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SYNTHESIS OF BIOLOGICALLY ACTIVE 1'-(2-OXO-2*H*-BENZOPYRAN--6-YL)- 5'-HYDROXY-2'-METHYLINDOLE-3'-AMIDO-2''-PHENYL--THIAZOLIDENE-4''-ONES

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Abstract: 6-Aminocoumarins on refluxing with ethyl acetoacetate in 1,2-dichloroethane gave two products: 3'-(2-oxo-2*H*-benzopyran-6-yl-amino)-but-2'-enoic acid ethyl ester **2a-c** and N-(-2-oxo-2*H*-benzopyran-6-yl)-3'-oxo-butyramide **3a-c**. Compounds **2a-c** on treatment with 1,4-benzoquinone in N_2-atmosphere yielded 1'-(2-oxo-2*H*-benzopyran-6-yl)-5'-hydroxy-2'-methyl-3'-carbethoxyindoles **4a-c**, which on further treatment with hydrazine hydrate gave 1'-(2-oxo-2*H*-benzopyran-6-yl)-5'-hydroxy-2'-methylindole-3'-acid hydrazides **5a-c**. These acid hydrazides were treated with benzaldehyde to give 1'-(2-oxo-2*H*-benzopyran-6-yl)-5'-hydroxy-2'-methylindole-3'-benzylidene hydrazides **6a-c**, which on further treatment with mercaptoacetic acid in 1,4-dioxane yielded 1'-(2-oxo-2*H*-benzopyran-6-yl)-5'-hydroxy-2'-methylindole-3'-amido-2''-phenylthiazolidene-4''-ones **7a-c**. The structures of the compounds have been established on the basis of spectral and analytical data. All compounds have been screened for their antimicrobial activity and have been found to exhibit significant antibacterial and antifungal activities.

Keywords: 6-aminocoumarins, Nenitzescu reaction, indole, thiazolidinone, antimicrobial activity

Coumarin derivatives have aroused considerable interest from the point of view of their versatile practical applications as well as their wide range of biochemical properties (1). Nitrogen mustards synthesized from 6-aminocoumarins exhibit carcinogenic activity (2). They are also known to possess antiviral (3) activity, especially effective against HIV_1 (4). Also the 4-thiazolidinone derivatives are known to possess various biological activities (5–17). Indole derivatives have been found to posses wide range of biological activities such as antidepressant (18), antihistamine (19), antidiabetic (20), anti-inflammatory (21), anthelmintic (22), antiallergic (23), and cardiovascular (24). By observing the biological importance of the above heterocycles, we thought to incorporate indole as well as thiazolidinone moiety on coumarin nucleus and scan for their antimicrobial activity.

EXPERIMENTAL

All compounds were confirmed by their spectral data and physical properties and all yields refer to the isolated yields. Melting points were taken in open capillaries and are uncorrected. Purity of the compounds was checked by TLC. FT-IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin Elmer 400 spectrometer using KBr. ^{1}H-NMR spectra were recorded on JEOL NMR AL300 (300 MHz) using TMS as standard and mass spectra on a Shimadzu GC-MS QP-2010.

3'-(2-oxo-2*H*-benzopyran-6-yl-amino)-but-2'-enoic acid ethyl esters **(2a-c)** and N-(-2-oxo-2*H*-benzopyran-6-yl)-3'-oxobutyramides (**3a-c)**

A mixture of 6-aminocoumarins (**1a-c)** (0.01 mole) and ethyl acetoacetate (0.01 mole) in 1,2-dichloroethane (20 mL) in the presence of 3 drops of conc. HCl was refluxed for 1 to 2 h, The organic layer was extracted with water, dried over sodium sulfate and an excess of 1,2-dichloroethane was removed under reduced pressure. The product obtained was purified by column chromatography (solvent system: petrolium ether:ethyl acetate, 80:20, v/v) to afford (**2a-c)** and **(3a-c**).

2a: IR (KBr, cm^{-1}): 3370 (-NH), 3045 (arom. CH), 1720 (C=O), 1735. ^{1}H-NMR ($CDCl_3$, 300

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MHz, δ, ppm): 1.24 (t, 3H, J = 6.6 Hz, CH_3), 1.98 (s, 3H, CH_3), 4.27(q, 2H, J = 6.6 Hz, CH_2), 4.92 (s, 1H, = CH), 6.40 (d, 1H, J = 9 Hz, C_3-H), 7.20 (d, 1H, J = 9 Hz, C_8-H), 7.25 (d, 1H, J = 9 Hz, C_7-H), 7.28 (s, 1H, C_5-H), 7.80 (d, 1H, J = 9 Hz, C_4-H), 8.32 (s, 1H, -NH, D_2O-exchangeable).

