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Synthesis of biologically active 3-(2-oxo-*2H*-benzopyran-6-yl)-2-(-2-oxo-*2H*-benzopyran-6-ylimino)-thiazolidin-4-one and its derivatives

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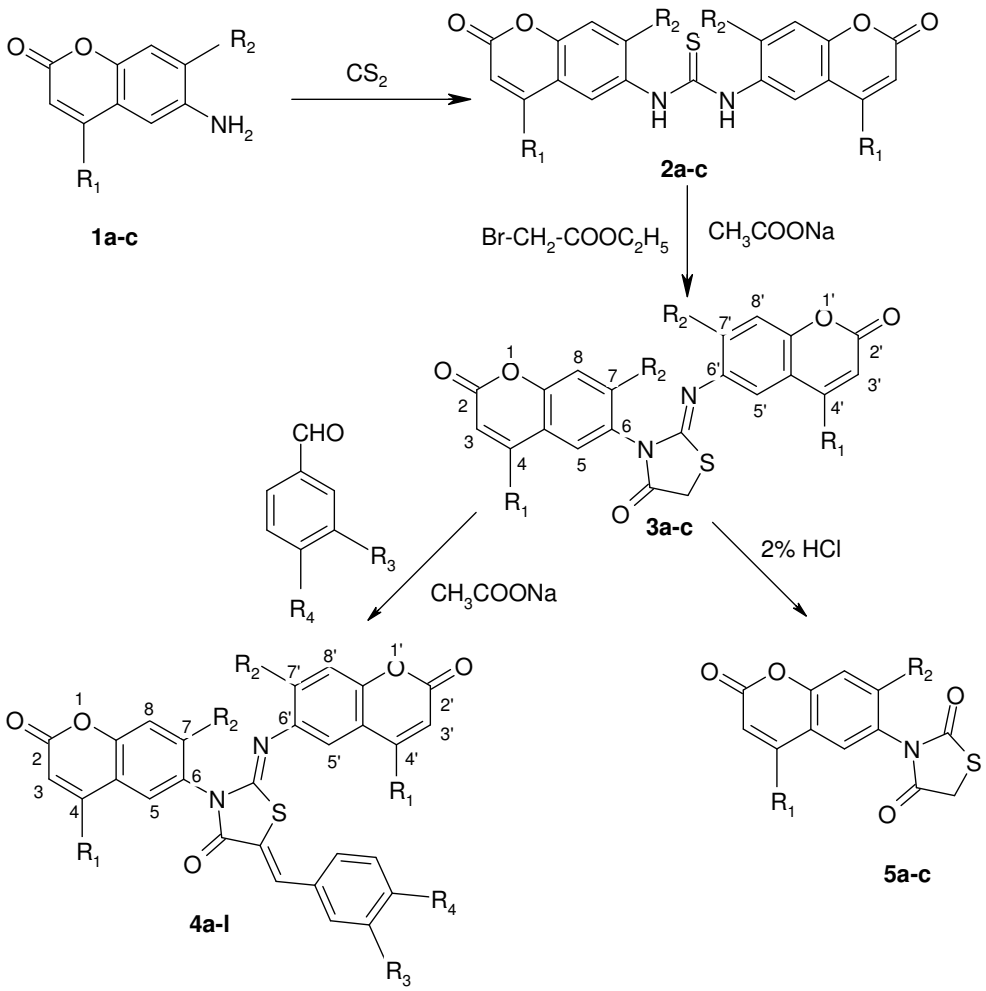
1,3-Bis-(2-oxo-*2H*-benzopyran-6-yl)-thioureas **2a-c** are obtained by refluxing 6-amino coumarins **1a-c** and carbon disulphide in absolute alcohol which upon treatment with ethyl bromoacetate in the presence of sodium acetate in ethanol to give 3-(2-oxo-*2H*-benzopyran-6-yl)-2-(-2-oxo-*2H*-benzopyran-6-ylimino)-thiazolidin-4-ones **3a-c**. The iminothiazolidinones **3a-c** are treated with various substituted aromatic aldehydes to give 3-(2-oxo-*2H*-benzopyran-6-yl)-2-(-2-oxo-*2H*-benzopyran-6-ylimino)-5-[1-(3-trifluoromethyl-phenyl)-methylidene]-thiazolidin-4-ones **4a-l**. Also the iminothiazolidinones **3a-c** are treated with 2% HCl to give 3-(2-oxo-*2H*-benzopyran-6-yl)-thiazolidine-2,4-diones **5a-c**. The structures of the compounds **2a-c**, **3a-c**, **4a-l** and **5a-c** 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 activities.

