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Synthesis and antimicrobial screening of 5-benzylidine-2-imino-3-(2-oxo-2*H*-benzopyran-6-yl)-thiazolidin-4-one and its derivatives

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2-imino-3-(2-oxo-2*H*-benzopyran-6-yl)-thiazolidin-4-one **4a-c** have been synthesized from 6-amino-coumarin as starting material. Condensation of iminothiazolidinone with different substituted aromatic aldehydes occurred at reactive methylene group present at C-5 position of thiazolidin-4-one ring and resulted in the formation of 5-arylidene-2-imino-3-(2-oxo-2*H*-benzopyran-6-yl)-thiazolidin-4-one **5a-i**. The formation of 2-imino-3-(2-oxo-2*H*-benzopyran-6-yl)-thiazolidin-4-one **4c** was confirmed by hydrolysis with 2% HCl to give 3-(2-oxo-2*H*-benzopyran-6-yl)-thiazolidine-2,4-dione **6c**. The structures of the compounds **2a-c**, **4a-c**, **5a-i** and **6c** have been established on the basis of spectral and analytical data. The compounds **5a-i** has been screened for their antimicrobial activity and has been found to exhibit significant antibacterial activities.

Keywords: Aminocoumarin, iminothiazolidinone, 4-thiazolidin-one, aromatic aldehydes, antimicrobial activity

There has been considerable interest in the chemistry of thiazolidin-4-one ring system, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities[1]. Thiazolidin-4-one ring occurs in nature; thus actithiazic acid [(–) 2-(5-carboxypentyl) thiazolidin-4-one)] isolated from *Streptomyces* strains exhibits highly specific *invitro* activity against *Mycobacterium tuberculosis*[2]. Thiazolidinone moiety are known to exhibit diverse bioactivities such as CNS stimulant anthelmintic[3], antibacterial[4], antifungal[5], analgesic[6,7], diurals, anti-inflammatory, anticonvulsant[8], antimicrobial[9], anti cancer[10], and anti-HIV[11]. Hence it is thought of interest to accommodate thiazolidin-4-one and 6-amino counarin in a single molecular framework and screen for their antimicrobial activity.

