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SYNTHESIS OF NOVEL BIOLOGICALlY ACTIVE HETEROCYCLIC COMPOUNDS FROM 2-OXO-2*H*-BENZOPYRAN-6-YL-IMIDAZOLIDINE

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Abstract: 6-Aminocoumarin on treatment with oxalyl chloride gives coumarinyl-6-isocynate **(1a-c)** which on treatment with glycine gives 1*H*-3-[2'-oxo-2'*H*-benzopyran-6'-yl]-5-imidazolidine-2, 4-dione **(2a-c). (2a-c)** when refluxed with *o*-chlorobenzaldehyde, *m*-hydroxybenzaldehyde, 3,4-dimethoxybenzaldehyde and 3-nitrobenzaldehyde separately gives 1*H*-5-(2''-chlorobenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl) imidazolidine-2,4-dione **(3a-c),** 1*H*-5-(3''-hydroxybenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl) imidazolidine-2,4-dione **(4a-c),** 1*H*-5-(3'',4''-dimethoxybenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl) imidazolidine-2,4-dione **(5a-c)** and 1*H*-5-(3''-nitrobenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl) imidazolidine-2,4-dione **(6a-c**), respectively. 3-(2''-Chlorophenyl)-3a,4-dihydro-6-(2'-oxo-2'*H*-benzopyran-6'-yl) imidazo[4,5-*c*]isoxazol-5-one **7a-c** is obtained from **(3a-c)** and hydroxylamine hydrochloride while 2,3a,4-trihydro-3-(3''-hydroxyphenyl)-6-(2'-oxo-2'*H*-benzopyran-6'-yl) imidazo[4,5-*c*]pyrazol-5-one **(8a-c)** obtained by reaction of **(4a-c)** with hydrazine hydrate. Compound **(5a-c)** on treatment with urea gives 5,7-dihydro-2-hydroxy-6-(3'',4''-dimethoxyphenyl)-9-(2'-oxo-2'*H*-benzopyran-6'-yl) purin-8-one **(9a-c)** and compound **(6a-c)** on treatment with thiourea gives 5,7-dihydro-2-mercapto-6-(3''-nitrophenyl)-9-(2'-oxo-2'*H*-benzopyran-6'-yl)purin-8-one **(10a-c).** The structures of the compounds have been established on the basis of spectral analytical data. All the compounds have been screened for their antimicrobial activities against three bacterial strains *S. aureus, S. typhi and E. coli*. Compounds **2b, 3b, 4b, 5b, 6b, 7b, 8b, 9b** and **10b** with the presence of methyl groups at C_7' and C_8' of coumarin moiety were found to be more active than others.

Keywords: 6-aminocoumarin, imidazole, isoxazole, pyrazole, purine, mercaptopurine, antimicrobial activity

It is well known that coumarin and its derivatives possess anti-inflammatory (1), antimicrobial (2), antitubercular (3), antipyretic (4), analgesic (5), antioxidant (6) and cytotoxic activities (7). The combination of imidazolidine with coumarin definitely shows the significant biological activity and imidazole has become an important part of many pharmaceuticals. Synthetic imidazoles are present in fungicides and antifungal, antiprotozoal and antihypertensive medicines. They are also valuable in treatment of many systemic fungal infections (8). Heterocycles such as isoxazoles, pyrazoles and purines form an important class of drugs and drug intermediates. Particularly, substituted isoxazoles are well known to possess bactericidal activity (9). Also many pyrazoles and its analogues have varied antibacterial (10) and anti-inflammatory (11) activity. Purines are the constituents of nucleic acids and their structures are present in several coenzymes involved in cellular reduction and oxidation processes like nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD). Substituted purines are tested for replacement and sparing of guanine and inhibitory action (12) with animal microorganism *Tetrahymena Geleii*. In light of abovementioned biological activities, we thought of synthesizing chalcones of 1*H*-3-[2'-oxo-2'*H*-benzopyran-6'-yl]-5-imidazolidine-2,4-dione and further, from this moiety, various fused heterocycles such as imidazole, imidazo-isoxazole, imidazo-pyrazole, purine with the parent molecule, which can be tested for their various biological activity.

EXPERIMENTAL

Structures of 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-

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IR spectra (v_{max} in cm^{-1}) were recorded on a Perkin Elmer 400 spectrometer using KBr discs. ^{1}H-NMR spectra were recorded on JEOL NMR AL300 (300 MHz) using TMS as an internal standard and mass spectra were obtained on a Shimadzu GC-MS QP-2010 apparatus.

1*H*-3-[2'-oxo-2'*H*-benzopyran-6'-yl]-5-imidazolidine-2,4-diones **(2a-c)**

A mixture of glycine (0.002 mol), coumarinyl-6-isocynate **1a-c** (0.002 mol) and triethylamine (1 mL) in ethanol (15 mL) was refluxed for 8 h. The completion of reaction was monitored by TLC. An excess of ethanol was removed by distillation and the reaction mixture was neutralized by using 1:1 HCl and then poured into ice-cold water. The precipitate was filtered off, washed with water and recrystallized from ethanol to give **2a-c**.

2a: m.p. 140–142°C; yield: 65%; IR (KBr, cm^{-1}): 3242 (>NH), 2950 (-CH), 1731 (>C=O), 1682 (-CONH), 1585, 1575. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.37 (s, 3H, C_7'-CH_3), 4.0 (s, 2H, C_5-CH_2), 6.29 (d, 1H, *J* = 9 Hz, C_3'-H), 7.69 (s, 3H, C_8'-CH_3), 7.35 (s, 1H, C_5'-H), 7.70 (d, 1H, *J* = 9 Hz, C_4'-H), 8.0 (s, 1H, -NH, D_2O exchangeable).