Keywords: 6-Amino coumarin, iminothiazolidinone, 4-thiazolidinone, aromatic aldehydes, antibacterial activity

Coumarin derivatives have aroused considerable interest from the viewpoint 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 and especially effective against HIV_1[4]. Also the 4-thiazolidinone derivatives are known to possess antibacterial[5–7], antifungal[8,9], antiviral[10,11], antituberculosis[12–14], anticonvulsant[15,16] and anticancer[17] activities. By observing the importance of the above compounds 4-thiazolidinone moiety in coumarin is combined which may possess above biological activity.

Result and Discussion

1,3-Bis-(2-oxo-*2H*-benzopyran-6-yl)-thioureas **2a-c** is obtained by refluxing 6-amino coumarins **1a-c** and carbon disulphide in absolute alcohol which upon treatment with ethyl bromoacetate in the presence of sodium acetate in ethanol give 3-(2-oxo-*2H*-benzopyran-6-yl)-2-(-2-oxo-*2H*-benzopyran-6-ylimino)-thiazolidin-4-ones **3a-c**. The IR spectrum of compound **3b** in KBr showed band at 3061, 2962 cm^{-1} for –CH stretching and 1724 cm^{-1} for >C=O etc. The ^1H NMR spectrum of compound **3b** in $CDCl_3$ showed a singlet at δ 4.09 for two protons of –CO-CH_2- group. The mass spectrum of **3b** showed molecular ion peak at *m/z* 460 (base peak). The iminothiazolidinones **3a-c** are treated with various substituted aromatic aldehydes to give 3-(2-oxo-*2H*-benzopyran-6-yl)-2-(2-oxo-*2H*-benzopyran-6-ylimino)-5-[1-(3-trifluoromethyl-phenyl)-methylidene]-thiazolidin-4-ones **4a-l**. The IR spectrum of compound **4e** in KBr showed band at 3065, 2969 cm^{-1} for –CH stretching, at 1719 cm^{-1} for >C=O of coumarins and thiazolidinones etc. The ^1H NMR spectrum of compound **4e** in DMSO-d_6 showed presence of singlet at δ 2.16, 2.38, 2.40 and 2.45 for three protons of four methyl group at $C_{4'}$, C_4, $C_{7'}$, and C_7 respectively. Singlet observed at δ 6.26 and 6.48 for one proton each at $C_{3'}$ and C_3 respectively. Multiplet observed at δ 7.03-8.03 for eight aromatic protons and one – C=CH proton. The absence of a singlet at δ 4.09 for two protons of –CO-CH_2- group also proved the product formation. The mass spectrum of **4e** showed molecular ion peak at *m/z* 616 gave further evidence in support of the structure assigned. Also the iminothiazolidinones **3a-c** are treated with 2% HCl to give 3-(2-oxo-*2H*-benzopyran-6-yl)-thiazolidine-2,4-diones **5a-c** (**Scheme I**). The IR spectrum of compound **5b** in KBr showed band at 2969 cm^{-1} for –CH stretching, at 1744 and 1710 cm^{-1} for >C=O etc. The ^1H NMR spectrum of compound **5b** in $CDCl_3$ showed a singlet at δ 4.26



1a, **2a**, **3a**, **5a**:	R_1 = H,	R_2 = CH_3	**4a**: R_1 = H,	R_2 = CH_3,	R_3 = H,	R_4=H.
1b, **2b**, **3b**, **5b**:	R_1 = CH_3,	R_2 = CH_3	**4b**:R_1 = CH_3,	R_2 = CH_3,	R_3 = H,	R_4=H.
1c, **2c**, **3c**, **5c**:	R_1 = H,	R_2 = H	**4c**: R_1 = H,	R_2 = H,	R_3 = H ,	R_4=H.
			4d:R_1 = H,	R_2 = CH_3,	R_3 = CF_3,	R_4=H.
			4e:R_1 = CH_3,	R_2 = CH_3,	R_3 = CF_3,	R_4=H.
			4f:R_1 = H,	R_2 = H,	R_3 = CF_3,	R_4=H.
			4g:R_1 = H,	R_2 = CH_3,	R_3 = F,	R_4=H.
			4h:R_1 = CH_3,	R_2 = CH_3,	R_3 = F,	R_4=H.
			4i: R_1 = H,	R_2 = H,	R_3 = F,	R_4=H.
			4j:R_1 = H,	R_2 = CH_3,	R_3 = H,	R_4=F
			4k:R_1 = CH_3,	R_2 = CH_3,	R_3 = H,	R_4=F.
			4l: R_1 = H,	R_2 = H,	R_3 = H,	R_4=F.

