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Studies on the synthesis and antimicrobial activity of 2-oxo-2*H*-chromene-3-carbohydrazide derivatives

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ABSTRACT

*2-(2-Oxo-2H-chromene-3-carbonyl)hydrazinyl)carbonylbenzoic acids (**2a,b**) and 4-oxo-4-(2-(2-oxo-2H-chromene-3-carbonyl)hydrazinyl)butanoic acids (**3a,b**) were synthesized from the reaction of 2-oxo-2H-chromene-3-carbohydrazides (**1a,b**) with phthalic anhydride and succinic anhydride, respectively. Sugar hydrazones (**4a-f**) were prepared by treating compound **1a,b** with aldoses. Acetylation of **4a-f** with acetic anhydride at room temperature gave the poly-O-acetyl derivatives (**5a-f**) whereas, treatment of sugar hydrazones **4a-f** with boiling acetic anhydride afforded the corresponding 1,3,4-oxadiazoline derivatives (**6a-f**). The synthesized compounds were screened for their antimicrobial activity.*

Key words: 2-Oxo-2*H*-chromene, 1,3,4-oxadiazoline, acyclic *C*-nucleosides, antimicrobial activity.

INTRODUCTION

Among the heterocyclic compounds, 2-oxo-2*H*-chromenes are associated with a broad spectrum of biological activities. Many 2-oxo-2*H*-chromenes have been reported to possess antibacterial[1] , antifungal[2] ,antiviral[3],anti-inflammatory[4] ,anticonvulsant[5] ,antidepressant[6] ,antitubercular[7] , antidiabetic[8] , and anticancer[9] properties . They also served as versatile precursors for many organic transformations in the synthesis of a number of drug-like molecules[10,11] . On the other hand, the acyclic *C*-nucleosides possess a wide range of biological properties, including antimicrobial[12] ,anti-hepatitis B virus[13] , and antitumor[14] activities. Additionally 1,3,4-oxadiazole derivatives are gaining importance in the heterocyclic family because of their broad spectrum of biological activities such as antimicrobial[15] ,anti-HIV[16] ,anti-inflammatory[17] ,anticancer[18] , antioxidant[19], anti-tubercular[20] , anticonvulsant[21] .Owing to these facts, our aim in the present work was the synthesis and antimicrobial evaluation of 2*H*-chromen-2-one derivatives, their *C*-nucleosides and oxadiazolyl analogues.

MATERIALS AND METHODS

All the chemicals used were that of analytical grade. Melting points were uncorrected, determined in open capillary. Purity of the compounds was checked by TLC on silica gel. IR spectra was recorded by using JASCO FT/IR-300 E spectrometer from a KBr plated sample. ^{1}H- NMR spectra was recorded on a Bruker supercon FT NMR (400 MHz) spectrometer in DMSO-*d6* as solvent and TMS as an internal standard. The chemical shifts are expressed in δ units. The mass spectral data were obtained with a Micro Spectrometer model 7070 at 70 eV and a 90 ^{o}C inlet temperature. Elemental analyses were performed on a Perkin-Elmer 240 microanalyser in the Faculty of Science, Cairo University.

Synthesis of 2-(2-oxo-2H-chromene-3-carbonyl)hydrazinyl)carbonylbenzoic acids(2a,b):
A solution of **1a,b** (0.01 mole) and phtalic anhydrides (0.01 mole) in dry toluene was stirred at room temperature for overnight. The solvent was evaporated under vacuum and the precipitate was recrystallized from ethanol.

2-(6-Bromo2-oxo-2H-chromene-3-carbonyl)hydrazinyl)carbonylbenzoic acid (2a):
Yield: 68%; mp: 274-276 ^{o}C; IR (KBr): υ (cm^{-1}) 3315 (OH), 3268, 3231 (NH), 1710 (lactone CO),1694, 1666 (C=O); ^{1}H-NMR δ: 6.91-8.16 (m, 7H, Ar-H), 9.41 (s, 1H, pyran-CH4), 10.39 (s, 2H, NH), 12 ppm (s,1H,COOH); EI-MS: *m/z* 430 [M+1]. Anal. calcd. for $C_{18}H_{11}BrN_2O_6$: C 50.14, H 2.57, N 6.50. Found: C 50.13, H 2.57, N 6.51.

2-(5,6-Benzo-2-oxo-2H-chromene-3-carbonyl)hydrazinyl)carbonylbenzoic acids (2b):
Yield: 70%; mp: 282-284 °C; IR (KBr): υ (cm^{-1}) 3324 (OH), 3253, 3224 (NH), 1715 (lactone CO),1690, 1665 (C=O); ^{1}H-NMR δ: 6.73-8.12 (m, 10H, Ar-H), 9.34 (s, 1H, pyran-CH4), 10.22 (s, 2H, NH), 12.20 ppm (s,1H,COOH);; EI-MS: *m/z* 402 [M+]. Anal. calcd. for $C_{22}H_{14}BrN_2O_6$: C 65.67, H 3.51, N 6.96. Found: C 65.66, H 3.52, N 6.96.