2b: m.p. 150–152°C; yield: 73%; IR (KBr, cm^{-1}): 3240 (>NH), 2955 (-CH), 1730 (>C=O), 1680 (-CONH), 1590, 1580, 1570. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.35 (s, 3H, C_7'-CH_3), 2.47 (s, 3H, C_4'-CH_3), 4.20 (s, 2H, C_5-CH_2), 6.25 (s, 1H, C_3'-H), 7.12 (s, 1H, C_8'-H), 7.32 (s, 1H, C_5'-H), 8.20 (s, 1H, -NH, D_2O exchangeable). MS: m/z (%): 272 (M^+, 100), 257 (42), 244 (10), 173 (14), 158 (50), 148 (26), 143 (33), 118 (92), 99 (32), 71 (40), 57 (15) and 42 (22).

2c: m.p. 141–143°C; yield: 71%; IR (KBr, cm^{-1}): 3245 (>NH), 2952 (-CH), 1732 (>C=O), 1683 (-CONH), 1580, 1555. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 4.10 (s, 2H, C_5-CH_2), 6.31 (d, 1H, *J* = 9 Hz, C_3'-H), 7.10 (d, 1H, *J* = 9 Hz, C_8'-H), 7.30 (s, 1H, C_5'-H), 7.50 (d, 1H, *J* = 9 Hz, C_7'-H), 7.71(d, 1H, *J* = 9 Hz, C_4'-H), 8.30 (s, 1H, -NH, D_2O exchangeable).

1*H*-5-(2''-chlorobenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl) imidazolidine -2,4-dione **(3a-c)**

Compound **(2a-c)** (0.01 mol) was dissolved in glacial acetic acid (10 mL). To this solution fused sodium acetate (0.015 mol) and *o*-chlorobenzaldehyde (0.01 mol) were added and the mixture was refluxed for 5 h. It was then cooled and poured onto crushed ice. The resulting solid was washed with water and recrystallized from ethanol.

3a: **m**.p. 155–157°C; yield: 69%; IR (KBr, cm^{-1}): 3242 (>NH), 2935 (-CH), 1710 (>C=O), 1682 (-CONH), 1608, 1602 1532, 1530. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.32 (s, 3H, C_7'-CH_3), 6.36 (d, 1H, *J* = 9 Hz, C_3'-H), 6.68–6.91 (m, 6H, Ar-H), 7.48 (s, 1H, >CH-), 8.59 (s, 1H, -NH, D_2O exchangeable).

3b: m.p. 162–164°C; yield: 66%; IR (KBr, cm^{-1}): 3245 (>NH), 2930 (-CH), 1715 (>C=O), 1685 (-CONH), 1610, 1600, 1550, 1535. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.35 (s, 3H, C_7'-CH_3), 2.43 (s, 3H, C_4'-CH_3), 6.25 (s, 1H, C_3'-H), 6.74–7.02 (m, 6H, Ar-H), 7.45 (s, 1H, >CH-), 8.54 (s, 1H, -NH, D_2O exchangeable). MS: m/z (%): 394 (M^+, 48), 396 (M^+ + 2, 16), 379 (80), 366 (70), 338 (41), 283 (44), 227 (45), 221 (9), 206 (44), 173 (100), 118 (83), 111 (85), 110 (17), 82 (18), 95 (39), 90 (21), 89 (10), 76 (45), 67 (31) and 54 (25).

3c: m.p. 154–156°C; yield: 70%; IR (KBr, cm^{-1}): 3247 (>NH), 2930 (-CH), 1705 (>C=O), 1675 (-CONH), 1605, 1528, 1515. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 6.39 (d, 1H, *J* = 9 Hz, C_3'-H), 6.80–7.13 (m, 7H, Ar-H), 7.49 (s, 1H, >CH-), 8.60 (s, 1H, -NH, D_2O exchangeable).

3-(2''-Chlorophenyl)-3a,4-dihydro-6-(2'-oxo-2'*H*-benzopyran-6'-yl)imidazo[4,5-*c*]isoxazol-5-one **(7a-c)**

A mixture of **(3a-c)** (0.01 mol) in ethanol (20 mL) and fused sodium acetate (0.01 mol) dissolved in minimum amount of hot acetic acid was added to a solution of hydroxylamine hydrochloride (0.01 mol) in ethanol (10 mL). The reaction was refluxed for 10 h and then poured onto crushed ice. The resulting solid was purified by column chromatography (60–120 mesh silica) using elutent n-hexane and ethyl acetate (8:2, v/v).

7a: **m**.p. 170–172°C; yield: 59%; IR (KBr, cm^{-1}): 3240 (>NH), 2930 (-CH), 1726 (>C=O), 1662 (-CONH), 1585, 1542, 1527, 782. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 2.30 (s, 3H, C_7'-CH_3), 4.70 (s, 1H, -CH-), 5.23 (s, 1H, C_3-H), 6.32 (d, 1H, *J* = 9 Hz, C_3'-H), 6.96–7.26 (m, 6H, Ar-H), 7.70 (d, 1H, *J* = 9 Hz, C_4'-H), 9.00 (s, 1H, -NH, D_2O exchangeable).

