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RESEARCH ARTICLE

A Novel and Efficient Synthesis of Various 7-Hydroxy-9(Furo[2,3-b]Quinolin-2-Yl)*6H*- Benzo[c]Coumarins and Evaluation of their Antimicrobial Activity

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ABSTRACT

A series of novel 7-hydroxy-9-(furo[2,3-*b*]quinolin-2-yl)6*H*-benzo[*c*]coumarins **(3a-l)** has been synthesized by reacting various 3-coumarinoyl methyl pyridinium bromide salts **(1a-d)** with appropriate 2-acetyl-furo[2,3-*b*]quinoline **(2a-c)** in the presence of sodium acetate in refluxing acetic acid. All the synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-APT and mass spectral analysis. All the synthesized compounds have been screened for their *invitro* anti-bacterial and anti-fungal activities. Some of the compounds have been found to be active against some bacterial and fungal pathogens compared to standard drugs. Among the synthesized derivatives, compounds **3c, 3d, 3f** and **3j** were found to be most efficient members of the series.

KEYWORDS

Furo[2,3-b]quinoline, benzo[*c*]coumarin, antimicrobial activity, broth dilution method

INTRODUCTION

Benzo[*c*]coumarins form an important class of coumarin derivatives and isolated from plant and animal sources and are mainly metabolic products of microorganisms[1-2]. Many benzo[*c*]coumarin derivatives are isolated as natural products and are synthesized in laboratories as well. Alternariol[3] and its related derivatives like Autumnariol, Autumnariniol[4] and Altenuisol[5] are toxic secondary metabolites of various Alternaria fungi. Gilvocarcin[6], Ravidomycin[7] and Chrysomycins[8] are c-glycoside antibiotics. They are isolated from various strains of streptomyces species. Arnottin[9] and Defucogilvocarcin[10] are natural products of the class of Gilvocarcine family and possess an antitumor activity[11].

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Many benzo[*c*]coumarin derivatives are reported to possess various biological activities like antibiotic[12], anticancer[13], antiviral[14], anti-mutagenic[15], anti-proliferative[16], anti-allergic[17], cytotoxic[18] antioxidant[19] etc. A literature survey for the synthesis of benzo[*c*]coumarins revealed that in majority of the reports on the synthesis of benzo[*c*]coumarins, the compounds have been synthesized by the lactonization of appropriately substituted biphenyl derivatives[20-23]. In the present work we have synthesized some new benzo[*c*]coumarin derivatives utilizing a novel and distinct approach.

Morever, furoquinoline alkaloids are a group of alkaloids with simple structures. The simplest member of this group is dictamnine and most widespread member is skimianine. These alkaloids were found to possess wide range of biological activities such as anti-allergic, anti-inflamattory, cytotoxic and antiplatelet aggregation[24-27].

Thus considering the importance of furoquinoline derivatives it was thought worthwhile to incorporate this moiety in benzo[*c*]coumarin as a substituent group and therefore in the present work synthesis of various 9-(furo[2,3-*b*]quinolin-2-yl)-7-hydroxy-*6H*-benzo[*c*]coumarins has been carried out.

MATERIALS AND METHOD

Experimental

All the melting points are uncorrected. All reactions were performed with commercially available reagents and they were used without further purification. Organic solvents were purified by standard methods and stored over molecular sieves. All the IR spectra (KBr disc) were recorded on Shimadzu FT-IR 8400-S spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Advance400 spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. The chemical shift (δ) is reported in ppm using chloroform-d as a solvent and calibrated standard solvent signal. Mass spectra were recorded on Shimadzu QP 2010 spectrometer. Column chromatography was performed with silica gel 60–120 mesh (Merck, Mumbai, India.). All the compounds were routinely checked for completion of the reaction on silica gel 60 F254 TLC plates and their spots were visualized by exposure to a UV lamp, iodine vapour or $KMnO_4$ reagents. Compounds 3-coumarinoyl methyl pyridinium bromide salt **(1a-d)**[28-31] was prepared according to literature procedure.

Preparation of 2-acetyl-furo[2,3-b]quinolines(2a-c):

The following general procedure was used. In a 250 mL round bottom flask equipped with a condenser, a mixture of an appropriate 2-hydroxy-3-formyl-quinoline (0.1mol), chloroacetone (0.1mol), dimethylformamide (90mL) was taken. To this anhydrous potassium carbonate (0.1 mol) was added and the reaction mixture was stirred for two hours at room temperature. Then after the reaction mixture was refluxed for 8 hours. It was allowed to come to room temperature. The solid obtained was filtered out and washed with cold water. It was recrystallized from chloroform-hexane to white crystals.

2-Acetyl-furo[2,3-b]quinoline (2a): R_3 = H, yield = 76% ; mp 115°C; Anal. Calcd. For $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.63%. Found: C, 73.85; H, 4.14; N, 6.21%. IR (KBr, ν_{max}, cm^{-1}); 1615 (C=O stretching), 1485 and 1541 (aromatic C=C and C=N stretchings), 2927 (aliphatic C-H stretching), 3041 (aromatic C-H stretching).^{1}H NMR (400MHz, $CDCl_3$, δ): 2.56(3H, singlet, CH3), 7.71-8.39 (6H, multiplet, aromatic protons.