Scheme I

for two protons of –CO-CH_2- group. Singlet at 6.30, 7.30 and 7.34 for one proton each at C_3, C_8 and C_5 respectively. The disappearances of other coumarin peak prove the product formation. All compounds have been screened for their antimicrobial activity and have been found to exhibit significant antibacterial activity.

Antimicrobial activity

All the synthesized compounds **2a-c**, **3a-c**, **4a-l** and **5a-c** were screened for their antibacterial activity against *S. aureus*, *S. typhi* and *E. coli* (**Table I**) by the drug diffusion method[18]. The zone of inhibition was measured in mm and was compared with standard drug. DMSO was used as a blank and streptomycin was used as antibacterial standard. All the compounds were tested at 100 µg/ mL and 250 µg/ mL concentration.

From the antimicrobial screening of the compounds **2a-c**, **3a-c**, **4a-l** and **5a-c**, it could observe that the introduction of fluorine, trifluoromethyl derivatives

Table I — Antibacterial activity of compounds **2a-c, 3a-c, 4a-l** and **5a-c**

Compd	Zone of inhibition in mm					
	S. aureus		*S. typhi*		*E. coli*	
	100µg	250µg	100µg	250µg	100µg	250µg
2a	-	11	11	13	14	15
2b	-	10	-	12	12	14
2c	-	9	-	10	-	11
3a	14	15	14	16	15	16
3b	12	13	14	15	14	15
3c	10	11	14	15	14	15
4a	13	14	12	14	14	15
4b	12	14	13	14	14	16
4c	-	12	12	14	13	14
4d	15	16	17	19	16	18
4e	13	15	17	20	15	17
4f	13	15	15	17	15	17
4g	14	16	15	17	16	19
4h	14	15	17	18	15	16
4i	11	13	12	14	12	13
4j	13	15	14	15	15	16
4k	14	16	15	17	16	18
4l	11	13	12	14	13	15
5a	16	18	15	17	16	17
5b	15	16	15	16	16	17
5c	14	16	14	15	15	17

Disc size: 6.35mm Standard: Streptomycin Control: DMSO
Duration: 24 hr. resistant (11mm/less) intermediate(12-14mm) sensitive(15mm/more)

4d-l and 4-thiazolidinones **5a-c** show significant antibacterial activities, also iminothiazolidinone derivatives **3a-c** show comparable antibacterial activity.

Experimental Section

Melting points were taken in open capillaries and are uncorrected. Homogeneity of the compounds was checked on TLC. IR spectra (ν in cm^{-1}) were recorded on a Perkin-Elmer FTIR, ^1H NMR on 300 MHz JEOL NMR AL300 using TMS as standard and mass spectra on a Shimadzu GC-MS QP-2010. All the compounds gave satisfactory elemental analysis.

1,3-Bis-(2-oxo-*2H*-benzopyran-6-yl)-thiourea 2a-c. General Procedure

6-Amino coumarins (**1a-c**, 0.01 mole) and carbon disulphide (2 mL) in absolute alcohol (15 mL) was refluxed for 6 hr, excess of alcohol was removed under pressure, it was then allowed to cool at room temperature. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol to give **2a-c**.

2a: Mol. Formula $C_{21}H_{16}N_2O_4S$, m.p. 253-56°C, yield: 86%; IR (KBr): 3354 (-NH), 1710 (>C=O), 1628, 1557, 1425, 1233, 1123, 824 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.32 (s, 6H, C_7, $C_{7'}$-CH_3), 6.41 (d, 2H, J = 9 Hz, C_3, $C_{3'}$-H), 7.32 (s, 2H, C_8, $C_{8'}$-H), 7.55 (s, 2H, C_5, $C_{5'}$-H), 8.03 (d, 2H, J = 9 Hz, C_4, $C_{4'}$-H), 9.39 (s, 2H, 2X > NH, D_2O exchangeable).