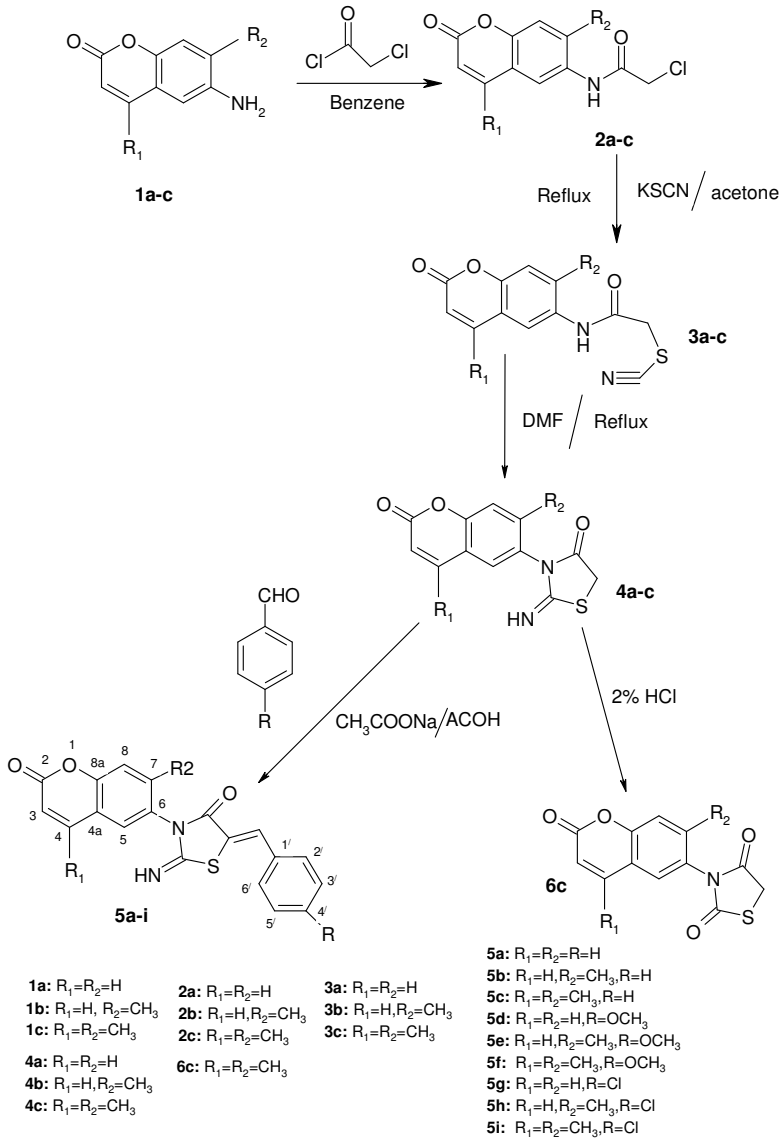
Result and Discussion

2-chloro-*N*-[2-oxo-2*H*-benzopyran-6-yl]-acetamide **2a-c** was obtained by refluxing 6-aminocoumarin **1a-c** and chloroacetyl chloride in dry benzene. Compound **2a-c** on treatment with potassium thiacyanate in acetone was expected to give cyclized product 2-imino-3-(2-oxo-2*H*-benzopyran-6-yl)-thiazolidin-4-one **4a-c.** However 2-(thiocyanato)-acetamido-coumarin-6-yl **3a-c** intermediate was obtained which showed a sharp band in IR spectrum at 2150 cm^{-1} for -CN stretching. The cyclization of 2-(thiocyanato)-acetamide derivatives were carried out in highly polar aprotic solvent DMF at 150-155 ^oC for 4 hr. to afford **4a-c**. In its IR spectrum it showed absence of band at 2150 cm^{-1} for –CN. The ^1H NMR spectrum of compound **4c** in $CDCl_3$ showed a singlet at 4.10 for two protons. A broad signal in ^1H NMR was observed at δ 8.05 for the imino group which is D_2O exchangeable. The mass spectrum of **4c** showed molecular ion peak at *m/z* 288 which is also base peak.

In order to confirm the structure of 2-imino-3-(2-oxo-2*H*-benzopyran-6-yl) thiazolidin-4-one **4a-c**. Compound **4c** was hydrolyzed with HCl to yield 3-(2-oxo-2*H*- benzopyran-6-yl)-thiazolidin-2,4-dione **6c**. The IR spectrum of compound **6c** in KBr showed band at 2969 for –CH stretching, at 1725 and 1690 cm^{-1} for >C=O Groups, along with other bands at 1558, 1446, 1269, 1075, 1020, 853 cm^{-1} etc. The disappearance of bands at 3440 cm^{-1} (-NH) group further proved the product formation. The reactive methylene group present at C-5 of 2-iminothiazolidin-4-one **4a-c** has been condensed with various aromatic aldehydes to yield 5-arylidene-2-imino-3-(2-oxo-2*H*-benzopyran-6-yl)-4-thiazolidinone **5a-i (Scheme I)**. The IR spectrum of compound **5c** in KBr showed band at 3354(-NH), 3065, 2969 for –CH stretching, at 1710 cm^{-1} for >C=O of coumarin, along with other bands at 1639, 1406, 1255, 1089, 807 cm^{-1}.

Anti-microbial activity

The compounds **5a-i** has been screened for their antimicrobial activity by cup plate[12] method and have found to exhibit significant biological activity (**Table 1**). The compounds **5a-i** screened for their antibacterial activity against *Bacillus subtilis*, *Escherichia coli.* and antifungal activity against *Candida albicans*, *Aspergillus niger* by cup plate method at different concentrations (50 and 100 μg/mL) using DMSO as solvent. The zone of



Scheme I

inhibition of the growth was measured in mm. The activity was compared with the standard drugs. A commercial antibacterial streptomycin (50, 100 μg/mL) and antifungal griseofulvin (50, 100 μg/mL) drug was also tested under similar conditions for comparison. The results of antimicrobial activity shows that compounds **5f**, **5i** have significant activity compared to the standards, the rest of the compounds show moderate to good activity.