2b: IR (KBr, cm^{-1}): 3374 (-NH), 3040 (arom. CH), 1735, 1722 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.21 (t, 3H, J = 6.6 Hz, CH_3), 1.84 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.24 (q, 2H, J = 6.6 Hz, CH_2), 4.90 (s, 1H, =CH), 6.40 (d, 1H, J = 9 Hz, C_3-H), 7.21 (s, 1H, C_8-H), 7.25 (s, 1H, C_5-H), 7.85 (d, 1H, J = 9 Hz, C_4-H), 8.32 (s, 1H, -NH, D_2O-exchangeable).

2c: IR (KBr, cm^{-1}): 3371 (-NH), 3045 (arom. CH), 1740, 1715 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.25 (t, 3H, J = 6.6 Hz, CH_3), 1.90 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.24 (q, 2H, J = 6.6 Hz, CH_2), 4.92 (s, 1H, =CH), 6.25 (s, 1H, C_3-H), 7.14 (s, 1H, C_8-H), 7.26 (s, 1H, C_5-H), 8.11 (s, 1H, -NH, D_2O-exchangeable). ^{13}C-NMR ($CDCl_3$, 300 MHz, δ, ppm): 14.8 (CH_3 of OCH_2CH_3), 17.5 (C_7), 19.0 (C_4), 21.5 (C_4’), 60.5 (OCH_2CH_3), 90.0(C_2’), 112.0–140.2 (6 aromatic carbons), 150.5 (C_{8a}), 154.4 (C_4), 156.2 (C_3’), 161.0 (C=O of coumarin), 162.0 (C=O of ester). MS: m/z (%): 301 (M^+, 19), 255 (100), 256 (20), 229 (30), 204 (15), 197 (40), 185 (32), 174 (40), 160 (10), 119 (15), 89 (2).

3a: IR (KBr, cm^{-1}): 3367 (-NH), 2992 (arom. CH), 1718 (C=O), 1697, 1672 (amide stretching). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.14 (s, 3H, C_1’-H), 3.59 (s, 2H, C_3’-H), 6.47 (d, 1H, J = 9 Hz, C_3-H), 7.18 (d, 1H, J = 9 Hz, C_8-H), 7.25 (d, 1H, J = 9 Hz, C_7-H), 7.34 (s, 1H, C_5-H), 7.80 (d, 1H, J = 9 Hz, C_4-H), 9.67 (s, 1H, -NH, D_2O-exchangeable).

3b: IR (KBr, cm^{-1}): 3364 (-NH), 2982 (arom. CH), 1715 (C=O), 1690, 1667 (amide stretching). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.22 (s, 3H, C_1’-H), 2.37 (s, 3H, C_7-H), 3.68 (s, 2H, C_3’-H), 6.42 (d, 1H, J = 9 Hz, C_3-H), 7.14 (s, 1H, C_8-H), 7.25 (s, 1H, C_5-H), 7.72 (d, 1H, J = 9 Hz, C_4-H), 9.78 (s, 1H, -NH, D_2O-exchangeable).

3c: IR (KBr, cm^{-1}): 3380 (-NH), 3082 (arom. CH), 1720 (C=O), 1700, 1660 (amide stretching). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.21 (s, 3H, C_1’-H), 2.35 (s, 3H, C_7-H), 2.43 (s, 3H, C_4-H), 3.68 (s, 2H, C_3’-H), 6.25 (s, 1H, C_3-H), 7.14 (s, 1H, C_8-H), 7.26 (s, 1H, C_5-H), 9.50 (s, 1H, -NH, D_2O-exchangeable). MS: m/z (%):273 (M^+, 15) 259 (10), 245 (20), 230 ($M^+ – COCH_3$, 5), 215 (10), 189 (100), 174 (25), 161 (86), 160 (60), 132 (20), 116 (20), 91 (15).