2b: Mol. Formula $C_{23}H_{20}N_2O_4S$, m.p. 272-74°C, yield: 80%; IR (KBr): 3342 (-NH), 1698 (>C=O), 1621, 1552, 1421, 1248, 869 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.36 (s, 6H, C_4, $C_{4'}$-CH_3), 2.40 (s, 6H, C_7, $C_{7'}$-CH_3), 6.36 (s, 2H, C_3, $C_{3'}$-H), 7.33 (s, 2H, C_8, $C_{8'}$-H), 7.61 (s, 2H, C_5, $C_{5'}$-H), 9.41 (s, 2H, 2X > NH, D_2O exchangeable).

2c: Mol. Formula $C_{19}H_{12}N_2O_4S$, m.p. 213-15°C, yield: 83%; IR (KBr): 3356 (-NH), 1705 (>C=O), 1623, 1551, 1435, 1223, 1131, 834 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.52 (d, 2H, J = 9 Hz, C_3, $C_{3'}$-H), 7.33-7.74 (m, 8H, coumarine moiety), 9.40 (s, 2H, 2X > NH, D_2O exchangeable).

3-(2-Oxo-*2H*-benzopyran-6-yl)-2-[2-oxo-*2H*-benzopyran-6-ylimino]-thiazolidin-4-ones 3a-c. General Procedure

A mixture of (**2a-c**, 0.01 mole), ethyl bromoacetate (0.01 mole) and fused sodium acetate (0.02 mole) in absolute alcohol (20 mL) was refluxed for 16 hr (TLC

monitored). The resulting mixture was cooled, excess of alcohol was removed under pressure, and the residue poured into crushed ice. The solid thus obtained was filtered, washed with water, dried and recrystallized from ethanol to give **3a-c**.

3a: Mol. Formula $C_{23}H_{16}N_2O_5S$, m.p. 185-87°C, yield: 74%; IR (KBr): 3065, 2969 (-CH), 1719 (>C=O), 1639, 1544, 1406, 1255, 1089, 1032, 807 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.28 (s, 3H, $C_{7'}$-CH_3), 2.45 (s, 3H, C_7-CH_3), 4.11 (s, 2H, CH_2), 6.40-6.48 (m, 2H, C_3, $C_{3'}$-H), 7.22-7.95 (m, 6H, $C_{8'}$, C_8, $C_{5'}$, C_5, $C_{4'}$ and C_4-H).

3b: Mol. Formula $C_{25}H_{20}N_2O_5S$, m.p. 199-201°C, yield: 69%; IR (KBr): 3061, 2962 (-CH), 1724 (>C=O), 1632, 1552, 1416, 1260, 1095, 1027, 803 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.18 (s, 3H, $C_{4'}$-CH_3), 2.39 (s, 3H, C_4-CH_3), 2.41 (s, 3H, $C_{7'}$-CH_3), 2.45 (s, 3H, C_7-CH_3), 4.09 (s, 2H, CH_2), 6.25 (s, 1H, $C_{3'}$-H), 6.31 (s, 1H, C_3-H), 7.02 (s, 1H, $C_{8'}$-H), 7.17 (s, 1H, C_8-H), 7.37 (s, 1H, $C_{5'}$-H), 7.50 (s, 1H, C_5-H); mass (*m/z* %): M^+ 460(100), 445(18), 418(23), 400(13), 333(22), 272(53), 245(59), 230(31), 212(44), 199(75), 189(14), 171(54), 131(46), 117(69), 104(85), 91(65).

3c: Mol. Formula $C_{21}H_{12}N_2O_5S$, m.p. 169-72°C, yield: 68%; IR (KBr): 3055, 2952 (-CH), 1715 (>C=O), 1645, 1554, 1399, 1247, 1092, 1044, 805 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.08 (s, 2H, CH_2), 6.49-6.58 (m, 2H, $C_{3'}$, C_3-H), 7.30-7.90 (m, 8H, $C_{8'}$, C_8, $C_{5'}$, C_5, $C_{7'}$, C_7, $C_{4'}$ and C_4-H).

3-(2-Oxo-*2H*-benzopyran-6-yl)-2-(2-oxo-*2H*-benzopyran-6-ylimino)-5-[1-(3-trifluoromethyl-phenyl)-methylidene]-thiazolidin-4-ones 4a-l. General Procedure

A mixture of (**3a-c**, 0.01 mole), aryl aldehydes (0.01 mole) and fused sodium acetate (0.015 mole) in glacial acetic acid (15 mL) was refluxed for 6 hr. The resulting mixture was cooled and the residue poured into crushed ice and neutralized by adding 10% sodium bicarbonate solution. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol to give **4a-l**.