7b: m.p. 177–179°C; yield: 55%; IR (KBr, cm^{-1}): 3240 (>NH), 2955 (-CH), 1730 (>C=O), 1680 (-CONH), 1590, 1580, 1570. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 2.32 (s, 3H, C_7'-CH_3), 2.45 (s, 3H, C_4'-CH_3), 4.71 (s, 1H, -CH-), 5.20 (s, 1H, C_3-H), 6.25 (s, 1H, C_3'-H), 6.90–7.13 (m, 6H, Ar-H), 9.20 (s, 1H, -NH, D_2O exchangeable). MS: m/z (%): 409 (M^+,42), 411 (M^+ + 2, 14), 394 (72), 381 (76), 270 (33), 255 (16), 240 (41), 236 (4), 236 (8), 208 (34), 173 (100), 158 (22), 148 (11), 143 (27), 133 (51), 125 (18), 118 (74), 115 (36), 97 (33), 89 (10) and 80 (4).

7c: m.p. 165–167°C; yield: 52%; IR (KBr, cm^{-1}): 3245 (>NH), 2942 (-CH), 1720 (>C=O), 1630 (-C=N-) 1670 (-CONH), 1585, 1543, 1530, 778. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 4.75 (s, 1H, -CH-), 5.29 (s, 1H, C_3-H), 6.35 (d, 1H, *J* = 9 Hz, C_3'-H), 6.85–7.19 (m, 7H, Ar-H), 7.75 (d, 1H, *J* = 9 Hz, C_4'-H), 8.80 (s, 1H, -NH, D_2O exchangeable).

1*H*-5-(3''-hydroxybenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl)imidazolidine -2,4-dione **(4a-c)**

Compound **(2a-c)** (0.01 mol) was dissolved in glacial acetic acid (10 mL). To this solution, fused sodium acetate (0.015 mol) and *m*-hydroxybenzaldehyde (0.01 mol) was added and the mixture was refluxed for 8 h. It was then cooled and poured onto crushed ice. The resulting solid was washed with water and recrystallized from ethanol.

4a: m.p. 153–155°C; yield: 63%; IR (KBr, cm^{-1}): 3395 (-OH), 2952 (-CH), 1722 (>C=O), 1683 (-CONH), 1602, 1590, 1560, 1545. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.36 (s, 3H, C_7'-CH_3), 6.30 (d, 1H, *J* = 9 Hz, C_3'-H), 5.00 (s, 1H, -OH, D_2O exchangeable) 7.15–7.29 (m, 6H, Ar-H), 7.40 (s, 1H, >CH-), 7.71 (d, 1H, *J* = 9 Hz, C_4'-H), 8.70 (s, 1H, -NH, D_2O exchangeable).

4b: m.p. 169–171°C; yield: 65%; IR (KBr, cm^{-1}): 3390 (-OH), 2955 (-CH), 1720 (>C=O), 1680 (-CONH), 1608, 1602, 1580, 1535. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.34 (s, 3H, C_7'-CH_3), 2.40 (s, 3H, C_4'-CH_3), 5.20 (s, 1H, -OH, D_2O exchangeable) 6.25 (s, 1H, C_3'-H), 7.08–7.31 (m, 6H, Ar-H), 7.42 (s, 1H, >CH-), 8.90 (s, 1H, -NH, D_2O exchangeable). MS: m/z (%): 376 (M^+, 100), 361 (63), 283 (63), 268 (21), 255 (36), 203 (82), 175 (19), 173 (53), 148 (59), 118 (95), 115 (25), 90 (15), 93 (8), 89 (12), 87 (10) and 76 (40).

4c: m.p. 150–152°C; yield: 69%; IR (KBr, cm^{-1}): 3392 (-OH), 2953 (-CH), 1725 (>C=O), 1681 (-CONH), 1602, 1580, 1576. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 6.32 (d, 1H, *J* = 9 Hz, C_3'-H), 5.10 (s, 1H, -OH, D_2O exchangeable), 6.59–6.73 (m, 7H, Ar-H), 7.43 (s, 1H, >CH-), 7.73 (d, 1H, *J* = 9 Hz, C_4'-H), 9.00 (s, 1H, -NH, D_2O exchangeable).

2,3a,4-Trihydro-3-(3''-hydroxyphenyl)-6-(2'-oxo-2'*H*-benzopyran-6'-yl)imidazo[4,5-*c*]pyrazol-5-one **(8a-c)**

A mixture of **(4a-c)** (0.01 mol) and hydrazine hydrate (0.01 mol) in the presence of piperidine (1 mL) in ethanol (15 mL) was refluxed for 6–7 h. The reaction was monitored by TLC. The reaction mixture was then poured onto crushed ice. The resulting solid was purified by column chromatography (60–120 mesh silica) using elutent n-hexane and ethyl acetate (9:1, v/v).

8a: m.p. 168–170°C; yield: 51%; IR (KBr, cm^{-1}): 3342 (-OH), 3235 (-NH), 2942 (-CH), 1715 (>C=O), 1680 (-CONH), 1595, 1575, 1562. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 2.32 (s, 3H, C_7'-CH_3), 4.70 (s, 1H, -CH-), 5.10 (s, 1H, C_3-H), 5.20 (s, 1H, -OH, D_2O exchangeable), 6.31 (d, 1H, *J* = 9 Hz, C_3'-H), 6.70–7.10 (m, 6H, Ar-H), 7.72 (d, 1H, *J* = 9 Hz, C_4'-H), 9.00 (s, 1H, -NH, D_2O exchangeable).

