shifted to a more upfield region (δ 5.62 – 5.64) and appeared as a broad singlet peak compared to methine of biscoumarin. We thus turned our attempt to characterize this compound by means of other spectroscopic methods. The mass spectra of both compounds showed a molecular ion peak at m/z 508.9840 and 492.9892, respectively, which is in accordance with a cyclization reaction by the removal of one water molecule from the corresponding biscoumarin. However, IR spectra of both compounds showed similar characteristic absorption bands at 1600 – 1700 cm^{-1} and 2900 – 3500 cm^{-1} due to carbonyl and OH group, respectively.

Conclusion

In conclusion, a series of new 6-chloro-4-hydroxy substituted biscoumarin and benzopyrano dicoumarin derivatives of compound (1-18**)** were synthesized in moderately good yield and characterized by using different spectroscopic techniques such as ^{1}H, ^{13}C Nuclear Magnetic Resonanes (NMR), fourier transform infrared spectroscopy (IR), mass spectrometry (MS) and melting point. A further study to investigate the potential pharmacological activity is in progress.

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References

1. Appendino, G., Cravotto, G., Tagliapietra, S., Ferraro, S., Nano, G. M., Palmisano, G. (1991). The chemistry of coumarin derivatives synthesis of 3-Alkyl-4-Hydroxycoumarins by reductive fragmentation of 3,3'-alkylidene-4,4'-dihydroxybis[coumarins]. *Helvetica Chimica Acta*, 74: 1451 – 1458.
2. Manolov, I., Maichle-Moessmer, C., Danchev, N. (2006). Synthesis, computational study and cytotoxic activity of new 4-hydroxycoumarin derivatives. *European Journal of Medicinal Chemistry,* 41 (4): 882 – 890.
3. Khan, K. M., Rahim, F., Wadood, A., Kosar, N., Taha, M., Lalani, S., Khan, S., Fakhri, M. I., Junaid, M., Rehman, W., Khan, M., Perveen, S., Sajid, M. and Choudhary, M. I. (2014). Synthesis and molecular docking studies of potent a-glucosidase inhibitors based on biscoumarin skeleton. *European Journal of Medicinal Chemistry*, 81:245 – 252.
4. Khan, K. M., Iqbal, S., Lodhi, M. A. and Maharvi, G. M. (2004). Biscoumarin: new class of urease inhibitors: Economical synthesis and activity. *Bioorganic and Medicinal Chemistry,* 12(8): 1963 – 1968.

5. Talhi, O., Schnekenburger, M., Panning, J., Diana, Pinto, G. C., Fernandes, J. A., Almeida Paz, F. A., Jacob, C., Diederich, M. and Silva, A. M. S. (2014). Bis(4-hydroxy-2H-chromen-2-one): synthesis and effects on leukemic cell lines proliferation and NF-jB regulation. *Bioorganic and Medicinal Chemistry,* 22: 3008 – 3015.
6. Qu, D., Li, J., Yang, X. H., Zhang, Z. D., Luo, X. X., Li, M. K. and Li, X. (2014). New biscoumarin derivatives: synthesis, crystal structure, theoretical study and antibacterial activity against *Staphylococcus aureus. Molecules,*19 (2): 19868 – 19879.
7. Xu, J., Ai, J., Liu, S., Peng, X., Yu, L., Geng, M. and Nan, F. (2014). Design and synthesis of 3,3'-biscoumarin-based c-Met inhibitors. *Organic and Biomolecular Chemistry,* 12: 3721 – 3734.
8. Khurana, J. M. and Kumar, S. (2009). Tetrabutylammonium bromide (TBAB): a neutral and efficient catalyst for the synthesis of biscoumarin and 3,4-dihydropyrano[*c*]chromene derivatives in water and solvent free conditions. *Tetrahedron Letters,* 50 (28): 4125 – 4127.
9. Kidwai, M., Bansal, V., Mothsra, P., Saxena, S., Somvanshi, R. K., Day, S. and Singh, T. P. (2007). Molecular iodine: a versatile catalyst for the synthesis of bis (4-hydroxycoumarin) methanes in water. *Journal Molecular Catalysis A,* 268(1-2): 76 – 81.
10. Khurana, J. M. and Kumar, S. (2010). Ionic Liquid: an efficient and recyclable medium for the synthesis of octahydroquinazolinone and biscoumarin derivatives. *Monatshefte fur Chemie,* 141(5): 561 – 564.
11. Li, W., Wang, Y., Wang, Z., Dai L. and Wang, Y. (2011). Novel SO_3H-functionalized ionic liquids based on benzimidazolium cation: efficient and recyclable catalysts for one-pot synthesis of biscoumarin derivatives. *Catalysis Letters* 141(11): 1651 – 1658.
12. Mehrabi, H. and Abusaidi, H. (2010). Synthesis of biscoumarin and 3,4-dihydropyrano[*c*]chromene derivatives catalyzed by sodium dodecyl sulfate(SDS) in neat water. *Journal Iranian Chemical Society,* 7(4): 890 – 894.
13. Pawar, B., Shinde, V. and Chaskar, A. (2013). N-dodecylbenzene sulfonic acid (DBSA) as a novel bronsted acid catalyst for the synthesis of bis(indolyl) methanes and bis(4- hydroxyl coumarin-3-yl)methanes in water. *Green Sustainability Chemistry,* 3: 56 – 60.
14. Karimian, R., Piri, F., Safari, A. A., Davarpanah, S. J. (2013). One-pot and chemoselective synthesis of bis(4-hydroxycoumarin) derivatives catalyzed by nano silica chloride. *Journal Nanostructure Chemistry,* 3: 52 – 57.
15. Tabatabaeian, K., Heidari, H., Khorshidi, A., Mamaghani, M. and Mahmoodi, N. O. (2012). Synthesis of biscoumarin derivatives by the reaction of aldehydes and geneous catalyst. *Journal Serbian Chemical Society,* 77(4): 407 – 413.
16. Siddiqui, Z. N., Forooq, F. (2011). Zn (Proline)2: a novel catalyst for the synthesis of dicoumarols. *Catalysis Science Technology,* 1: 810 – 816.
17. Hamdi, N., Puerta, M. C. and Valerga, P. (2008). Synthesis,structure,antimicrobialand antioxidant investigations of dicoumarol and related compounds. *European Journal of Medicinal Chemistry,* 43: 2541 – 2548.