4-Oxo-4-(2-(2-oxo-2H-chromene-3-carbonyl)hydrazinyl)butanoic acids (3a,b):
A solution of 4 (0.01 mole) and succinic anhydride (0.01 mole) in dry toluene was stirred at room temperature for 14 h. The solvent was evaporated and the product was recrystallized from methanol.

4-Oxo-4-(2-(6-bromo-2-oxo-2H-chromene-3-carbonyl)hydrazinyl)butanoic acids (3a):
Yield: 70%; mp: 250-252 °C; IR (KBr): υ (cm^{-1}) 3415 (OH), 3235, 3021 (NH), 1708(lactone CO),1680, 1669 (C=O); ^{1}H-NMR δ: 2.45 (4H, s, CH_2CH_2) 6.94-7.45 (m, 3H, Ar-H), 9.33 (s, 1H, pyran-CH4), 10.16 (s, 2H, NH), 12.10 (1H, br s, COOH); EI-MS: *m/z* 383 [M+]. Anal. calcd. for $C_{14}H_{11}BrN_2O_6$: C 43.89, H 2.89, N 7.31. Found: C 43.88, H 2.90, N 7.32.

4-Oxo-4-(2-(5,6-benzo-2-oxo-2H-chromene-3-carbonyl)hydrazinyl)butanoic acids (3b):
Yield: 77%; mp: 270-272 °C; IR (KBr): υ (cm^{-1}) 3410 (OH), 3245, 3067 (NH), 1714(lactone CO),1682, 1665 (C=O); ^{1}H-NMR δ: 2.40 (4H, s, CH_2CH_2) 6.90-7.67 (m, 6H, Ar-H), 9.21 (s, 1H, pyran-CH4), 10.23 (s, 2H, NH), 12.13 (1H, br s, COOH); EI-MS: *m/z* 354 [M+]. Anal. calcd. for $C_{18}H_{14}N_2O_6$: C 61.02, H 3.98, N 7.91. Found: C 61.02, H 3.99, N 7.92.

General procedure for the preparation of sugar carbohydrazones (4a-f):
To a well stirred mixture of the respective monosaccharide [D-xylose, D-glucose, D-galactose] (0.01 mole) in water (5 ml), glacial acetic acid (0.5 ml) in ethanol (10 ml) was added to the carbohydrazide derivatives **1a,b** (0.01 mole). The mixture was heated under reflux for 3 h and the resulting solution was concentrated and left to cool. The formed precipitate was filtered off, washed with water and ethanol, dried, and recrystallized from ethanol.

D-Xylose (6-bromo-2-oxo-2H-chromen-3-yl)carbohydrazone (4a)
Yield: 80%; mp: 134-136 °C; IR (KBr): υ (cm^{-1}) 3412-3369 (OH), 1710 (C=O), 1609 (C=N); ^{1}H-NMR δ: 3.37-3.68 (m, 4H, 3′-H, 4′-H, 5′-2H,), 4.25 (m, 1H, 2′-H), 4.45 (brs, 3H, 3OH), 5.09 (brs, 1H, OH), 7.64-7.77 (m, 4H, 1′-H, 3Ar-H), 9.6 (s, 1H, pyran-CH4), 10.50 ppm (brs, 1H, NH). EI-MS: *m/z* 416 [M+]. Anal. Calcd. For $C_{15}H_{15}BrN_2O_7$; C, 43.39; H, 3.64; N, 6.75. Found: C, 43.38; H, 3.63; N, 6.77.

D-Glucose (6-bromo-2-oxo-2H-chromen-3-yl)carbohydrazone (4b)
Yield: 77%; mp: 156-158 °C; IR (KBr): υ (cm^{-1}) 3420-3370 (OH), 1714 (C=O), 1607 (C=N). ^{1}H-NMR (300 MHz,DMSO-*d6*): δ 3.35-3.78 (m, 5H, 3′-H, 4′-H, 5′-H, 6′-2H), 4.22 (m, 1H, 2′-H,), 4.70 (brs,3H,3OH), 5.17 (brs, 2H, 2OH), 7.74-7.97 (m, 4H, 1′-H,3 Ar-H), 9.31 (s, 1H, pyran-CH4), 10.60 (brs,1H, NH) ppm. EI-MS: *m/z* 446 [M+]. Anal. Calcd. For $C_{16}H_{17}BrN_2O_8$; C, 43.16; H, 3.85; N, 6.29. Found: C, 43.16; H, 3.84; N, 6.28.