8b: m.p. 179–181°C; yield: 61%; IR (KBr, cm^{-1}): 3340 (-OH), 3250 (-NH), 2945 (-CH), 1719 (>C=O), 1684 (-CONH), 1598, 1570, 1560. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 2.35 (s, 3H, C_7'-CH_3), 2.44 (s, 3H, C_4'-CH_3), 4.76 (s, 1H, -CH-), 5.00 (s, 1H, -OH, D_2O exchangeable), 5.13 (s, 1H, C_3-H), 6.29 (s, 1H, C_3'-H), 6.74–7.06 (m, 6H, Ar-H), 9.20 (s, 1H, -NH, D_2O exchangeable), 10.20 (s, 1H, -NH, D_2O exchangeable). MS: m/z (%): 390 (M^+, 80), 375 (66), 297 (60), 282 (41), 217 (85), 189 (40), 173 (90), 158 (21), 148 (40), 124 (11), 118 (100), 90 (10), 89 (05), 96 (17), 93 (23) and 76 (33).

8c: m.p. 166–168°C; yield: 55%; IR (KBr, cm^{-1}): 3345 (-OH), 3220 (-NH), 2940 (-CH), 1712 (>C=O), 1682 (-CONH), 1590, 1580, 1565. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 4.81 (s, 1H, -CH-), 4.90 (s, 1H, -OH, D_2O exchangeable), 5.15 (s, 1H, C_3-H), 6.30 (d, 1H, *J* = 9 Hz, C_3'-H), 6.81–7.23 (m, 7H, Ar-H), 7.70 (d, 1H, *J* = 9 Hz, C_4'-H), 9.10 (s, 1H, -NH, D_2O exchangeable), 10.3 (s, 1H, -NH, D_2O exchangeable).

1*H*-5-(3'',4''-dimethoxybenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl)imidazolidine-2,4-dione **(5a-c)**

Compound **(2a-c)** (0.01 mol) was dissolved in glacial acetic acid (10 mL). To this solution, fused sodium acetate (0.015 mol) and 3,4-dimethoxybenzaldehyde (0.01 mol) was added and the mixture was refluxed for 10 h. It was then cooled and poured onto crushed ice. The resulting solid was washed with water and recrystallized from ethanol.

5a: m.p. 191–193°C; yield: 56%; IR (KBr, cm^{-1}): 3242 (>NH), 2930 (-CH), 1732 (>C=O), 1680 (-CONH), 1608, 1580, 1550, 1535, 1248, 1040. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.38 (s, 3H, C_7'-CH_3), 3.75 (s, 6H, -OCH_3), 6.30 (d, 1H, *J* = 9 Hz, C_3'-H), 6.64–6.79 (m, 5H, Ar-H), 7.39 (s, 1H, >CH-), 7.70 (d, 1H, *J* = 9 Hz, C_4'-H), 8.50 (s, 1H, -NH, D_2O exchangeable).

5b: m.p. 201–203°C; yield: 62%; IR (KBr, cm^{-1}): 3240 (>NH), 2932 (-CH), 1730 (>C=O), 1675 (-CONH), 1610, 1590, 1545, 1540, 1250, 1042. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.36 (s, 3H, C_7'-CH_3), 2.45 (s, 3H, C_4'-CH_3), 3.79 (s, 6H, -OCH_3), 6.29 (s, 1H, C_3'-H), 6.64–6.79 (m, 5H, Ar-H), 7.42

Table 1. Antibacterial activity of compounds **2a-c**, **3a-c**, **4a-c**, **5a-c**, **6a-c**, **7a-c**, **8a-c**, **9a-c** and **10a-c**.

Compd.	Zone of inhibition in mm					
	E. coli		*S. typhi*		*S. aureus*	
	50 mg	100 mg	50 mg	100 mg	50 mg	100 mg
2a	13	15	15	16	16	18
2b	15	18	17	19	19	21
2c	12	13	14	17	15	17
3a	13	14	14	17	14	15
3b	14	17	16	19	16	19
3c	12	13	13	15	15	17
4a	12	15	13	16	16	19
4b	15	19	16	19	18	20
4c	12	13	12	14	15	17
5a	14	15	15	17	15	18
5b	16	17	19	20	16	19
5c	13	16	14	16	14	16
6a	12	14	14	15	15	17
6b	15	18	18	20	17	20
6c	12	13	12	15	14	15
7a	14	17	14	18	19	17
7b	16	19	18	20	19	21
7c	13	15	13	19	15	16
8a	14	17	15	19	17	19
8b	18	20	19	21	20	21
8c	12	15	13	15	16	18
9a	15	18	17	18	17	19
9b	18	20	20	21	20	21
9c	12	14	13	15	16	18
10a	14	17	16	19	17	19
10b	19	20	20	21	20	22
10c	13	16	14	16	16	18

Disc size: 6.35 mm, standard: streptomycin, control: DMSO, Duration: 24 h, resistant (11 mm and less), intermediate (12–14 mm), sensitive (15 mm and more)