1’-(2-oxo-2*H*-benzopyran-6-yl)-5’-hydroxy-2’-methyl-3’-carbethoxyindoles **(4a-c)**

A mixture of **2a-c** (0.01 mole) and 1,4-benzoquinone (0.01 mole) in 1,2-dichloroethane (20 mL) was refluxed for 7 h under N_2. The excess of 1,2-dichloroethane was removed under reduced pressure. The product obtained was purified by column chromatography (solvent system: petrolium ether:ethyl acetate 80:20, v/v) to afford (**4a-c**).

4a: IR (KBr, cm^{-1}): 3386(-OH), 2928 (C-H strech.), 1740, 1712 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.42 (t, 3H, J = 6.6 Hz, CH_3), 2.72 (s, 3H, CH_3), 4.40 (q, 2H, J = 6.6 Hz, CH_2), 6.30 (s, 1H, OH, D_2O exchangeable), 6.42 (d, 1H, J = 9 Hz, C_3-H), 7.12 (d, 1H, J = 9 Hz, C_8-H), 7.23 (d, 1H, J = 9 Hz, C_7-H), 7.34 (s, 1H, C_5-H), 7.42 (d, 1H, J = 9 Hz, C_6’-H), 7.68 (d, 1H, J = 9 Hz, C_7’-H), 7.92 (s, 1H, C_4’-H), 8.04 (d, 1H, J = 9Hz, C_4-H).

(4b) IR (KBr, cm^{-1}): 3440 (-OH), 3045 (arom. CH), 1735, 1722 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.38 (t, 3H, J = 6.6 Hz, CH_3), 2.45 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 4.39 (q, 2H, J = 6.6 Hz, CH_2), 6.30 (s, 1H, OH, D_2O exchangeable), 6.46 (d, 1H, J = 9 Hz, C_3-H), 6.98 (s, 1H, C_8-H), 7.25 (s, 1H, C_5-H), 7.40 (d, 1H, J = 9 Hz, C_6’-H), 7.63 (d, 1H, J = 9 Hz, C_7’-H), 7.86 (s, 1H, C_4’-H), 7.96 (d, 1H, J = 9 Hz, C_4-H).

(4c) IR (KBr cm^{-1}): 3440 (-OH), 3009 (arom. CH), 1735, 1722 (C=O). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 1.36 (t, 3H, J = 6.6 Hz, CH_3), 2.35 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.72 (s, 3H, C_2’-H), 4.29 (q, 2H, J = 6.6 Hz, CH_2), 6.25 (s, 1H, C_3-H), 6.43 (s, 1H, OH, D_2O exchangeable), 7.14 (s, 1H, C_8-H), 7.35 (s, 1H, C_5-H), 7.48 (d, 1H, J = 9 Hz, C_6’-H), 7.68 (d, 1H, J = 9 Hz, C_7’-H), 7.92 (s, 1H, C_4’-H); ^{13}C-NMR ($CDCl_3$, 300 MHz, δ, ppm): 14.0 (CH_3 of OCH_2CH_3), 15.2 (CH_3 attached to C_2’), 18.2 (C_7), 19.4 (C_4), 58.5 (CH_2 of OCH_2CH_3), 107.0–150.0 (15 aromatic carbons), 154.0 (C_4), 161.0 (C=O of coumarin), 162.0 (C=O of ester). MS: m/z (%): 391 (M^+, 28), 376 (10), 375 (14), 346 (30), 333 (10), 259 (100) 217 (20), 215 (10), 174 (20), 146 (10), 145 (25), 127 (19), 126 (5), 118 (2), 116 (19), 94 (10), 90 (5), 89 (15), 185 (15), 77 (40), 71 (10), 57 (10), 43 (20).

1’-(2-oxo-2*H*-benzopyran-6-yl)-5’-hydroxy-2’-methylindole-3’-acid hydrazides **(5a-c)**

A mixture of **3a-c** (0.01 mole), hydrazine hydrate (0.04 mole) in ethanol (15 mL) was refluxed for 10 h. The reaction mixture was cooled and poured on crushed ice. The product obtained was filtered, dried and recrystallized from ethanol and isolated as **5a-c**.