D-Galactose (6-bromo-2-oxo-2H-chromen-3-yl)carbohydrazone (4c)
Yield: 82%; mp: 171-172 °C; IR (KBr): υ (cm^{-1}) 3418-3372 (OH), 1714 (C=O), 1607 (C=N).^{1}H-NMR (300 MHz, DMSO-*d6*): δ 3.30-3.58 (m, 5H, 3′-H, 4′-H, 5′-H, 6′-2H), 4.12 (m, 1H, 2′-H,), 4.56 (brs, 3H,3OH), 5.10 (brs, 2H, 2OH), 7.65-7.86 (m, 4H, 1′-H, Ar-H), 9.52 (s, 1H, pyran-CH4), 10.55 (brs, 1H, NH) ppm. EI-MS: *m/z* 446 [M+]. Anal. Calcd. For $C_{16}H_{17}BrN_2O_8$; C, 43.16; H, 3.85; N, 6.29. Found: C, 43.17; H, 3.85; N, 6.30.

D-Xylose (2-oxo-2H-5,6-benzochromen-3-yl)carbohydrazone (4d)
Yield: 74%; mp: 222-224 °C; IR (KBr): υ (cm^{-1}) 3411-3356 (OH), 1716 (C=O), 1609 (C=N); ^{1}H-NMR δ: 3.32-3.65 (m, 4H, 3′-H, 4′-H, 5′-2H,), 4.11 (m, 1H, 2′-H), 4.55 (brs, 3H, 3OH), 5.12 (brs, 1H, OH), 7.11-7.86 (m, 7H, 1′-H, 6Ar-H), 9.25 (s, 1H, pyran-CH4), 10.31 ppm (brs, 1H, NH). EI-MS: *m/z* 386 [M+]. Anal. Calcd. For $C_{19}H_{18}N_2O_7$; C, 59.07; H, 4.70; N, 7.25. Found: C, 59.06; H, 4.71; N, 7.26.

D-Glucose (2-oxo-2H-5,6-benzochromen-3-yl)carbohydrazone (4e)
Yield: 81%; mp: 272-274 °C; IR (KBr): υ (cm^{-1}) 3420-3368 (OH), 1714 (C=O), 1607 (C=N). ^{1}H-NMR (300 MHz,DMSO-*d6*): δ 3.31-3.83 (m, 5H, 3′-H, 4′-H, 5′-H, 6′-2H), 4.42 (m, 1H, 2′-H), 4.74 (brs, 3H,3OH), 5.09 (brs, 2H, 2OH), 7.21-7.86 (m, 4H, 1′-H,6 Ar-H), 9.03 (s, 1H, pyran-CH4), 10.84 (brs,1H, NH) ppm. EI-MS: *m/z* 416 [M+]. Anal. Calcd. For $C_{20}H_{20}N_2O_8$; C, 57.69; H, 4.84; N, 6.73. Found: C, 57.69; H, 4.83; N, 6.74.

D-Galactose (2-oxo-2H-5,6-benzochromen-3-yl)carbohydrazone (4f)
Yield: 85%; mp: 280-282 °C; IR (KBr): υ (cm^{-1}) 3420-3370 (OH), 1714 (C=O), 1607 (C=N).^{1}H-NMR (300 MHz, DMSO-*d6*): δ 3.30-3.58 (m, 5H, 3′-H, 4′-H, 5′-H, 6′-2H), 4.12 (m, 1H, 2′-H,), 4.56 (brs, 3H,3OH), 5.10 (brs, 2H, 2OH), 7.65-7.86 (m, 7H, 1′-H, 6Ar-H), 9.61 (s, 1H, pyran-CH4), 10.55 (brs, 1H, NH) ppm. EI-MS: *m/z* 416 [M+]. Anal. Calcd. For $C_{20}H_{20}N_2O_8$; C, 57.69; H, 4.84; N, 6.73. Found: C, 57.70; H, 4.84; N, 6.72.

***General procedure for the preparation of O-acetylsugar carbohydrazones* 5a-f.**
To a solution of the sugar hydrazones **4a-f** (0.01 mole) in pyridine (5 ml), acetic anhydride (3 ml) was added and the mixture was stirred at room temperature for 5 h. The resulting solution was poured onto crushed ice and the product that separated out was filtered off, washed with a solution of sodium hydrogen carbonate followed by water and then dried. The products were recrystallized from ethanol.

2,3,4,5- Tetra-O-acetyl-D-xylose (6-bromo-2-oxo-2H-chromen-3-yl)carbohydrazone (5a)
Yield: 85%; mp: 168-170 °C; IR (KBr): υ (cm^{-1}) 3230 (NH), 1717 (C=O), 1658 (C=O), 1607 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.91, 1.96, 2.05, 2.09 (4s, 12H, $4CH_3$), 3.31 (s, 2H, CH_2), 4.40-4.47 (m, 1H, 4′-H), 5.00-5.08 (m, 1H, 3′-H), 5.35-5.40 (m, 1H, 2′-H), 6.93 (s, 1H, CH), 7.65-7.77 (m, 3H, Ar-H), 9.03 (s, 1H, pyran-CH4), 11.76 (br s, 1H, NH) ppm. Anal. Calcd. For $C_{19}H_{23}BrN_2O_7$; C, 48.42; H, 4.92; N, 5.94. Found: C, 48.43; H, 4.92; N, 5.93.