4a: Mol. Formula $C_{30}H_{20}N_2O_5S$, m.p. 185-88°C, yield: 72%; IR (KBr): 3049, 2974 (-CH), 1710 (>C=O), 1634, 1540, 1253, 1065, 1020, 811 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.24 (s, 3H, $C_{7'}$-CH_3), 2.40 (s, 3H, C_7-CH_3), 6.36-6.45 (m, 2H, $C_{3'}$, C_3-H), 7.00-7.94 (m, 12H, Ar-H and -C=CH).

4b: Mol. Formula $C_{32}H_{24}N_2O_5S$, m.p. 199-201°C, yield: 76%; IR (KBr): 3065, 2969 (-CH), 1719 (>C=O), 1639, 1544, 1406, 1255, 1089, 1032, 807 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.17 (s, 3H, $C_{4'}$-CH_3), 2.38 (s, 3H, C_4-CH_3), 2.41 (s, 3H, $C_{7'}$-CH_3), 2.45 (s, 3H, C_7-CH_3), 6.25 (s, 1H, $C_{3'}$-H), 6.30 (s, 1H, C_3-H), 7.01-8.00 (m, 10H, Ar-H and -C=CH).

4c: Mol. Formula $C_{28}H_{16}N_2O_5S$, m.p. 170-73°C, yield: 68%; IR (KBr): 3033, 2949 (-CH), 1705 (>C=O), 1640, 1557, 1399, 1103, 1064, 809 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.45-6.55 (m, 2H, $C_{3'}$, C_3-H), 7.02-8.03 (m, 14H, Ar-H and -C=CH).

4d: Mol. Formula $C_{31}H_{19}F_3N_2O_5S$, m.p. 159-61°C, yield: 59%; IR (KBr): 3059, 2963 (-CH), 1717 (>C=O), 1644, 1546, 1422, 1273, 1079, 1040, 801 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.25 (s, 3H, $C_{7'}$-CH_3), 2.41 (s, 3H, C_7-CH_3), 6.39-6.46 (m, 2H, $C_{3'}$, C_3-H), 7.09-7.98 (m, 11H, Ar-H and -C=CH).

4e: Mol. Formula $C_{33}H_{23}F_3N_2O_5S$, m.p. 169-70°C, yield: 56%; IR (KBr): 3065, 2969 (-CH), 1719 (>C=O), 1639, 1544, 1406, 1255, 1089, 1032, 807 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.16 (s, 3H, $C_{4'}$-CH_3), 2.38 (s, 3H, C_4-CH_3), 2.40 (s, 3H, $C_{7'}$-CH_3), 2.45 (s, 3H, C_7-CH_3), 6.26 (s, 1H, $C_{3'}$-H), 6.48 (s, 1H, C_3-H), 7.03-8.03 (m, 9H, Ar-H and -C=CH); mass (*m/z* %): M^+ 616(8), 544(5), 475(9), 460(100), 445(9), 386(11), 272(24), 245(43), 231(26), 212(40), 199(83), 189(45), 171(72), 160(29), 144(30), 130(22), 115(58), 91(27), 77(21).

4f: Mol. Formula $C_{29}H_{15}F_3N_2O_5S$, m.p. 145-48°C, yield: 54%; IR (KBr): 3047, 2956 (-CH), 1715 (>C=O), 1640, 1547, 1409, 1241, 1099, 1054, 814 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.48-6.55 (m, 2H, $C_{3'}$, C_3-H), 7.02-8.03 (m, 13H, Ar-H and -C=CH).

4g: Mol. Formula $C_{30}H_{19}FN_2O_5S$, m.p. 145-48°C, yield: 60%; IR (KBr): 3077, 2979 (-CH), 1730 (>C=O), 1629, 1559, 1429, 1381, 1194, 1119, 828 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.20 (s, 3H, $C_{7'}$-CH_3), 2.37 (s, 3H, C_7-CH_3), 6.38-6.49 (m, 2H, $C_{3'}$, C_3-H), 6.88-8.06 (m, 11H, Ar-H and -C=CH).

4h: Mol. Formula $C_{32}H_{23}FN_2O_5S$, m.p. 154-57°C, yield: 62%; IR (KBr): 3075, 2980 (-CH), 1734 (>C=O), 1636, 1549, 1433, 1321, 1132, 1080, 834 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.15 (s, 3H, $C_{4'}$-CH_3), 2.31(s, 3H, C_4-CH_3), 2.38 (s, 3H, $C_{7'}$-CH_3), 2.41 (s, 3H, C_7-CH_3), 6.22 (s, 1H, $C_{3'}$-H), 6.34 (s, 1H, C_3-H), 6.98-7.96 (m, 9H, Ar-H and -C=CH).