5a: IR (KBr, cm^{-1}): 3540(-OH), 3394, 3381 (NH and NH_2 stretch.), 3050 (arom. CH), 1722 (C=O), 1685 (amide). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.72 (s, 3H, CH_3), 5.52 (s, 2H, NH_2, D_2O exchangeable), 6.40 (s, 1H, OH, D_2O exchangeable), 6.48 (d, 1H, *J* = 9 Hz, C_3-H), 7.12 (d, 1H, *J* = 9 Hz, C_8-H), 7.24 (d, 1H, *J* = 9 Hz, C_7-H), 7.30 (s, 1H, C_5-H), 7.40 (d, 1H, *J* = 9 Hz, C_6'-H), 7.66 (d, 1H, *J* = 9Hz, C_7'-H), 7.84 (s, 1H, C_4'-H), 8.02 (d, 1H, *J* = 9 Hz, C_4-H), 8.24 (s, 1H, NH, D_2O exchangeable).

5b: IR (KBr, cm^{-1}): 3442 (-OH), 3381 (NH and NH_2 stretch), 3045 (arom. CH), 1722 (C=O), 1685 (amide). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.41 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 5.52 (s, 2H, NH_2, D_2O exchangeable), 6.38 (s, 1H, OH, D_2O exchangeable), 6.42 (d, 1H, *J* = 9 Hz, C_3-H), 6.64 (s, 1H, C_8-H), 7.25 (s, 1H, C_5-H), 7.30 (d, 1H, *J* = 9 Hz, C_6'-H), 7.40 (d, 1H, *J* = 9 Hz, C_7'-H), 7.64 (s, 1H, C_4'-H), 7.82 (d, 1H, *J* = 9.4 Hz, C_4-H), 8.39 (s, 1H, NH, D_2O exchangeable).

5c: IR (KBr, cm^{-1}): 3418 (-OH), 3383, 3320 (NH and NH_2 stretch.), 2920 (arom. CH), 1723 (C=O), 1680 (amide). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.35 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 5.29 (s, 2H, NH_2, D_2O exchangeable), 6.25 (s, 1H, C_3-H), 6.43 (s, 1H, OH, D_2O exchangeable), 7.14 (s, 1H, C_8-H), 7.24 (s, 1H, C_5-H), 7.30 (d, 1H, *J* = 9 Hz, C_6'-H), 7.48 (d, 1H, *J* = 9 Hz, C_7'-H), 7.68 (s, 1H, C_4'-H), 9.22 (s, 1H, NH, D_2O exchangeable). MS: m/z (%): 377 (M^+, 15), 361 (10), 318 (20), 277 (10), 275 (20), 249 (5), 234 (20), 230 (100), 229 (20), 203 (10), 189 (70), 175 (20), 161 (15), 131 (5), 129 (15), 114 (10), 118 (2), 77 (40), 60 (10), 59 (2).

1'-(2-oxo-2*H*-benzopyran-6-yl)-5'-hydroxy-2'-methylindole-3'-benzylidene hydrazides **(6a-c)**

A mixture of **5a-c** (0.01 mole) and benzaldehyde (0.01 mole) in acetic acid was refluxed for 7 h. The reaction mixture was cooled and poured on crushed ice; the product obtained was filtered, dried and recrystallized from ethanol to give **6a-c**.

6a: IR (KBr, cm^{-1}): 3341 (-OH), 3362, 3012 (arom. CH), 1724 (C=O), 1678 (amide). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.71 (s, 3H, CH_3), 5.88 (s, 1H, OH, D_2O exchangeable), 6.40 (d, 1H, *J* = 9 Hz C_3-H), 7.12 (d, 1H, *J* = 9.0 Hz, C_8-H), 7.23 (s, 1H, C_5-H), 7.30–7.76 (m, 10H, 5H of Ph, C_7-H, C_4'-H, C_6'-H, C_7'-H and N=CH proton), 7.82 (d, 1H, *J* = 9.3 Hz, C_4-H), 9.21 (s, 1H, NH, D_2O exchangeable).

6b: IR (KBr, cm^{-1}): 3512 (-OH), 3394, 3045 (arom. CH), 1718 (C=O), 1635 (amide). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.37 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 5.78 (s, 1H, OH, D_2O exchangeable), 6.35 (d, 1H, *J* = 9 Hz, C_3-H), 7.12 (s, 1H, C_8-H), 7.25 (s, 1H, C_5-H), 7.34–7.78 (m, 9H, 5H of Ph, C_4'-H, C_6'-H, C_7'-H and N=CH proton), 7.82 (d, 1H, *J* = 9 Hz, C_4-H), 9.40 (s, 1H, NH, D_2O exchangeable).