2,3,4,5,6-Penta-O-acetyl- D-Glucose (6-bromo-2-oxo-2H-chromen-3-yl)carbohydrazone (5b)
Yield: 77%; mp: 162-164 °C; 92%, mp 190-192 oC; IR (KBr): υ (cm^{-1}) 3238 (NH), 1710 (C=O), 1660 (C=O), 1610 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.90, 1.95, 1.97, 2.07, 2.11 (5s, 15H, $5CH_3$), 3.45 (s, 2H, CH_2), 4.08-4.15 (m, 1H, 5′-H), 4.40-4.47 (m, 1H, 4′-H), 5.00-5.08 (m, 1H, 3′-H), 5.35-5.40 (m, 1H, 2′-H), 6.93 (s, 1H, CH), 7.19-7.33 (m, 3H, Ar-H), 9.41 (s, 1H, pyran-CH4), 10.11 (brs, 1H, NH) ppm. EI-MS: *m/z* 516 [M+]. Anal. Calcd. For $C_{21}H_{27}BrN_2O_8$; C, 48.94; H, 5.28; N, 5.44. Found: C, 48.93; H, 5.28; N, 5.45.

2,3,4,5,6-Penta-O-acetyl-D-Galactose (6-bromo-2-oxo-2H-chromen-3-yl)carbohydrazone (5c)
Yield: 66%; mp: 154-156 °C; IR (KBr): υ (cm^{-1}) 3323 (NH), 1720 (C=O), 1658 (C=O), 1604 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.92, 1.94, 1.98, 2.06, 2.10 (5s, 15H, $5CH_3$), 3.22 (s, 2H, CH_2), 4.05-4.11 (m, 1H, 5′-H), 4.38-4.41 (m, 1H, 4′-H), 5.01-5.09 (m, 1H, 3′-H), 5.31-5.44 (m, 1H, 2′-H), 6.94 (s, 1H, CH), 7.02-7.29 (m, 3H, Ar-H), 9.33 (s, 1H, pyran-CH4), 10.29 (brs, 1H, NH) ppm. EI-MS: *m/z* 516 [M+]. Anal. Calcd. For $C_{21}H_{27}BrN_2O_8$; C, 48.94; H, 5.28; N, 5.44. Found: C, 48.94; H, 5.26; N, 5.43.

2,3,4,5-Tetra-O-acetyl-D-Xylose (2-oxo-2H-5,6-benzochromen-3-yl)carbohydrazone (5d)
Yield: 76%; mp: 180-182 °C; IR (KBr): υ (cm^{-1}) 3311 (NH), 1718 (C=O), 1654 (C=O), 1609 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.90, 1.93, 2.02, 2.09 (4s, 12H, $4CH_3$), 3.33 (s, 2H, CH_2), 4.36-4.42 (m, 1H, 4′-H), 5.01-5.09 (m, 1H, 3′-H), 5.35-5.40 (m, 1H, 2′-H), 6.89 (s, 1H, CH), 7.81-7.92 (m, 6H, Ar-H), 9.03 (s, 1H, pyran-CH4), 10.81 (brs, 1H, NH) ppm. EI-MS: *m/z* 442 [M+]. Anal. Calcd. For $C_{23}H_{26}N_2O_7$; C, 62.43; H, 5.92; N, 6.33 . Found: C, 62.44; H, 5.92; N, 6.32.

2,3,4,5,6-Penta-O-acetyl-D-Glucose (2-oxo-2H-5,6-benzochromen-3-yl)carbohydrazone (5e)
Yield: 80%; mp: 220-222 °C; IR (KBr): υ (cm^{-1}) 3423 (NH), 1735 (C=O), 1658 (C=O), 1607 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.92, 1.96, 1.98, 2.07, 2.13 (5s, 15H, $5CH_3$), 3.56 (s, 2H, CH_2), 4.05-4.19 (m, 1H, 5′-H), 4.41-4.49 (m, 1H, 4′-H), 5.00-5.08 (m, 1H, 3′-H), 5.45-5.55 (m, 1H, 2′-H), 6.96 (s, 1H, CH), 7.19-7.33 (m, 6H, Ar-H),

9.49 (s, 1H, pyran-CH4), 10.88 (brs, 1H, NH) ppm. EI-MS: *m/z* 486 [M+]. Anal. Calcd. For $C_{25}H_{30}N_2O_8$; C, 61.72; H, 6.22; N, 5.76 . Found: C, 61.72; H, 6.21; N, 5.77.