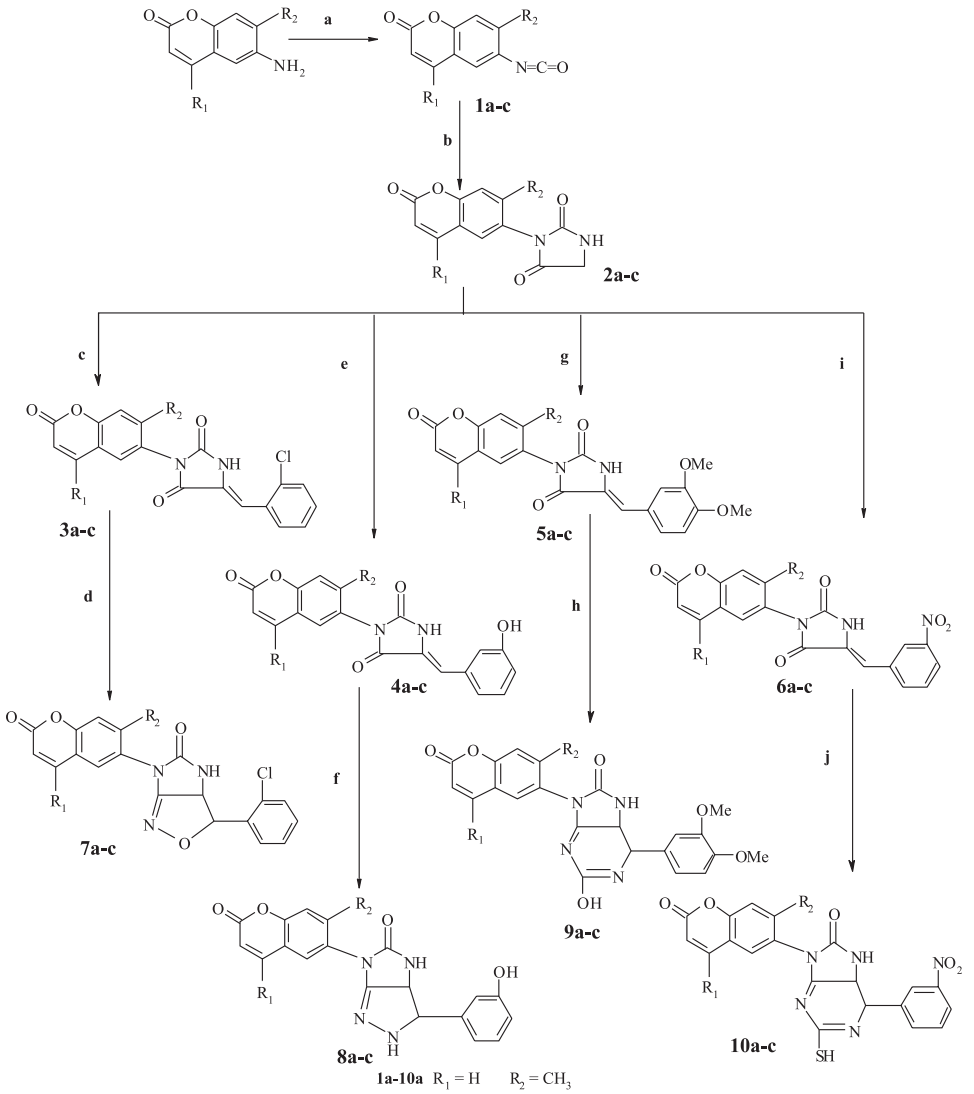
(s, 1H, >CH-), 8.80 (s, 1H, -NH, D_2O exchangeable). MS: m/z (%): 420 (M^+, 92), 283 (55), 268 (45), 253 (42), 247 (40), 173 (15), 137 (100), 115 (10), 110 (75), 105 (15), 82 (5), 54 (1) and 32 (20).

5c: m.p. 180–182°C; yield: 60%; IR (KBr, cm^{-1}): 3245 (>NH), 2933 (-CH), 1729 (>C=O), 1682 (-CONH), 1605, 1582, 1525, 1515, 1245, 1038. ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 3.72 (s, 6H, $-OCH_3$), 6.32 (d, 1H, J = 9 Hz, C_3'-H), 6.69–6.85 (m, 6H, Ar-H), 7.40 (s, 1H, >CH-), 7.68 (d, 1H, J = 9 Hz, C_4'-H), 8.70 (s, 1H, -NH, D_2O exchangeable). 5,7-Dihydro-2-hydroxy-6-(3'',4''-dimethoxyphenyl)-9-(2'-oxo-2'*H*-benzopyran-6'-yl)purin-8-one **(9a-c)**

To a mixture of **(5a-c)** (0.01 mol) and urea (0.01 mol in 10 mL of ethanol) in ethanol (15 mL), NaOH (10%, 1 mL) was added dropwise and refluxed for 9 h. The reaction was monitored by TLC and at the end was poured onto crushed ice and neutralized with dil. HCl. The resulting solid was purified by column chromatography (60–120 mesh silica) using elutent n-hexane and ethyl acetate (9:1, v/v).

9a: m.p. 213–215°C; yield: 48%; IR (KBr, cm^{-1}): 3351 (-OH), 3235 (>NH), 2950 (-CH), 1730 (>C=O), 1682 (-CONH), 1588, 1582, 1570, 1242, 1042. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 2.30 (s, 3H, C_7'-CH_3), 3.80 (s, 6H, -OCH_3), 4.50 (s, 1H, C_5-H), 4.94 (s, 1H, C_6-H), 6.00 (s, 1H, -OH, D_2O exchangeable), 6.33 (d, 1H, J = 9 Hz, C_3'-H), 6.85–7.09 (m, 5H, Ar-H), 7.71 (d, 1H, J = 9 Hz, C_4'-H), 9.10 (s, 1H, -NH, D_2O exchangeable).