6c: IR (KBr, cm^{-1}): 3342 (-OH), 3371, 2905 (arom. CH), 1727 (C=O), 1670 (amide). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.26 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 5.94 (s, 1H, OH, D_2O exchangeable), 6.25 (s, 1H, C_3-H), 7.12 (s, 1H, C_8-H), 7.30 (s, 1H, C_5-H), 7.45–7.76 (m, 8H, 5H of Ph, C_6'-H, C_7'-H and N=CH proton), 7.84 (s, 1H, C_4'-H), 9.49 (s, 1H, NH, D_2O exchangeable). MS: m/z (%): 465 (M^+, 20), 318 (60), 303 (73), 289 (10), 274 (20), 212 (30), 197 (45), 176 (70), 174 (15), 155 (5), 148 (100), 146 (10), 126 (2), 119 (10), 118 (25), 90 (10), 77 (30), 59 (5), 28 (10).

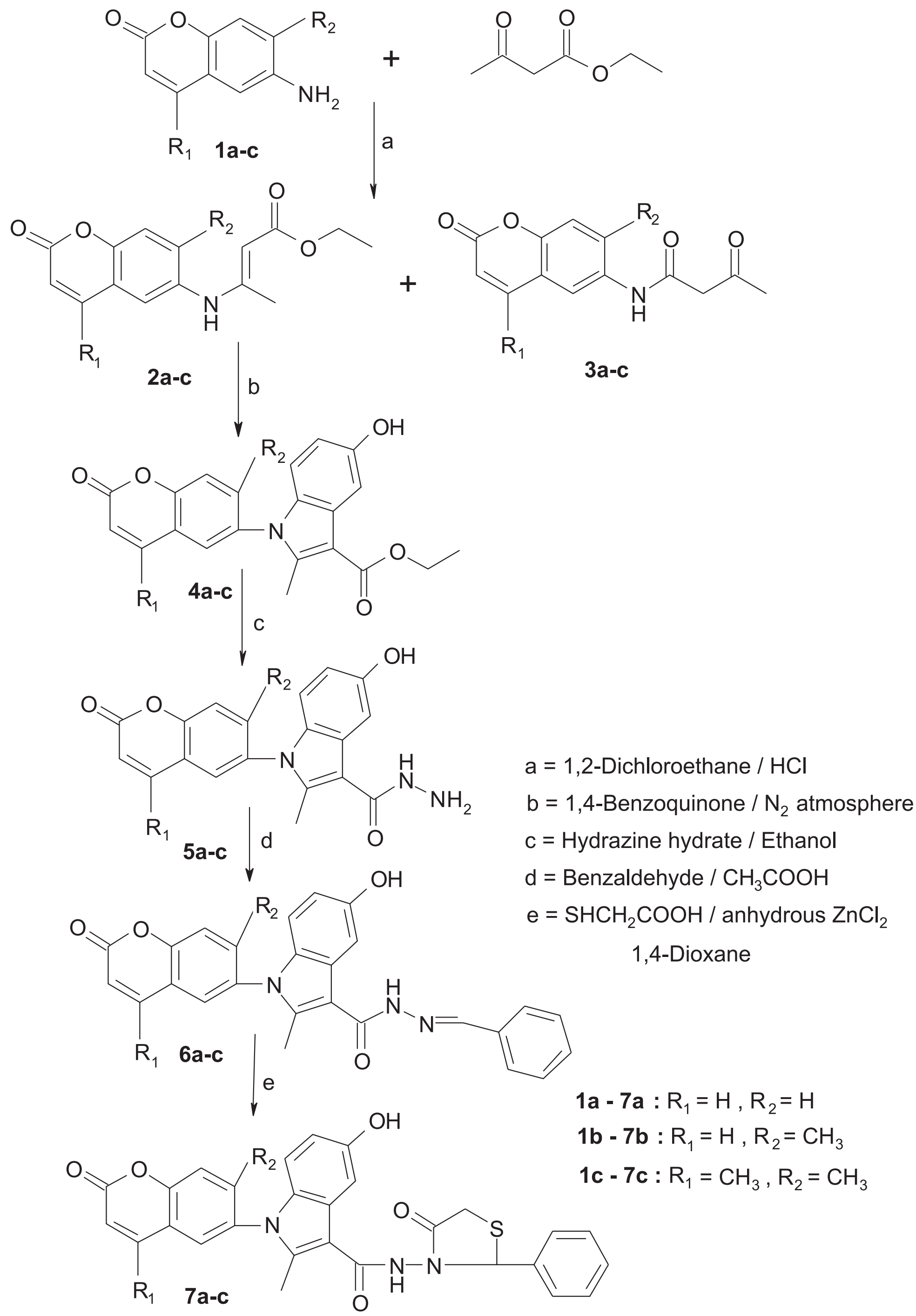
1'-(2-oxo-2*H*-benzopyran-6-yl)-5'-hydroxy-2'-methylindole-3'-amido-2''-phenylthiazolidene-4''-ones **(7a-c)**