6-Methyl-2-acetyl furo[2,3-b]quinoline(2b): R_3 = CH_3**,** Yield: 60%, mp 112 ˚C (lit[32]. mp 110˚C)

6-Chloro-2-acetyl-furo[2,3-b]quinoline (2c): R_3 = Cl, yield = 75% ; mp 135-137°C; Anal. Calcd. For $C_{13}H_8NO_2$: C, 63.56; H, 3.28; N, 5.70%. Found: C, 63.48; H, 3.16; N, 5.65 %. IR (KBr, ν_{max}, cm^{-1}); 1619 (C=O stretching), 1479 and 1538 (aromatic C=C and C=N stretchings), 2921(aliphatic C-H stretching), 3045 (aromatic C-H stretching).^{1}H NMR (400MHz, $CDCl_3$, δ): 2.68(3H, singlet, CH3), 7.45-8.35 (5H, multiplet, aromatic protons)

General procedure for the synthesis of 7-hydroxy-9-(furo[2,3-b]quinolin-2-yl)-6H-benzo[c]coumarins (3a-l):

In a 100 mL three necked round bottom flask equipped with a dropping funnel, condenser, guard tube and magnetic needle, a solution of an appropriate 3-coumarinoyl methyl pyridinium bromide salt **(1a-d)** (0.004 mol) was taken in a glacial acetic acid (15 mL). To this, sodium acetate (0.012 mol) was added with stirring. Then, appropriate 2-acetyl-furo[2,3-b]quinoline **(2a-c)** in glacial acetic acid (10 mL) was added with stirring at room temperature during 10 minutes. The reaction mixture was further stirred for 20 minutes at room temperature and then refluxed for 8 hours. It was then allowed to cool to room temperature and poured into cold water (75 mL). The crude solid obtained was then extracted with chloroform (3 x 30 mL). The combined chloroform extract was washed with water (3 x 20 mL). It was dried over anhydrous

sodium sulfate. The removal of chloroform under reduced pressure gave a solid product. This was purified by column chromatography using silica gel and chloroform-petroleum ether (60-80) (6:4) as an eluent. Thus, 9-(furo[2,3-b]quinolin-2-yl)-7-hydroxy-*6H*-benzo[c]coumarins **3a-l** were obtained as yellow colored solid, which were recrystallized from chloroform-hexane.

Analytical and Spectral Characterization

The structure of all the synthesized**(3a-l)** compounds were confirmed by elemental analysis and IR , ^{1}H-NMR, ^{13}C- NMR, and representative mass spectral data.

7-Hydroxy -9-(furo[2,3-b]quinolin-2-yl)-6H-benzo[c]coumarin (3a):White solid; yield = 64% ; mp 260-262°C; Anal. Calcd. For $C_{24}H_{13}NO_4$: C, 75.98; H, 3.45; N, 3.69%. Found: C, 75.95; H, 3.45; N, 3.69%. IR (KBr, ν_{max}, cm^{-1}); 1672(C=O stretching of δ-lactone of coumarin), 1609 (aromatic C=C stretching), 3104(aromatic C-H stretching), 3436 (O-H stretching).^{1}H NMR (400MHz, $CDCl_3$, δ) : 7.24-8.51 (11H, multiplet, aromatic protons), 10.24(1H, singlet, C_4'), 12.26(1H, singlet, -OH proton).^{13}C NMR (100MHz, $CDCl_3$, δ) : 106.39(CH), 111.46(CH), 114.48(CH), 120.16(CH), 121.08(C), 122.45(CH), 123.96(C), 125.07(C), 126.61(CH), 128.31(CH), 129.43(CH), 130.07(C), 131.14(CH), 132.45(CH), 137.06(CH), 137.61(C), 145.20(C), 148.42(C), 150.03(CH), 151.77(C), 152.36(C), 161.10(C), 162.59(C) and 164.48(CO of coumarin).

7-Hydroxy-9-(6-methylfuro[2,3-b]quinolin-2-yl)-6H-benzo[c]coumarin (3b): White solid; yield = 60% ; mp 239-241°C; Anal. Calcd. For $C_{25}H_{15}NO_4$: C, 76.33; H, 3.84; N, 3.56%. Found: C, 76.31; H, 3.80; N, 3.52%. IR (KBr, ν_{max}, cm^{-1}); ν_{max} 1687 (C=O stretching of δ-lactone of coumarin), 1614 (aromatic C=C stretching), 3069 (aromatic C-H stretching), 2939 (aliphatic C-H stretching), 3403 (O-H stretching).^{1}H NMR (400MHz, $CDCl_3$, δ): 2.50 (3H, s, CH_3), 7.24-8.54 (10H, m, Ar-H), 10.23(1H, s, C_4'), 12.20 (1H, s, -OH proton) (D_2O exchangeable).^{13}C NMR (100MHz, $CDCl_3$, δ) : 21.47(CH_3), 105.24(CH), 111.41(CH), 114.51(CH), 115.30(C), 119.84(CH), 121.33(C), 122.30(CH), 123.56(C), 123.91(C), 123.94(C), 125.54(CH), 128.62(CH), 131.49(CH), 132.59(CH), 136.73(CH), 141.52(C), 145.27(C), 149.45(C), 150.27(CH), 151.85(C), 161.03(C), 162.02(C), 162.63(C), 164.51(CO of coumarin).