9b: m.p. 222–224°C; yield: 54%; IR (KBr, cm^{-1}): 3355 (-OH), 3242 (>NH), 2952 (-CH), 1728 (>C=O), 1680 (-CONH), 1570, 1245, 1040. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 2.32 (s, 3H, C_7'-CH_3), 2.40 (s, 3H, C_4'-CH_3), 3.82 (s, 6H, -OCH_3), 4.55 (s, 1H, C_5-H), 4.92 (s, 1H, C_6-H), 5.90 (s, 1H, -OH, D_2O exchangeable), 6.24 (s, 1H, C_3'-H), 6.90–7.10 (m, 5H, Ar-H), 9.30 (s, 1H, -NH, D_2O exchangeable). MS: m/z (%): 462 (M^+, 92), 447



a) Oxalyl chloride, Toluene **b)** Glycine, EtOH **c)** *o*-Chlorobenzaldehyde, AcONa **d)** $NH_2OH{\cdot}HCl$, EtOH **e)** *m*-Hydroxybenzaldehyde, AcONa **f)** NH_2NH_2, EtOH **g)** 3,4-Dimethoxybenzaldehyde, AcONa **h)** Urea, EtOH **i)** 3-Nitrobenzaldehyde, AcONa **j)** Thiourea, EtOH

Scheme 1.

Table 2. Characterization data of compounds **2a-c**, **3a-c**, **4a-c**, **5a-c**, **6a-c**, **7a-c**, **8a-c**, **9a-c** and **10a-c**.

Compd.	Mol. formula	m.p. °C	Yield (%)	Elemental analysis. [Found (%) (Required)]			
				C	H	N	S
2a	$C_{13}H_{10}N_2O_4$	140–142	65	60.40 (60.47)	3.92 (3.90)	10.82 (10.85)	–
2b	$C_{14}H_{12}N_2O_4$	150–152	73	61.70 (61.76)	4.48 (4.44)	10.24 (10.29)	–
2c	$C_{11}H_8N_2O_4$	141–143	71	59.00 (59.02)	3.33 (3.30)	1.45 (1.47)	–
3a	$C_{20}H_{13}N_2O_4Cl$	155–157	69	63.05 (63.08)	3.41 (3.44)	7.32 (7.36)	–
3b	$C_{21}H_{15}N_2O_4Cl$	162–164	66	63.84 (63.89)	3.79 (3.83)	7.04 (7.10)	–
3c	$C_{19}H_{11}N_2O_4Cl$	154–156	70	62.18 (62.22)	2.95 (3.02)	7.62 (7.64)	–
4a	$C_{20}H_{14}N_2O_5$	153–155	63	66.24 (66.30)	3.86 (3.89)	7.70 (7.73)	–
4b	$C_{21}H_{16}N_2O_5$	169–171	65	66.94 (67.02)	4.23 (4.28)	7.42 (7.44)	–
4c	$C_{19}H_{12}N_2O_5$	150–152	69	65.50 (65.52)	3.45 (3.47)	8.01 (8.04)	–
5a	$C_{22}H_{18}N_2O_6$	191–193	56	65.05 (65.02)	4.42 (4.46)	6.85 (6.89)	–
5b	$C_{23}H_{20}N_2O_6$	201–203	62	65.75 (65.71)	4.75 (4.79)	6.62 (6.66)	–
5c	$C_{21}H_{16}N_2O_6$	180–182	60	64.32 (64.28)	4.08 (4.11)	7.11 (7.14)	–
6a	$C_{20}H_{13}N_3O_6$	212–214	61	61.34 (61.38)	3.32 (3.35)	10.49 (10.47)	–
6b	$C_{21}H_{15}N_3O_6$	229–231	67	62.20 (62.22)	3.71 (3.73)	10.40 (10.37)	–
6c	$C_{19}H_{11}N_3O_6$	199–201	55	60.45 (60.48)	2.91 (2.94)	11.12 (11.14)	–
7a	$C_{20}H_{14}N_3O_4Cl$	170–172	59	60.65 (60.69)	3.52 (3.57)	10.64 (10.62)	–
7b	$C_{21}H_{16}N_3O_4Cl$	177–179	55	61.53 (61.54)	3.90 (3.94)	10.28 (10.25)	–
7c	$C_{19}H_{12}N_3O_4Cl$	165–167	52	59.72 (59.78)	3.12 (3.17)	11.03 (11.01)	–
8a	$C_{20}H_{16}N_4O_4$	168–170	51	36.83 (63.82)	4.22 (4.28)	14.81 (14.89)	–
8b	$C_{21}H_{18}N_4O_4$	179–181	61	64.63 (64.61)	4.63 (4.65)	14.32 (14.35)	–
8c	$C_{19}H_{14}N_4O_4$	166–168	55	63.03 62.98)	3.85 (3.89)	15.43 (15.46)	–
9a	$C_{23}H_{20}N_4O_6$	213–215	48	62.31 (62.33)	4.75 (4.79)	12.10 (12.12)	–
9b	$C_{24}H_{22}N_4O_6$	222–224	54	62.94 (63.02)	5.01 (5.08)	11.74 (11.76)	–
9c	$C_{22}H_{18}N_4O_6$	202–204	45	61.54 (61.60)	4.44 (4.50)	12.45 (12.49)	–

Table 2. cont.

Compd.	Mol. formula	m.p. °C	Yield (%)	Elemental analysis. [Found (%) (Required)]			
				C	H	N	S
10a	$C_{21}H_{15}N_5O_5S$	240–242	52	56.08 (56.12)	3.32 (3.36)	15.55 (15.58)	7.15 (7.13)
10b	$C_{22}H_{17}N_5O_5S$	235–237	57	57.00 (57.01)	3.66 (3.70)	15.09 (15.11)	6.95 (6.92)
10c	$C_{20}H_{13}N_5O_5S$	229–231	61	55.13 (55.17)	2.95 (3.01)	16.04 (16.08)	7.39 (7.63)

(10), 432 (23), 431 (16), 400 (10), 370 (42), 325 (60), 310 (20), 295 (40), 289 (100), 173 (71), 152 (15), 143 (10), 137 (90), 135 (5), 107 (10), 105 (6) and 32 (8).