A mixture of **6a-c** (0.01 mole), mercaptoacetic acid (0.01 mole) in dry 1,4-dioxane (25 mL) and catalytic amount of anhydrous $ZnCl_2$ was refluxed for 5 to 7 h. The reaction mixture was cooled and poured on crushed ice; the product obtained was filtered, dried and recrystallized from ethanol to give **7a-c**.

7a: IR (KBr, cm^{-1}): 3456 (-OH), 3398, 2942 (arom. CH), 1715 (C=O), 1670 (amide). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.74 (s, 3H, CH_3), 3.87 (s, 2H, S-CH_2), 5.87 (s, 1H, thiazolidinone attached to aromatic ring), 5.94 (s, 1H, OH, D_2O exchangeable), 6.42 (d, 1H, *J* = 9 Hz, C_3-H), 7.12 (d, 1H, *J* = 9 Hz, C_8-H), 7.24 (d, 1H, *J* = 9 Hz, C_7-H), 7.30 (s, 1H, C_5-H), 7.40–7.76 (m, 8H, 5H of Ph, C_4'-H, C_6'-H and C_7'-H), 7.82 (d, 1H, *J* = 9 Hz, C_4-H), 8.28 (s, 1H, NH, D_2O exchangeable).

7b: IR (KBr, cm^{-1}): 3482 (-OH), 3382, 2981 (arom. CH), 1710 (C=O), 1635 (amide). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.44 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 4.12 (s, 2H, S-CH_2), 5.90 (s, 1H, thiazolidinone attached to aromatic ring), 6.34 (d, 1H, *J* = 9 Hz , C_3-H), 6.40 (s, 1H, OH, D_2O exchangeable), 7.12 (s, 1H, C_8-H), 7.30 (s, 1H, C_5-H), 7.38–7.79 (m, 8H, 5H of Ph, C_4'-H, C_6'-H and C_7'-H), 7.82 (d, 1H, *J* = 9 Hz, C_4-H), 8.42 (s, 1H, NH, D_2O exchangeable).

7c: IR (KBr, cm^{-1}): 3442 (-OH), 3398, 3040 (arom. CH), 1722 (C=O), 1674 (amide). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.39 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.03 (s, 3H, CH_3), 4.20 (s, 2H, S-CH_2), 5.74 (s, 1H, thiazolidinone attached to aromatic ring), 6.29 (s, 1H, C_3-H), 6.53 (s, 1H, OH, D_2O



Scheme 1.

exchangeable), 7.02 (s, 1H, C_8-H), 7.35 (s, 1H, C_5-H), 7.40–8.23 (m, 8H, 5H of Ph, C_4'-H, C_6'-H and C_7'-H), 9.34 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$, 300 MHz, δ, ppm): 14.8 (CH_3 attached to C_2'), 18.5 (C_7), 19.5 (C_4), 33.0 (CH_2-S, C_5''), 67.0 (C_2''), 108.0–140.0 (19 aromatic carbons), 150 (C_{8a}), 152 (C_5'), 154.0 (C_4), 157 (C=O attached to C_3'), 161.0 (C=O of coumarin), 182.0 (C=O of thiazolidinone). MS: m/z (%): 539 (M^+, 20), 524 (5), 523 (40), 522 (30), 481 (10), 462 (20), 434 (10), 420 (35), 403 (20), 363 (5), 320 (15), 219 (30), 191 (30), 189 (100), 176 (75), 148 (40), 146 (10), 136 (55), 118 (10), 77 (30), 69 (40), 59 (20).