4i: Mol. Formula $C_{28}H_{15}FN_2O_5S$, m.p. 139-42°C, yield: 64%; IR (KBr): 3077, 2975 (-CH), 1729 (>C=O), 1649, 1551, 1417, 1200, 1099, 1064, 811 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.46-6.53 (m, 2H, $C_{3'}$, C_3-H), 7.01-7.93 (m, 13H, Ar-H and -C=CH).

4j: Mol. Formula $C_{30}H_{19}FN_2O_5S$, m.p. 140-43°C, yield: 68%; IR (KBr): 3082, 2988 (-CH), 1734

(>C=O), 1629, 1559, 1429, 1381, 1194, 1119, 828 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.10 (s, 3H, $C_{7'}$-CH_3), 2.30 (s, 3H, C_7-CH_3), 6.38-6.49 (m, 2H, $C_{3'}$, C_3-H), 6.88-8.06 (m, 11H, Ar-H and -C=CH); mass (*m/z* %): M^+ 538(8), 516(11), 446(14), 432(100), 358(11), 259(21), 231(33), 217(22), 198(37), 185(75), 175(30), 157(45), 144(15), 130(22), 116(14), 103(21), 89(17), 77(39).

4k: Mol. Formula $C_{32}H_{23}FN_2O_5S$, m.p. 154-56°C, yield: 71%; IR (KBr): 3072, 2981 (-CH), 1739 (>C=O), 1633, 1563, 1377, 1160, 1110, 834 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.15 (s, 3H, $C_{4'}$-CH_3), 2.37 (s, 3H, C_4-CH_3), 2.40 (s, 3H, $C_{7'}$-CH_3), 2.43 (s, 3H, C_7-CH_3), 6.25 (s, 1H, $C_{3'}$-H), 6.33 (s, 1H, C_3-H), 6.94-7.86 (m, 9H, Ar-H and C=CH).

4l: Mol. Formula $C_{28}H_{15}FN_2O_5S$, m.p. 132-35°C, yield: 64%; IR (KBr): 3074, 2978 (-CH), 1725 (>C=O), 1644, 1541, 1245, 1089, 1059, 804 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.46-6.53 (m, 2H, $C_{3'}$, C_3-H), 7.04-8.01 (m, 13H, Ar-H and -C=CH).

3-(2-Oxo-*2H*-benzopyran-6-yl)-thiazolidine-2,4-di-ones 5a-c. General Procedure

A mixture of (**3a-c**, 7 mmole) was treated with 2% HCl (15 mL) and was refluxed for 3 hr. The resulting mixture was cooled and the reaction mixture was neutralized with solid sodium bicarbonate. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol to give **5a-c**.

5a: Mol. Formula $C_{13}H_9NO_4S$, m.p. 165-67°C, yield: 42%; IR (KBr): 2979 (-CH), 1739, 1715 (>C=O), 1542, 1464, 1269, 1083, 1012, 855 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.37 (s, 3H, C_7-CH_3), 4.27 (s, 2H, CH_2), 6.39 (d, 1H, *J* = 9 Hz, C_3-H), 7.34 (s, 1H, C_8-H), 7.39 (s, 1H, C_5-H), 7.89 (d, 1H, *J* = 9 Hz, C_4-H).

5b: Mol. Formula $C_{14}H_{11}NO_4S$, m.p. 175-77°C, yield: 45%; IR (KBr): 2969 (-CH), 1744, 1710 (>C=O), 1558, 1446, 1269, 1075, 1020, 853 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.21 (s, 3H, C_4-CH_3), 2.40 (s, 3H, C_7-CH_3), 4.26 (s, 2H, CH_2), 6.30 (s, 1H, C_3-H), 7.30 (s, 1H, C_8-H), 7.34 (s, 1H, C_5-H).

5c: Mol. Formula $C_{12}H_7NO_4S$, m.p. 149-51°C, yield: 40%; IR (KBr): 2964 (-CH), 1740, 1707 (>C=O), 1565, 1436, 1244, 1065, 1027, 833 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.25 (s, 2H, CH_2), 6.45 (d, 1H, *J* = 9 Hz, C_3-H), 7.30-7.94 (m, 4H, C_4, C_5, C_7 and C_8-H).

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