7-Hydroxy-9-(6-chlorofuro[2,3-b]quinolin-2-yl)-6H-benzo[c]coumarin (3c): White solid; yield = 59% ; mp 220-221°C; Anal. Calcd. For $C_{24}H_{12}ClNO_4$: C, 69.66; H, 2.92; N, 3.38%. Found: C, 69.61; H, 2.89; N, 3.34%. IR (KBr, ν_{max}, cm^{-1}); ν_{max} 1686 (C=O stretching of δ-lactone of coumarin), 1617 (aromatic C=C stretching), 3063 (aromatic C-H stretching), 3409 (O-H stretching). ^{1}H NMR (400MHz, $CDCl_3$, δ) : 7.25-8.65 (10H, m, Ar-H), 10.12(1H, s, C_4'), 12.34 (1H, s, -OH proton) (D_2O exchangeable).^{13}C NMR (100MHz, $CDCl_3$, δ) : 106.34(CH), 111.36(CH), 114.42(CH), 118.12(CH), 121.21(C), 122.52(CH), 124.03(C), 125.14(C), 128.43(CH), 129.50(CH), 130.17(C),131.22(CH), 132.42(CH), 137.09(CH), 139.64(C), 145.31(C), 148.61(C), 150.11(CH), 151.88(C), 152.48(C), 153.70(C), 161.22(C), 162.75(C), 163.99(CO of coumarin).

7-Hydroxy-4-methoxy-9-(furo[2,3-b]quinolin-2-yl)-6H-benzo[c]coumarin (3d): White solid; yield = 59% ; mp 167-168°C; Anal. Calcd. For $C_{25}H_{15}NO_5$: C, 73.35; H, 3.69; N, 3.42%. Found: C, 73.30; H, 3.71; N, 3.39%. IR (KBr, ν_{max}, cm^{-1}); ν_{max} 1671 (C=O stretching of δ-lactone of coumarin), 1615 (aromatic C=C stretching), 2920 (aliphatic C-H stretching), 3061 (aromatic C-H stretching), 3429 (O-H stretching). ^{1}H NMR (400MHz, $CDCl_3$, δ) : 3.56 (3H, s, OCH_3), 7.24-8.52 (10H, m, Ar-H), 10.26(1H, s, C_4'), 12.23 (1H, s, -OH proton) (D_2O exchangeable).^{13}C NMR (100MHz, $CDCl_3$, δ) : 55.36(OCH_3),106.44(CH), 111.32(CH), 114.62(CH), 115.36(C), 120.03(CH), 121.49(C), 122.40(CH), 123.73(C), 123.77(C), 124.02(C), 125.01(CH), 128.68(CH), 131.61(CH), 136.85(CH), 141.52(C), 145.36(CH), 149.51(C), 150.34(CH), 151.93(C), 153.02(C), 160.98(C), 162.11(C), 164.62(CO of coumarin).

7-Hydroxy-4-methoxy-9-(6-methylfuro[2,3-b]quinolin-2-yl)-6H-benzo[c]coumarin (3e): White solid; yield = 57% ; mp 169-171°C; Anal. Calcd. For $C_{26}H_{17}NO_5$: C, 73.75; H, 4.05; N, 3.31%. Found: C, 73.71; H, 4.01; N, 3.26%. IR (KBr, ν_{max}, cm^{-1}); ν_{max} 1680 (C=O stretching of δ-lactone of coumarin), 1609 (aromatic C=C stretching), 3064 (aromatic C-H stretching), 2922 (aliphatic C-H stretching), 3430 (O-H stretching). ^1H NMR (400MHz, $CDCl_3$, δ) : 2.31 (3H, s, CH_3), 3.35 (3H, s, OCH_3), 7.25-8.42 (9H, m, Ar-H), 10.23(1H, s, C_4'), 12.19 (1H, s, -OH proton) (D_2O exchangeable).^{13}C NMR (100MHz, $CDCl_3$, δ) : 23.35(CH_3), 55.73(OCH_3), 107.04(CH), 111.45(C), 115.17(C), 120.16(CH), 121.08(C), 122.44(CH), 123.95(C), 125.07(C), 126.62(CH), 128.31(CH), 129.43(CH), 130.07(C), 131.14(CH), 132.44(CH), 137.05(CH), 137.62(C), 145.20(C), 148.42(C), 150.03(CH), 151.77(C), 152.35(C), 161.10(C), 162.58(C) and 164.71(CO of coumarin)