9c: m.p. 202–204°C; yield: 45%; IR (KBr, cm^{-1}): 3345 (-OH), 3252 (>NH), 2955 (-CH), 1732 (>C=O), 1680 (-CONH), 1589, 1571, 1240, 1040. ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 3.81 (s, 6H, $-OCH_3$), 4.53 (s, 1H, C_5-H), 4.99 (s, 1H, C_6-H), 6.10 (s, 1H, -OH, D_2O exchangeable), 6.35 (d, 1H, *J* = 9 Hz, C_3'-H), 6.95–7.22 (m, 6H, Ar-H), 7.72 (d, 1H, *J* = 9 Hz, C_4'-H), 9.50 (s, 1H, -NH, D_2O exchangeable).

1*H*-5-(3''-nitrobenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl)imidazolidine-2,4-dione **(6a-c)**

Compound **(2a-c)** (0.01 mol) was dissolved in glacial acetic acid (10 mL). To this solution, fused sodium acetate (0.015 mol) and 3-nitrobenzaldehyde (0.01 mol) was added and the mixture was refluxed for 8 h. It was then cooled and poured onto crushed ice. The resulting solid was washed with water and recrystallized from ethanol.

6a: m.p. 212–214°C; yield: 61%; IR (KBr, cm^{-1}): 3242 (>NH), 2952 (-CH), 1729 (>C=O), 1682 (-CONH), 1602, 1590, 1550, 1352 ($-NO_2$). ^{1}H-NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.33 (s, 3H, C_7'-CH_3), 6.32 (d, 1H, *J* = 9 Hz, C_3'-H), 6.72–7.03 (m, 6H, Ar-H), 7.39 (s, 1H, >CH-), 7.70 (d, 1H, *J* = 9 Hz, C_4'-H), 8.80 (s, 1H, -NH, D_2O exchangeable).

6b: m.p. 229–231°C; yield: 67%; IR (KBr, cm^{-1}): 3245 (>NH), 2950 (-CH), 1732 (>C=O), 1685 (-CONH), 1605, 1595, 1560, 1549, 1350 ($-NO_2$). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 2.35 (s, 3H, C_7'-CH_3), 2.46 (s, 3H, C_4'-CH_3), 6.25 (s, 1H, C_3'-H), 6.80–7.12 (m, 6H, Ar-H), 7.40 (s, 1H, >CH-), 8.90 (s, 1H, -NH, D_2O exchangeable). MS: m/z (%): 405 (M^+, 100), 359 (70), 283 (44), 268 (22), 255 (23), 232 (40), 186 (42), 173 (35), 143 (41), 122 (60), 110 (10), 82 (5), 76 (5), 54 (9) and 46 (10).

6c: m.p. 199–201°C; yield: 55%; IR (KBr, cm^{-1}): 3240 (>NH), 2948 (-CH), 1730 (>C=O), 1680 (-CONH), 1601, 1585, 1545, 1348 (NO_2). ^{1}H NMR ($CDCl_3$, 300 MHz, δ, ppm): 6.33 (d, 1H, *J* = 9 Hz, C_3'-H), 6.77–7.15 (m, 7H, Ar-H), 7.42 (s, 1H, >CH-), 7.71 (d, 1H, *J* = 9 Hz, C_4'-H), 8.80 (s, 1H, -NH, D_2O exchangeable).

5,7-Dihydro-2-mercapto-6-(3''-nitrophenyl)-9-(2'-oxo-2'*H*-benzopyran-6'-yl)purin-8-one **(10a-c)**

To a mixture of **(6a-c)** (0.01 mol) and thiourea (0.01 mol) in ethanol (10 mL), NaOH (10%, 1 mL) was added dropwise and then the mixture was refluxed for 10 h. The reaction was monitored by TLC and at the end was poured onto crushed ice and neutralized with dil. HCl. The resulting solid is purified by column chromatography (60–120 mesh silica) using elutent petrolium ether and ethyl acetate (9:1, v/v).

10a: m.p. 240–242°C; yield: 52%; IR (KBr, cm^{-1}): 3242 (>NH), 2950 (-CH), 2548 (-SH), 1725 (>C=O), 1685 (-CONH), 1590, 1582, 1560, 1548, 1338 ($-NO_2$). ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 2.39 (s, 3H, C_7'-CH_3), 3.42 (s, 1H, -SH), 4.90 (s, 1H, C_5-H), 5.23 (s, 1H, C_6-H), 6.30 (d, 1H, *J* = 9 Hz, C_3'-H), 6.91-7.12 (m, 6H, Ar-H), 7.72 (d, 1H, *J* = 9 Hz, C_4'-H), 9.52 (s, 1H, -NH, D_2O exchangeable).