2,3,4,5,6-Penta-O-acetyl-D-Galactose (2-oxo-2H-5,6-benzochromen-3-yl)carbohydrazone (5f)
Yield: 65%; mp: 232-234 °C; IR (KBr): υ (cm^{-1}) 3423 (NH), 1735 (C=O), 1658 (C=O), 1607 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.93, 1.97, 1.99, 2.09, 2.14 (5s, 15H, $5CH_3$), 3.35 (s, 2H, CH_2), 4.01-4.09 (m, 1H, 5′-H), 4.32-4.39 (m, 1H, 4′-H), 5.01-5.09 (m, 1H, 3′-H), 5.35-5.65 (m, 1H, 2′-H), 6.77 (s, 1H, CH), 7.01-7.78 (m, 6H, Ar-H), 9.35 (s, 1H, pyran-CH4), 10.21 (brs, 1H, NH) ppm. EI-MS: *m/z* 486 [M+]. Anal. Calcd. For $C_{25}H_{30}N_2O_8$; C, 61.72; H, 6.22; N, 5.76 . Found: C, 61.71; H, 6.23; N, 5.76.

General procedure for the preparation of oxadiazoline derivatives(6a-f):
A solution of sugar hydrazones **4a-f** (0.01 mole) in acetic anhydride (15 ml) was heated under reflux for 2 h. The resulting solution was poured onto crushed ice, and the product that separated out was filtered off, washed with a solution of sodium hydrogen carbonate followed by water and then dried. The products were recrystallized from ethanol.

4-Acetyl-2-(6-bromo-2-oxo-2H-chromen-3-yl)-5-(1,2,3,4-tetra-O-acetyl-D-xylotetritolyl)- 2,3-dihydro-1,3,4-oxadiazoline (6a)
Yield: 80%; mp: 153-155 °C; IR (KBr): υ (cm^{-1}) 1710 (C=O), 1606 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.91, 1.92, 2.07, 2.09, 2.12 (5s, 15H, $5CH_3CO$), 3.51 (s, 2H, CH_2), 5.62-5.78 (m,3H, 2′-H, 3′-H, 4′-H), 6.90 (s, 1H, CH), 7.11-7.23 (m, 4H, 1′-H, Ar-H), 9.40 (s, 1H, pyran-CH4), 10.14 (brs, 1H, NH) ppm. EI-MS: *m/z* 626 [M+1]. Anal. Calcd. For $C_{25}H_{25}BrN_2O_{12}$; C, 48.01; H, 4.03; N, 4.48 . Found: C, 48.02; H, 4.02; N, 4.47.

4-Acetyl-2-(6-bromo-2-oxo-2H-chromen-3-yl)-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl)- 2,3-dihydro-1,3,4-oxadiazoline (6b)
Yield: 74%; mp: 175-177 °C; IR (KBr): υ (cm^{-1}) 1711 (C=O), 1606 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.95, 1.94, 2.06, 2.09, 2.14 (5s, 15H, $5CH_3CO$), 3.58 (s, 2H, CH_2), 4.11-4.19 (m,5H, 4′-H,

5′-H, 2CH), 5.57-5.87 (m, 2H, 2′-H, 3′-H), 6.99 (s, 1H, CH), 7.23-7.36 (m, 4H, 1′-H, Ar-H), 9.52 (s, 1H, pyran-CH4), 10.36 (brs, 1H, NH) ppm. EI-MS: *m/z* 698 [M+1]. Anal. Calcd. For $C_{28}H_{29}BrN_2O_{14}$; C, 48.22; H, 4.19; N, 4.02 . Found: C, 48.21; H, 4.19; N, 4.03.

4-Acetyl-2-(6-bromo-2-oxo-2H-chromen-3-yl)-5-(1,2,3,4,5-penta-O-acetyl-D-galactopentitolyl)- 2,3-dihydro-1,3,4-oxadiazoline (6c)
Yield: 69%; mp: 144-146 °C; IR (KBr): υ (cm^{-1}) 1710 (C=O), 1608 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.96, 1.98, 2.04, 2.06, 2.15 (5s, 15H, $5CH_3CO$), 3.61 (s, 2H, CH_2), 4.08-4.12 (m,5H, 4′-H,

5′-H, $2CH_2$), 5.61-5.73 (m, 2H, 2′-H, 3′-H), 6.99 (s, 1H, CH), 7.15-7.33 (m, 4H, 1′-H, Ar-H), 9.44 (s, 1H, pyran-CH4), 10.77 (brs, 1H, NH) ppm. EI-MS: *m/z* 698 [M+1]. Anal. Calcd. For $C_{28}H_{29}BrN_2O_{14}$; C, 48.22; H, 4.19; N, 4.02 . Found: C, 48.21; H, 4.19; N, 4.03.