7-Hydroxy-4-methoxy-9-(6-chlorofuro[2,3-b]quinolin-2-yl)-6H-benzo[c]coumarin (3f): White solid; yield = 58% ; mp 180-182°C; Anal. Calcd. For $C_{25}H_{14}ClNO_5$: C, 67.65; H, 3.18; N, 3.16%. Found: C, 67.32; H, 3.21; N, 3.12%. IR (KBr, ν_{max}, cm^{-1}); ν_{max} 1683 (C=O stretching of δ-lactone of coumarin), 1624 (aromatic C=C stretching), 3090 (aromatic C-H stretching), 2920 (aliphatic C-H stretching), 3417 (O-H stretching). ^1H NMR (400MHz, $CDCl_3$, δ): 3.26 (3H, s, OCH_3), 7.24-8.51 (9H, m, Ar-H), 10.26(1H, s, C_4'-H), 12.23(1H, s, -OH proton) (D_2O exchangeable). ^{13}C NMR (100MHz, $CDCl_3$, δ) : 55.49(OCH_3),106.23(CH), 111.49(CH), 114.53(CH), 115.87(C), 118.31(CH), 122.55(CH), 122.68(C), 124.02(CH), 124.42(CH), 127.49(C), 129.50(CH), 134.98(C), 136.22(CH), 139.88(C), 141.16(C), 145.77(C), 148.13(C), 149.27(CH), 150.40(C), 153.58(C), 160.33(C), 161.28(C), 162.30(CO of coumarin).

2-Bromo-7-hydroxy-9-(furo[2,3-b]quinolin-2-yl)-6H-benzo[c]coumarin (3g): White solid; yield = 55% ; mp 248-250°C; Anal. Calcd. For $C_{24}H_{12}BrNO_4$: C, 62.90; H, 2.64; N, 3.06%. Found: C, 62.85; H, 42.60; N, 3.01%. IR (KBr, ν_{max}, cm^{-1}); ν_{max} 1673 (C=O stretching of δ-lactone of coumarin), 1616 (aromatic C=C stretching), 3077 (aromatic C-H stretching), 2918 (aliphatic C-H stretching), 3417 (O-H stretching). ^1H NMR (400MHz, $CDCl_3$, δ) : 7.60-9.06 (11H, m, Ar-H), 12.00 (1H, s, -OH proton) (D_2O exchangeable).^{13}C NMR (100MHz, $CDCl_3$, δ) : 106.42(CH), 110.31(C), 114.23(C), 115.21(C), 119.45(CH), 122.18(CH), 122.88(C), 124.21(CH), 124.23(CH), 125.66(C), 127.56(C), 127.79(CH), 129.85(CH), 132.53(CH), 133.96(C), 136.36(CH), 138.23(C), 141.73(C), 145.58(CH), 149.23(CH), 151.89(C), 153.58(C) ,157.83 and 162.31(CO of coumarin)

2-Bromo-7-hydroxy-9-(6-methylfuro[2,3-b]quinolin-2-yl)6H-benzo[c]coumarin (3h): White solid; yield = 59% ; mp 212-214°C; Anal. Calcd. For $C_{25}H_{14}BrNO_4$: C, 63.58; H, 2.99; N, 2.97%. Found: C, 63.52; H, 2.94; N, 2.99%. IR (KBr, ν_{max}, cm^{-1}); ν_{max} 1686 (C=O stretching of δ-lactone of coumarin), 1613 (aromatic C=C stretching), 3057 (aromatic C-H stretching), 2920 (aliphatic C-H stretching), 3419 (O-H stretching). ^1H NMR (400MHz, $CDCl_3$, δ) : 2.50 (3H, s, CH_3), 7.44-8.61 (9H, m, Ar-H), 12.26 (1H, s, -OH proton) (D_2O exchangeable).^{13}C NMR (100MHz, $CDCl_3$, δ) : 22.52(CH_3), 106.06(CH), 112.22(C), 114.52(C), 118.10(CH), 119.02(CH), 122.26(CH), 122.98(CH), 124.75(CH), 125.50(CH), 126.68(C), 128.60(C), 128.95(CH), 129.35(C), 132.44(C), 135.43(C), 141.52(C), 145.79(CH), 148.27(C), 149.08(CH), 151.81(C), 154.51(C), 155.09(C) and 164.27(CO of coumarin).