RESULTS

3-(2-Oxo-2*H*-benzopyran-6-yl-amino)-but-2-enoic acid ethyl esters **2a-c** and N-(2-oxo-2*H*-benzopyran-6-yl)-3-oxobutyramides **3a-c** were obtained by refluxing 6-aminocoumarin with ethyl acetoacetate in 1,2-dichloroethane in the presence of conc. HCl. **2c** was obtained in 34% yield and **3c** was obtained in 52% yield. The IR, ^{1}H-NMR and ^{13}C NMR spectra of compound **2c** corresponded well with the structure proposed. The mass spectrum of compound **2c** showed molecular ion peak M^+ at 301. The respective spectra of other compounds obtained also confirmed the structures as presented in experimental part.

With an intension to prepare 5-hydroxyindole derivatives *via* Nenitzescu reaction (25–27), compounds **2a-c** were further treated with 1,4-benzoquinone in nitrogen atmosphere to yield 1'-(2-oxo-2*H*-benzopyran-6-yl)-5'-hydroxy-2'-methyl-3'-carbethoxyindole **4a-c**, which gave violet colorization with $FeCl_3$ indicating the presence of phenolic OH group. The IR spectrum of compound **4c** showed broad band at 3440 cm^{-1} for -OH stretching, at 1735 cm^{-1} for ester >C=O and at 1720 cm^{-1} for >C=O stretching of coumarin. The ^{1}H-NMR spectrum of compound **4c** in $CDCl_3$ showed a singlet at δ 6.43 ppm for -OH proton which was D_2O exchangeable, it also showed absences of peak at δ 8.11 ppm for NH proton, which further proved the product formation. Compounds **4a-c** were treated with hydrazine hydrate to yield 1'-(4,7-dimethyl-2-oxo-2*H*-ben-

Table 1. Antibacterial and antifungal activities of compound **2a-c** to **7a-c**.

Comp.	*B. subtilis*		*E. coli*		*C. albicans*		*A. niger*	
	100 µg/mL	250 µg/mL	100 µg/mL	250 mg/mL	100 µg/mL	250 µg/mL	100 µg/mL	250 µg/mL
2a	+	++	+	++	-	+	+	++
2b	+	++	+	++	+	+++	+	++
2c	++	+++	+	++	-	+++	+	++
3a	+	++	-	++	-	+	+	++
3b	-	+	-	++	+	++	+	++
3c	+	++	+	++	+	++	+	++
4a	-	++	++	++	-	+	+	+
4b	-	++	+	++	-	++	+	+
4c	++	+++	++	+++	-	++	+	++
5a	+	++	+	++	-	+	+	++
5b	+	++	+	++	+	++	+	++
5c	++	+++	+	++	+	+	+	++
6a	+	++	+	++	+	++	+	++
6b	+	++	+	++	+	++	+	++
6c	++	+++	++	++	+	++	++	+++
7a	+	+++	+	++	+	++	+	++
7b	+	++	+	++	+	++	+	++
7c	++	++++	++	+++	+	++	++	+++
Sm	+++	++++	+++	++++				
Gf					+++	++++	+++	++++

Sm = streptomycin, zone of inhibition diameter in mm: (-) < 8, (+) 8–10, (++) 10–16, (+++) 16–22, (++++) 22–27. Gf = griseofulvin, zone of inhibition diameter in mm: (-) < 7, (+) 7–10, (++) 12–18, (+++) 18–22, (++++) 22–28

Table 2. Characterization data of compounds (**2a-c**), (**3a-c**), (**4a-c**), (**5a-c**), (**6a-c**), (**7a-c**).