4-Acetyl-2-(2-oxo-2H-5,6-benzochromen-3-yl)-5-(1,2,3,4-tetra-O-acetyl-D-xylotetritolyl)- 2,3-dihydro-1,3,4-oxadiazoline (6d)
Yield: 83%; mp: 234-236 °C; IR (KBr): υ (cm^{-1}) 1715 (C=O), 1603 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.92, 1.99, 2.06, 2.09, 2.12 (5s, 15H, $5CH_3CO$), 3.60 (s, 2H, CH_2), 5.12-5.67 (m, 3H, 2′-H, 3′-H, 4′-H), 6.34 (s, 1H, CH), 7.06-7.96 (m, 7H, 1′-H, Ar-H), 9.35 (s, 1H, pyran-CH4), 10.37 (brs, 1H, NH) ppm. EI-MS: *m/z* 596 [M+]. Anal. Calcd. For $C_{29}H_{28}N_2O_{12}$; C, 58.39; H, 4.73; N, 4.70 . Found: C, 58.40; H, 4.73; N, 4.71.

4-Acetyl-2-(2-oxo-2H-5,6-benzochromen-3-yl)-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl)- 2,3-dihydro-1,3,4-oxadiazoline(6e)
Yield: 62%; mp: 243-245 °C; IR (KBr): υ (cm^{-1}) 1710 (C=O), 1606 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.97, 1.99, 2.05, 2.07, 2.16 (5s, 15H, $5CH_3CO$), 3.62 (s, 2H, CH_2), 4.09-4.13 (m,5H, 4′-H,

5′-H, $2CH_2$), 5.60-5.72 (m, 2H, 2′-H, 3′-H), 6.96 (s, 1H, CH), 7.14-7.94 (m, 7H, 1′-H, Ar-H), 9.51 (s, 1H, pyran-CH4), 10.85 (brs, 1H, NH) ppm. EI-MS: *m/z* 668 [M+]. Anal. Calcd. For $C_{32}H_{32}N_2O_{14}$; C, 57.48; H, 4.82; N, 4.19 . Found: C, 57.48; H, 4.81; N, 4.18.

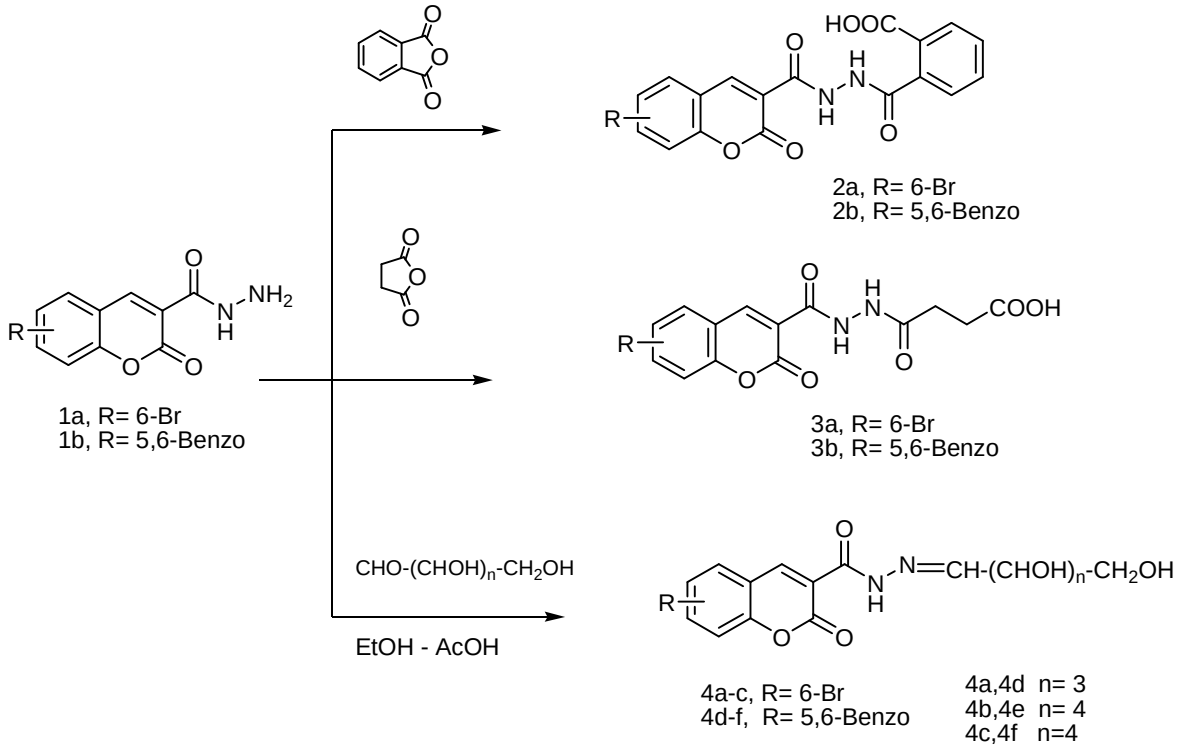
4-Acetyl-2-(2-oxo-2H-5,6-benzochromen-3-yl)-5-(1,2,3,4,5-penta-O-acetyl-D-galactopentitolyl)- 2,3-dihydro-1,3,4-oxadiazoline(6f)
Yield: 66%; mp: 248-250 °C; IR (KBr): υ (cm^{-1}) 1708 (C=O), 1610 (C=N). ^{1}H-NMR (300 MHz, DMSO-*d6*): δ 1.89, 1.93, 2.01, 2.05, 2.16 (5s, 15H, $5CH_3CO$), 3.59 (s, 2H, CH_2), 4.07-4.18 (m,2H, 4′-H,