2-Bromo-7-hydroxy-9-(6-chlorofuro[2,3-b]quinolin-2-yl)6H-benzo[c]coumarin (3i): White solid; yield = 60% ; mp 271-273°C; Anal. Calcd. For $C_{24}H_{11}BrClNO_4$: C, 58.50; H, 2.25; N, 2.84%. Found: C, 58.47; H, 2.28; N, 2.87%. IR (KBr, ν_{max}, cm^{-1}); ν_{max} 1688 (C=O stretching of δ-lactone of coumarin), 1611 (aromatic C=C stretching), 2952 (aliphatic C-H stretching),3060 (aromatic C-H stretching), 3411 (O-H stretching) (D_2O exchangeable. ^1H NMR (400MHz, $CDCl_3$, δ) : 7.50-8.96 (9H, m, Ar-H), 12.25 (1H, s, -OH proton) (D_2O exchangeable).^{13}C NMR (100MHz, $CDCl_3$, δ) : 106.53(CH), 112.58(C), 114.13(CH), 119.35(CH), 122.79(C), 124.01(CH), 125.96(C), 127.15(C), 129.00(C), 129.60(CH), 131.48(C),

132.15(CH), 133.36(C), 135.35(C), 135.59(CH), 136.56(CH), 137.55(C), 145.62(CH), 147.72(C), 149.38(CH), 152.34(C), 153.56(C), 159.33(C), 163.17(CO of coumarin)

4-Hydroxy-2-(furo[2,3-b]quinolin-2-yl)-5H-dibenzo[c,f]coumarin (3j): White solid; yield =58%; mp 223-225°C; Anal. Calcd. For $C_{28}H_{15}NO_4$: C, 78.31; H, 3.52; N, 3.26%. Found: C, 78.29; H, 3.50; N, 3.28%. IR (KBr, ν_{max}, cm^{-1}); ν_{max} 1683 (C=O stretching of δ-lactone of coumarin), 1614 (aromatic C=C stretching), 3080 (aromatic C-H stretching), 3440 (O-H stretching). ^{1}H NMR (400MHz, $CDCl_3$, δ) : 7.59-9.31 (14H, m, aromatic protons), 11.36 (1H, singlet, -OH proton) (D_2O exchangeable).^{13}C NMR (100MHz, $CDCl_3$, δ) : 118.02(CH), 119.13(CH), 119.35(CH), 120.11(CH), 120.84(C), 121.16(C), 121.34(CH), 122.06(CH), 122.60(CH), 123.18(CH), 124.38(C), 125.01(CH), 125.12(C), 125.18(CH), 127.48(CH), 128.75(C), 129.96(CH), 139.64(CH), 142.49(C),142.99(C), 143.58(CH), 146.84(C), 147.80(C), 151.92(C), 152.56(C), 155.11(C), 155.27(C), 162.55(CO of coumarin)

4-Hydroxy-2-(6-methylfuro[2,3-b]quinolin-2-yl)-5H-dibenzo[c,f]coumarin (3k): White solid; yield = 61% ; mp 232-234°C; Anal. Calcd. For $C_{29}H_{17}NO_4$: C, 78.55; H, 3.86; N, 3.16%. Found: C, 78.51; H, 3.90; N, 3.14%. IR (KBr, ν_{max}, cm^{-1}); ν_{max} 1697 (C=O stretching of δ-lactone of coumarin), 1618 (aromatic C=C stretching), 3078 (aromatic C-H stretching), 2923 (aliphatic C-H stretching), 3420 (O-H stretching). ^{1}H NMR (400MHz, $CDCl_3$, δ): 2.50 (3H, s, CH_3), 7.52-9.38 (13H, m, Ar-H), 11.59 (1H, s, -OH proton) (D_2O exchangeable). ^{13}C NMR (100MHz, $CDCl_3$, δ): 23.28(CH_3), 118.65(CH), 119.25(CH), 119.28(C), 119.48(C), 120.14(CH), 120.36(CH), 121.20(C), 122.46(CH), 123.19(C), 124.15(C), 124.46(CH), 124.81(CH), 125.40(C), 128.06(CH), 128.52(CH), 128.80(CH),130.72(CH),132.15(CH), 132.51(C), 135.85(C), 139.41(CH), 142.49(C), 143.12(CH), 146.94(C), 148.33(C), 154.01(C), 162.92 (CO of coumarin)

4-Hydroxy-2-(6-chlorofuro[2,3-b]quinolin-2-yl)-5H-dibenzo[c,f]coumarin (3l): White solid; yield = 58%; mp 248-250°C; Anal. Calcd. For $C_{28}H_{14}ClNO_4$: C, 72.50; H, 3.04; N, 3.02%. Found: C, 72.48; H, 3.01; N, 3.12%. IR (KBr, ν_{max}, cm^{-1}); ν_{max} 1699 (C=O stretching of δ-lactone of coumarin), 1614 (aromatic C=C stretching), 3056 (aromatic C-H stretching), 3425 (O-H stretching). ^{1}H NMR (400MHz, $CDCl_3$, δ) : 7.56-9.31 (13H, m, Ar-H), 11.36 (1H, s, -OH proton) (D_2O exchangeable).^{13}C NMR (100MHz, $CDCl_3$, δ) : 118.02(CH), 119.12(CH), 119.18(C), 119.48(C), 120.49(CH), 120.75(CH), 121.64(C), 121.96(CH), 122.49(C), 123.99(C), 124.58(CH), 125.84(CH), 127.35(C), 127.35(CH), 128.84(CH), 129.11(CH), 129.34(CH) ,139.16(CH), 142.06(C), 142.60(CH), 143.18(C), 146.38(C), 148.01(C), 150.92(C), 151.56(C), 156.11(C), 156.27(C), 162.55(CO of coumarin).