Compd.	Mol. formula	m.p. °C	Yield (%)	Elemental analysis. Found (Calculated) (%)			
				C	H	N	S
2a	$C_{15}H_{15}NO_4$	242–244	32	65.93 (66.04)	5.53 (5.64)	5.12 (5.20)	-
2b	$C_{16}H_{17}NO_4$	222–224	30	66.89 (66.98)	5.97 (6.03)	4.87 (4.94)	-
2c	$C_{17}H_{19}NO_4$	235–237	34	67.77 (67.89)	6.36 (6.42)	4.65 (4.76)	-
3a	$C_{13}H_{11}NO_4$	184–186	63	63.69 (63.80)	4.55 (4.64)	5.71 (5.74)	-
3b	$C_{14}H_{13}NO_4$	194–196	60	64.89 (64.98)	5.05 (5.14)	5.42 (5.54)	-
3c	$C_{15}H_{15}NO_4$	163–165	52	65.93 (66.04)	5.53 (5.64)	5.14 (5.23)	-
4a	$C_{21}H_{17}NO_5$	226–228	43	69.42 (69.48)	4.72 (4.71)	3.85 (3.87)	-
4b	$C_{22}H_{19}NO_5$	248–250	40	70.02 (70.08)	5.07 (5.09)	3.72 (3.77)	-
4c	$C_{23}H_{21}NO_5$	232–234	37	70.60 (70.72)	5.46 (5.52)	3.58 (3.63)	-
5a	$C_{19}H_{15}N_3O_4$	186–188	70	65.33 (65.37)	4.34 (4.39)	12.04 (12.10)	-
5b	$C_{20}H_{17}N_3O_4$	204–206	68	66.14 (66.27)	4.74 (4.79)	11.54 (11.60)	-
5c	$C_{21}H_{19}N_3O_4$	214–216	72	66.86 (66.92)	5.07 (5.08)	11.15 (11.22)	-
6a	$C_{26}H_{19}N_3O_4$	218–220	69	71.39 (71.42)	4.38 (4.48)	9.62 (9.65)	-
6b	$C_{27}H_{21}N_3O_4$	209–211	65	71.82 (71.84)	4.70 (4.78)	9.31 (9.38)	-
6c	$C_{28}H_{23}N_3O_4$	244–246	70	72.28 (72.25)	4.98 (4.98)	9.07 (9.14)	-
7a	$C_{28}H_{21}N_3O_5S$	> 270	68	65.74 (65.82)	4.17 (4.20)	8.21 (8.25)	6.27 (6.30)
7b	$C_{29}H_{23}N_3O_5S$	> 270	73	66.24 (66.22)	4.41 (4.43)	8.00 (8.09)	6.11 (6.14)
7c	$C_{30}H_{25}N_3O_5S$	> 270	70	66.80 (66.92)	4.67 (4.70)	7.79 (7.86)	5.95 (6.94)

zopyran-6-yl)-5'-hydroxy-2'-methylindole-3'-acid hydrazides **5a-c**. The IR spectrum of compound **5c** showed band at 3383, and 3321 cm^{-1} for NH and NH_2 stretching bands. The ^{1}H-NMR of **5c** showed the presence of signal at δ 5.29 and δ 9.20 for the protons of $–NH_2$ and –NH group respectively which were D_2O exchangeable and showed the absence of triplet at δ 1.36 and a quartet at δ 4.29 for ethyl ester which was present in compound **4a-c**.

In order to prepare Schiffs bases, compounds **5a-c** were treated with benzaldehyde to give 1'-(2-oxo-2*H*-benzopyran-6-yl)-5'-hydroxy-2'-methylindole-3'-benzylidene hydrazides **6a-c**. Compounds **6a-c** were treated with mercaptoacetic acid in the presence of zinc chloride and yielded 1'-(2-oxo-2*H*-benzopyran-6-yl)-5'-hydroxy-2'-methylindole-3'-amido-2''-phenylthiazolidene-4''-ones **7a-c**. The spectral data were in agreement with the structures.

ANTIMICROBIAL SCREENING

Compounds **2a-c** to **7a-c** has been screened for their antimicrobial activity against *Bacillus subtilis*, *Escherichia coli*. and antifungal activity against *Candida albicans*, *Aspergillus Niger* by cup plate method (28) at different concentrations (100 and 250 mg/mL) using DMSO as solvent and exhibited significant biological activity (Tab. 1). The zones of inhibition of the growth were measured in millimeters. The activity was compared with the standard drugs: a commercial antibacterial streptomycin (100, 250 mg/mL) and antifungal griseofulvin (100, 250 mg/mL) tested under similar conditions. The results of antimicrobial activity show that compounds **2c**, **4c** and **7c** possess significant activity compared to the standards, the rest of the compounds shows moderate to good activity. Compound **4c** shows significant activity due to the presence of 5-hydroxy-3-ethoxyindole moiety combined to 6th position of coumarin and compound **7c** shows significant activity due to the presence of thiazolidene-4-one moiety attached to 5-hydroxyindole and coumarin moieties.

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