5′-H, $2CH_2$), 5.34-5.69 (m, 2H, 2′-H, 3′-H), 6.88 (s, 1H, CH), 7.11-7.99 (m, 7H, 1′-H, Ar-H), 9.35 (s, 1H, pyran-CH4), 10.22 (brs, 1H, NH) ppm. EI-MS: *m/z* 668 [M+]. Anal. Calcd. For $C_{32}H_{32}N_2O_{14}$; C, 57.48; H, 4.82; N, 4.19 . Found: C, 57.48; H, 4.81; N, 4.18.

RESULTS AND DISCUSSION

Phthalic anhydride was reacted with 2-oxo-2*H*-chromene-3-carbohydrazides (**1a,b**) in dry toluene to form 2-(2-oxo-2*H*-chromene-3-carbonyl)hydrazinyl)carbonylbenzoic acids(**2a-d**) (scheme 1). The Infrared of **2a,b** showed absorption bands at 3665-3315 for OH, 3268 and 3231 for NH, 1710 for CO of lactone ,and 1694,1667 cm^{-1} for CO. The ^{1}H-NMR of **2a**, as an example, confirm the presence of aromatic protons at δ 6.91-8.16 ppm . A singlet peak appears for a single proton reveals the presence of CH-4 proton of lactone ring at δ 9.41ppm. Another two singlet for 2NH protons and COOH appears at δ 10.39 and 12 ppm, respectively. 4-Oxo-4-(2-(2-oxo-2H-chromene-3-carbonyl)hydrazinyl)butanoic acids (**3a,b**) were also prepared via treatment **1a,b** with succinic anhydride. The structure of **3a,**b was confirmed by IR, Mass, and ^{1}H-NMR spectroscopy.

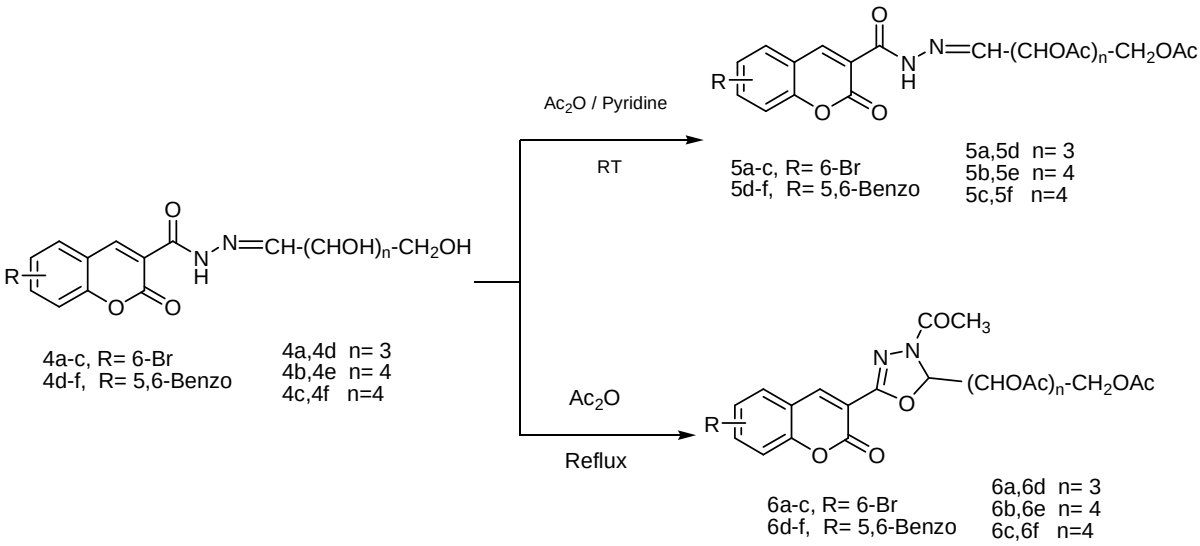
Treatment of carbohydrazides **1a,b** with the monosaccharides (D-xylose, D-glucose or D-galactose) in an aqueous ethanolic solution containing catalytic amount of glacial acetic acid, gave the corresponding hydrazinosugar derivatives (**4a-f)** (scheme 1). The IR spectra of compounds **4a-f** showed the presence of characteristic absorption bands corresponding to the hydroxyl groups in the region 3370-3420 cm^{-1}. The ^{1}H-NMR spectra showed the signals of the sugar chain protons at δ 3.35- 4.22 ppm, and the C-1 methine proton as doublet in the range δ 7.74-7.97 ppm.