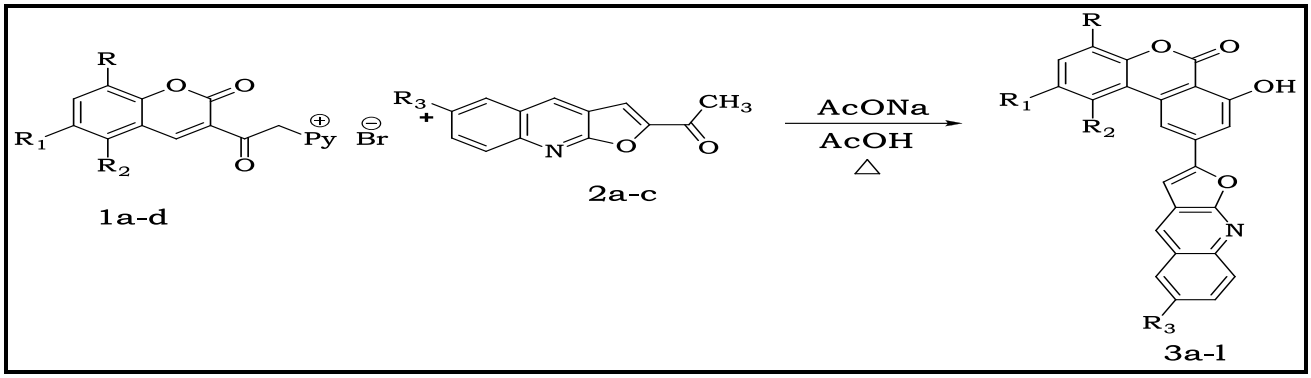
RESULTS AND DISCUSSION

Chemistry

With a view to synthesizing some new furoquinolinyl substituted benzo[*c*]coumarins adopting a new synthetic route, the present work was carried out. In the present work, various 7-hydroxy-9-(furo[2,3-*b*]quinolin-2-yl)*6H*-benzo[*c*]coumarins **(3a-l)** have been synthesized by reacting an appropriate 3-coumarinoyl methyl pyridinium bromide salt **(1a-d)** with 2-acetyl-furo[2,3-*b*]quinoline **(2a-c)**in the presence of sodium acetate in refluxing acetic acid.**(Scheme-1).**The structures of all the synthesized compounds **(3a-l)** were established by IR, ^{1}H-NMR, ^{13}C-NMR and selected mass spectral data are shown in experimental section **2.2.**