10b: m.p. 235–237°C; yield: 57%; IR (KBr, cm^{-1}): 3250 (>NH), 2948 (-CH), 2552 (-SH), 1730 (>C=O), 1680 (-CONH), 1585, 1565, 1552, 1340 ($-NO_2$). ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 2.37 (s, 3H, C_7'-CH_3), 2.49 (s, 3H, C_4'-CH_3), 3.45 (s, 1H, -SH), 4.92 (s, 1H, C_5-H), 5.29 (s, 1H, C_6-H), 6.28 (s, 1H, C_3'-H), 6.99–7.19 (m, 6H, Ar-H), 9.50 (s, 1H, -NH, D_2O exchangeable). MS: m/z (%): 463 (M^+, 70), 448 (43), 435 (7), 341 (41), 290 (40), 262 (9), 173 (100), 168 (45), 140 (17), 135 (30), 122 (23), 107 (5) and 33 (2).

10: m.p. 229–231°C; yield: 61%; IR (KBr, cm^{-1}): 3245 (>NH), 2952 (-CH), 2550 (-SH), 1728 (>C=O), 1688 (-CONH), 1585, 1575, 1565, 1550, 1340 (-NO_2). ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 3.40 (s, 1H, -SH), 4.95 (s, 1H, C_5-H), 5.20 (s, 1H, C_6-H), 6.31(d, 1H, *J* = 9 Hz, C_3'-H), 7.02–7.20 (m, 7H, Ar-H), 7.72 (d, 1H, *J* = 9 Hz, C_4'-H), 9.54 (s, 1H, -NH, D_2O exchangeable).

RESULTS

6-Coumarinyl isocynate **(1a-c)** was efficiently prepared by refluxing 6-aminocoumarin with oxalyl chloride in toluene. The intermediate oxamic chloride was heated to 140°C to effect a smooth thermal decomposition to the corresponding isocyanate, which was treated with glycine in ethanol to yield 1*H*-3-(2'-oxo-2'*H*-benzopyran-6'-yl)-5-imidazolidine-2,4-dione **(2a-c).** The IR spectrum of **2b** in KBr showed band at 3240 cm^{-1} for >NH stretching, at 2955 cm^{-1} for –CH- stretching, at 1730 and 1680 cm^{-1} for >C=O stretching of coumarin and –CONH group. The ^{1}H NMR spectrum of compound **2b** in $CDCl_3$ showed the presence of singlets at δ 2.35 and 2.47 ppm for three protons of each methyl groups at C_7' and C_4', respectively. Singlet at 4.20 ppm accounted for two protons of methylene group at C_5 and another singlet at 6.25 ppm was for a proton at C_3'. Singlets at 7.12 and 7.32 ppm were accounted for protons at C_8' and C_5', respectively. Singlet at 8.20 was assigned for one of >NH group which was D_2O exchangeable. The mass spectrum of **2b** showed molecular ion peak at m/z 272.

Compounds **(2a-c)** were dissolved in glacial acetic acid and refluxed with sodium acetate and with *o*-chlorobenzaldehyde, *m*-hydroxybenzaldehyde, 3,4-dimethoxybenzaldehyde and 3-nitrobenzaldehyde separately, yielding 1*H*-5-(2''-chlorobenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl)imidazolidine-2,4-diones **(3a-c),** 1*H*-5-(3''-hydroxybenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl)imidazolidine-2,4-diones **(4a-c),** 1*H*-5-(3'',4''-dimethoxybenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl)imidazolidine-2,4-diones **(5a-c)** and 1*H*-5-(3''-nitrobenzylidene)-3-(2'-oxo-2'*H*-benzopyran-6'-yl)imidazolidine-2,4-diones **(6a-c),** respectively.

Compounds **(4a-c), (5a-c)** and **(6a-c)** showed the identical spectra as those of **(3a-c)** compounds only different in aromatic protons.

In order to prepare compounds **(7a-c),** compounds **(3a-c)** were treated with hydroxylamine hydrochloride in ethanol**.** With an intension to synthesize compounds **(8a-c)**, compounds **(4a-c)** were treated with hydrazine hydrate.

In order to prepare compounds **(9a-c**), compounds **(5a-c)** were treated with urea in ethanol**.**

Compounds **(6a-c)** were treated with thiourea in ethanol yielding **(10a-c**).

All the spectral data confirmed the structures of the compounds obtained.

ANTIMICROBIAL SCREENING

All the synthesized compounds: **2a-c**, **3a-c**, **4a-c**, **5a-c**, **6a-c**, **7a-c**, **8a-c**, **9a-c** and **10a-c** were screened for their antibacterial activity by drug diffusion method by preparing the paper discs of the drug (13). The activity was tested against three bacterial strains *S. aureus, S. typhi and E. coli* (Table 1) at two concentrations (50 µg/mL and 100 µg/mL) using DMSO as a solvent. The activities of compounds were compared with streptomycin as antibacterial standard.

The bacteria were cultured on nutrient broth containing peptone (0.6%), yeast extract and sodium chloride prepared in distilled water and autoclaved at 15 lbs pressure at 121°C for 20 min. For drug diffusion, nutrient agar was prepared in sterile Petri plate. Agar agar (1.2%) was used as solidifying agent. Paper discs (6.35 mm) were prepared using Whatman filter paper no. 1, which were soaked in sterile compounds solutions under study and were placed onto the nutrient agar on which the bacteria were inoculated by spread plate technique. The plates were incubated at 37°C for 24 h.

The extent of inhibition was observed by measuring zones of inhibition in millimeters. As DMSO also has antimicrobial activity, DMSO was also used as blank and its zone of inhibition was also measured. From all the compounds tested, the zones of inhibition produced by compounds **2b, 3b, 4b, 5b, 6b, 7b, 8b, 9b** and **10b** were significant indicating the effect of methyl groups at C_7' and C_8' of coumarin moiety on the antibacterial activity.

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