Scheme 1

The per-*O*-acetylated sugar hydrazone derivatives (**5a-f**) were obtained via acetylating of **4a-f** with acetic anhydride in pyridine at room temperature (scheme 2). Mass spectrum of **5a-f** showed the signal of the molecular

ion peak which is in agreement with its molecular formula. The ^{1}H-NMR spectra of these derivatives showed the signals of the *O*-acetyl-methyl protons as singlets in the range δ 1.89-2.98 ppm. On the other hand, refluxing of the sugar hydrazones **4a-f** with acetic anhydride at 120 ^{o}C for 2 h gave the corresponding oxadiazoline derivatives (**6a-f**) (scheme 2). The structure of oxadiazoline derivatives was established by IR, ^{1}H-NMR and mass spectra.



Scheme 2

Table 1. Antimicrobial activity of the synthesized compounds

Compd.	Minimum Inhibitory Concentration (MIC, μgmL^{-1})					
	Gram +ve bacteria		***Gram -ve bacteria***		***Fungi***	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeuroginosa*	*Candida albicans*	*Aspergillus niger*
2a	250	250	200	200	50	125
2b	250	250	125	200	50	200
3a	1000	500	200	250	500	500
3b	200	500	250	500	250	250
4a	250	1000	250	150	125	500
4b	1000	250	250	250	500	200
4c	500	500	250	500	100	500
4d	1000	1000	500	1000	100	500
4e	250	500	250	250	125	500
4f	250	100	100	150	250	125
5a	250	250	500	500	500	500
5b	25	25	70	25	500	125
5c	70	70	200	100	200	200
5d	250	250	500	150	500	500
5e	250	250	250	200	1000	200
5f	500	500	125	250	500	200
6a	25	25	50	50	50	125
6b	500	500	500	500	100	500
6c	200	200	100	70	100	500
6d	250	250	100	200	125	250
6e	500	500	125	150	125	250
6f	100	100	250	70	200	500
Ampicillin	250	100	100	100	-	-
Nystatin	-	-	-	-	100	100

Antimicrobial Activity:

The *in vitro* antimicrobial activity of all the synthesized compounds was carried out by broth micro dilution method[22] . Mueller Hinton broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud Dextrose broth used for fungal nutrition. Inoculum size for test strain was adjusted to

108 $CFUmL^{-1}$ (Colony Forming Unit per milliliter) by comparing the turbidity. The compounds were screened *in vitro* for their antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus* (Gram-positive bacteria), *Escherichia coli* and *Pseudomonas sp.* (Gram-negative bacteria) , as well as, *Candida albicans* and *Aspergillus niger* (fungi). DMSO was used as vehicle to get desired concentration of compounds to test upon microbial strains. The lowest concentration, which showed no visible growth after spot subculture was considered as MIC for each compound. Ampicillin was used as standard antibacterial drug, whereas nystatin was used as standard antifungal drugs. The protocols were summarized in Table 1.

The examination of the data (Table 1) reveals that most of the compounds showed excellent antibacterial and antifungal activity when compared with ampicillin and nystatin. Against Gram positive pathogen *Staphylococcus aureus*, compounds **5b**,**5c** and 6a were found to be more efficient than ampicillin where as **4f** and **6f** were found to exhibit comparable activity, to ampicillin.

On the other hand, compounds **3b**,**5b**,**5c** , **6a** and **6f** shows better activity, and **2a-b**, **3b**, **4a**, **4e-f**, **5a**, **5d-e** and **6c-d** found equally potent, to ampicillin, against *B. subtilis*. Towards Gram negative strain *E. coli*, compounds **5b** and **6a** exhibited excellent activity comparable to ampicillin where as compounds **4f**, **6c** and 6d were found to show equal activity. The compounds **6c** and **6f** were found better active and **5c** is equally active than ampicillin towards *Pseudomonas sp.* The compound **5b** was highly active against all the tested Gram positive and negative pathogens. Against fungal pathogen *C. albicans*, compounds **2a**, **2b** and **6a** found better activity whereas, **4c**,**4d**,**6b** and **6c** were found to be equipotent compared to nystatin.

CONCLUSION

This paper describes the synthesis, spectral characterization, and screening of antimicrobial activity of some 2*H*-chromen-2-one derivatives bearing side chains, oxobutanoic acid and carbonylbenzoic acid derivatives, *C*-nucleosides and oxadiazolyl analogues. The oxadiazolyl derivative **6a** exhibited the highest antibacterial and antifungal activities comparable to standard antibiotics.

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