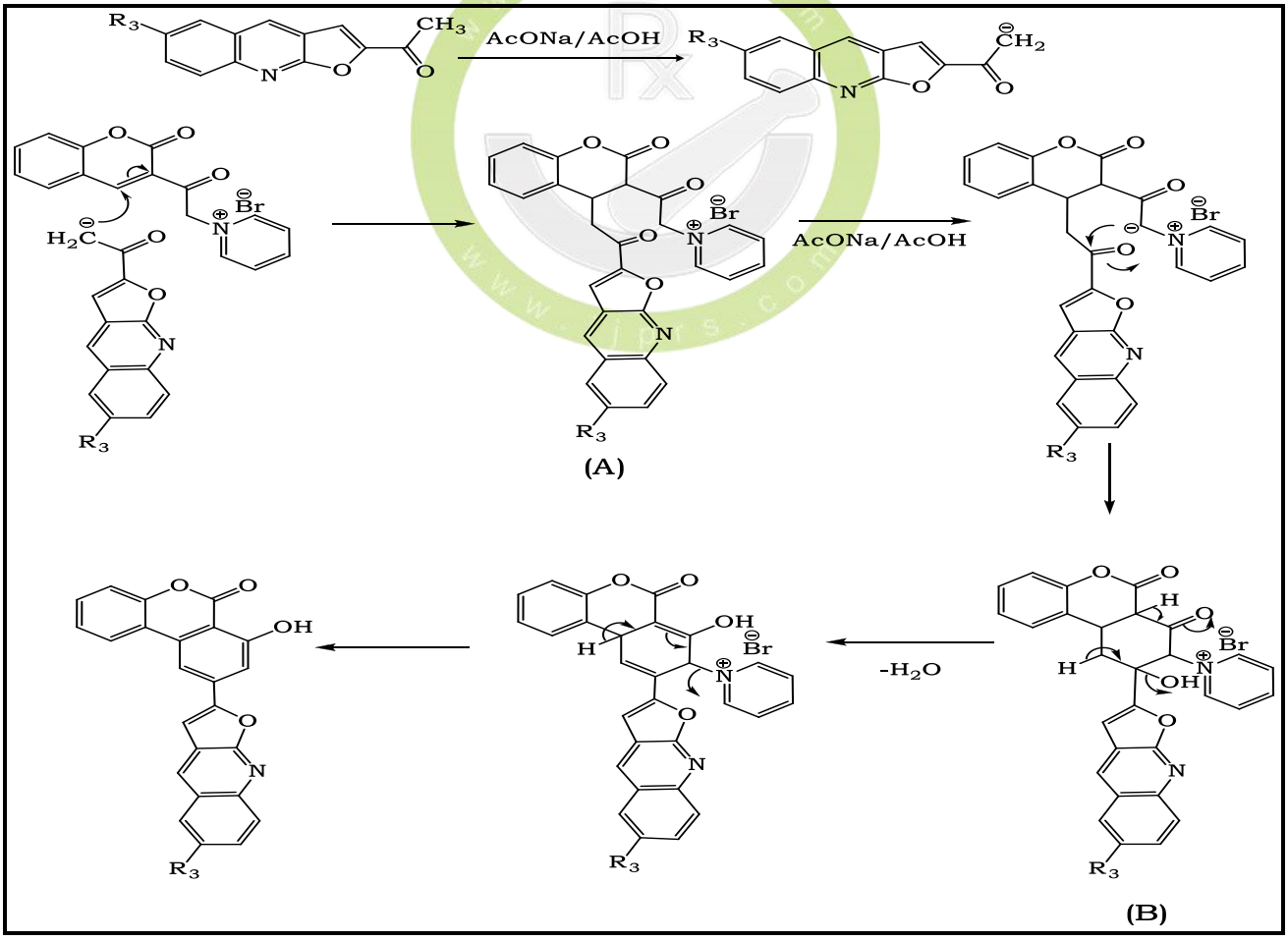
Mechanism

It is reported that reaction of α,β- unsaturated ketone with methyl ketone or ketone with active methylene group in the presence of sodium acetate results in a formation of 1,3,5- tri substituted benzene derivatives[33]. This novel reaction is utilized in the preparation of present compounds. Here the benzene ring has been built up between 3 and 4 position of coumarin nucleus by utilizing this reaction. The plausible mechanism for the synthesis of target compounds **(3a-l)** is shown in **Scheme-2**.



Compound	R	R_1	R_2	R_3	Compound	R	R_1	R_2	R_3
3a	H	H	H	H	**3g**	H	Br	OCH_3	H
3b	H	H	H	CH_3	**3h**	H	Br	Cl	CH_3
3c	H	H	H	Cl	**3i**	H	Br	H	Cl
3d	OCH_3	H	H	H	**3j**	H	-Benzo-		H
3e	OCH_3	H	H	CH_3	**3k**	H			CH_3
3f	OCH_3	H	H	Cl	**3l**	H			Cl

Scheme-1: Synthetic scheme for the compounds (3a-l)



Scheme-2: Plausible mechanism for the synthesis of target compounds (3a-l)

The reaction proceeds by the anion generation from the acetyl group of compound **(2a-d)**. This anion further adds to the 3,4-double bond of coumarin**(1a-c)** and results in the formation of intermediate **(A)** having 1,5-dione functionality. The active methylene group in **(A)** then gets cyclized with carbonyl group of furo[2,3-b]quinoline moiety resulting in the formation of intermediate **(B)** which finally gets converted into the product by loss of water molecule and subsequent aromatization. The reaction is smooth and results the furoquinolinyl substituted benzo[*c*]coumarins **(3a-l)** in good yield.

Biological Results

Antimicrobial Activity

The newly synthesized target compounds **(3a-l)** were evaluated for their *in vitro* antibacterial activity against two Gram positive bacteria *Staphylococcus aureus* (MTCC 96) and *Bacillus subtilis* (MTCC 441) and two Gram negative bacteria *Escherichia coli* (MTCC 443) and *Salmonella typhi* (MTCC 98). They were also evaluated for their *in vitro* antifungal activity against *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282) as fungal strains. Broth dilution method was used for the determination of the antibacterial and antifungal activity as recommended by NCCLS[34]. Ampicillin, Chloramphenicol and Norfloxacin were used as standard antibacterial drugs, whereas Griseofulvin and Nystatin were used as standard antifungal drugs. All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against above mentioned known drugs. Mueller-Hinton broth was used as the nutrient medium for the test bacteria and Sabouraud Dextrose broth was used for the test fungi. Inoculum size for the test strains was adjusted to 10^8 CFU (Colony Forming Unit per milliliter) per milliliter by comparing the turbidity. Each synthesized compound was diluted with DMSO so as to have the stock solution of 2000 $\mu g/$mL concentration as a stock solution. The results were recorded in the form of primary and secondary screening. The synthesized compounds **(3a-l)** were screened for their antibacterial and antifungal activity at the concentration of 1000, 500 and 250 $\mu g/$mL for the primary screening. The synthesized compound showing activity against microbes in the primary screening were further screened in a second set of dilution at concentrations of 200, 100, 62.5, 50 and 25 $\mu g/$mL. The suspension of 10 μL from each well were further incubated and growth was noted at 37°C after 24 hour for bacteria and 48 hour for fungi. The lowest concentration which showed no visible growth (turbidity) after spot subculture was considered as the minimum inhibitory concentration (MIC) for each compound. The investigation of the data summarized in **(Table-1)** reveals that many compounds were found to be active against Gram-positive bacteria while some of the compounds were found to be active against Gram-negative bacterial and fungal species as compared to that of the standard antimicrobial drugs.

Antimicrobial Evaluation

The compounds **(3a-l)** were screened for their *invitro* antibacterial and antifungal evaluation against various bacterial and fungal pathogens by broth dilution method. Ampicillin, Chloramphenicol, Norfloxacin, Griseofulvin and Nystatin were used as standard drugs. The values of MIC are summarized in **Table-1**. Upon evaluating the antimicrobial activity data, it was observed that compound **3c, 3h and 3k** (MIC = 200$\mu g/$mL) showed good activity compared to Ampicillin (MIC = 250$\mu g/$mL) against gram positive bacteria *B. subtilis* .The Compounds **3b, 3d , 3e , 3f, 3g and 3l** (MIC = 250$\mu g/$mL) exerted equipotent activity against gram positive bacteria *B. subtilis*. against *S. aureus*, Compounds **3j and 3l** (MIC = 100$\mu g/$mL) and Compounds **3d , 3e and 3k** (MIC = 125$\mu g/$mL) exhibited moderate activity compared to Ampicillin (MIC = 250$\mu g/$mL) against gram positive bacteria *S. aureus*. Compounds **3b and 3g** (MIC = 200$\mu g/$mL) showed better activity compared to Ampicillin (MIC = 250$\mu g/$mL) against gram positive bacteria *S. aureus*. Compounds **3a, 3c, 3h and 3i** (MIC = 250$\mu g/$mL) were found equipotent to Ampicillin (MIC = 250$\mu g/$mL) against gram positive bacteria *S. aureus*.

Table 1: *In vitro* Antimicrobial activity of compounds (3a-l)

Compound	Minimum Inhibitory Concentration (MIC, $\mu g mL^{-1}$)					
	Gram +ve bacteria		Gram –ve bacteria		Fungi	
	B.s.	*S.a.*	*E.c.*	*S.t.*	*A.n.*	*C.a.*
	MTCC441	MTCC96	MTCC443	MTCC98	MTCC282	MTCC227
3a	500	250	**100**	**100**	500	500
3b	250	**200**	500	250	200	500
3c	**200**	250	**62.5**	**100**	250	**250**
3d	250	**125**	**62.5**	**100**	500	1000
3e	250	**125**	**200**	250	500	1000
3f	250	500	**100**	**62.5**	1000	**250**
3g	250	**200**	**100**	200	1000	**200**
3h	**200**	250	**100**	200	500	**250**
3i	500	250	250	250	1000	**200**
3j	500	**100**	**62.5**	**100**	1000	>1000
3k	**200**	**125**	**100**	200	1000	1000
3l	**250**	**100**	200	250	>1000	1000
Ampicillin	250	250	100	100	-	-
Chloramphenicol	50	50	50	50	-	-
Norfloxacin	100	10	10	10	-	-
Griseofulvin	-	-	-	-	100	500
Nystatin	-	-	-	-	100	100

Compounds **3c, 3d, 3f and 3j** (MIC = 62.5μg/mL) exhibited outstanding activity compared to Ampicillin (MIC = 100μg/mL) against gram negative bacteria *E. coli and S. typhi* respectively. The compounds **3a, 3f, 3g, 3h and 3k** (MIC = 100μg/mL) and compounds **3a**, **3c, 3d, and 3j** (MIC = 100μg/mL) were found equipotent compared to Ampicillin (MIC = 100μg/mL) against *E. coli and S. typhi* respectively. Compound **3i and 3g** (MIC = 200μg/mL) and compounds **3c, 3f and 3h** (MIC = 250μg/mL) were found to be more active against *C. albicans* compared to Griseofulvin (MIC = 500μg/mL). Compounds **3a and 3b** (MIC = 500μg/mL) were found equipotent to Griseofulvin (MIC = 500μg/mL) against *C. albicans.*

It is perceived from the antimicrobial data that almost all the tested derivatives **3a-l** was found to be potent against the gram positive bacterial strains. Among all the tested compounds, the compounds **3c, 3d, 3f** and **3j** were found to be more efficient members of the series.

Majority of the synthesized compounds were active against Gram-positive bacteria *viz. Bacillus subtilis* (MTCC 441) and *Staphylococcus aureus* (MTCC 96), Gram-negative bacteria *viz. Escherichia coli* (MTCC 443) and *Salmonella typhi* (MTCC 98). Some of the synthesized compounds were found sufficiently potent to inhibit fungal pathogen *viz. Candida albicans* (MTCC 227).

CONCLUSION

A novel and efficient protocol for the synthesis of a series of furoquinolinyl substituted benzo[*c*]coumarin derivatives was described and the synthesized compounds were screened for their *in vitro* antimicrobial evaluation. The results indicated that all the synthesized compounds

shown good antibacterial activity. In particular, compounds **3c**, **3d**, **3f** and **3j** exhibited the more potent inhibitory activity against bacterial and fungal pathogens as compared to other compounds and emerged as potential lead compounds for further investigations.

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