Experimental Section

General: Melting points were taken in open capillaries and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer FTIR, NMR (^1H and ^{13}C) on 300 MHz JEOL NMR AL300 using TMS as standard and $CDCl_3$ as a solvent. Chemical shifts are given in parts per million (ppm). Mass spectra (GC-MS) were taken on Shimadzu GC-MS QP-2010. Elamental analyses were carried out at IIT, Mumbai. All products were purified by recrystallisation. The reaction was followed up and purity of the products is carried out on pre-coated TLC plates (Silica gel 60 F_{254}, Merck), visualizing the spots in ultraviolet light. Column chromatography is performed on Merck silica gel (60-120 mesh).

2-Chloro-*N*-[2-oxo-2H-benzopyran-6-yl]-acetamide **2a-c** Chloroacetylchloride (0.02 mole) was added to a solution of 6-amino-coumarin (0.02 mole)

Table I — Antimicrobial activities of **5a-i**

Compd	*B. subtilis*		*E. coli*		*C. albicans*		*A. niger*	
	50 ppm	100 ppm	50 ppm	100 ppm	50 ppm	100 ppm	50 ppm	100 ppm
5a	+	++	+	++	-	+	+	++
5b	+	+ +	+	+ +	+	+ +	+	++
5c	+ +	+ +	+	+ +	+	+	+	++
5d	+	+ +	+ +	+ +	+	+ +	+	+ +
5e	+	+ +	+	+ +	+	++	+	++
5f	++	+ +++	++	+ +++	++	++	++	+++
5g	+	+ +	+	+ +	+	+ +	+	+ +
5h	+ +	+ +	+ + +	+ + +	++	+ +	+	+ +
5i	+ +	++++	+ +	+ + +	++	+ ++	++	+ ++
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

in dry benzene (60 mL) at 0-5°C under stirring, which was subsequently refluxed for 6 hr. on water-bath. The completion of the reaction was monitored by TLC. The solvent was removed by distillation. The solid obtained was recrystallised by ethyl acetate-hexane to yield compound **2a-c**

2a: Mol. Formula $C_{11}H_8O_3NCl$, m.p. 170°C, yield 68%; IR (KBr): 3370 (-NH), 3050 (arom -CH), 1720 (C=O), 1682, 1028, 689 (C-Cl) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.25 (s, 2H, CH_2), 6.28 (d, 1H, *J* = 9Hz, C_3-H), 7.20 (d, 1H, *J* = 9Hz, C_8-H), 7.25 (d, 1H, *J* = 9Hz, C_7-H), 7.28 (s, 1H, C_5-H), 7.60 (d, 1H, *J* = 9Hz, C_4-H), 8.35 (s, 1H, NH, D_2O-exchangable). Cald. for $C_{11}H_8O_3NCl$: C, 55.60; H, 3.39; N, 5.89, Found: C, 55.48; H, 3.29; N, 5.89%

2b: Mol. Formula $C_{12}H_{10}O_3NCl$, m.p. 185°C; yield 65%; IR: (KBr): 3373 (-NH), 3052 (arom-CH), 1725(C=O), 1681, 1028, 691(C-Cl) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 4.30 (s, 2H, CH_2), 6.25 (d, 1H, *J* = 9Hz, C_3-H), 7.21 (s, 1H, C_5-H), 7.25 (s, 1H, C_8-H), 7.55 (d, 1H, *J* = 9Hz, C_4-H), 8.30 (s, 1H, NH, D_2O-exchangable); Calcd for $C_{12}H_{10}O_3NCl$: C, 57.27; H, 4.01; N, 5.89. Found: C, 57.15; H, 4.05; N, 5.76%.

2c: Mol. Formula $C_{13}H_{12}O_3NCl$, m.p. 210°C, yield 60%; IR: (KBr): 3372 (-NH), 3045 (arom -CH), 1720 (C=O), 1685, 1025, 687(C-Cl) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.30 (s, 2H, CH_2), 6.21 (s, 1H, C_3-H), 7.19 (s, 1H, C_8-H), 7.28 (s, 1H, C_5-H), 8.43 (s, 1H, -NH, D_2O-exchangable); MS, *m/z* (%): (M+) 265 (100), (M+2) 267 (34), 247(15), 216(40), 189(66), 160(44), 77(32). Calcd for $C_{13}H_{12}O_3NCl$: C, 58.77; H, 4.55; N, 5.27. Found: C, 58.62; H, 4.49; N, 5.17%.

2-(thiocyanato)-acetamido-coumarin **3a-c** A mixure of **2a-c** (0.014 mole), and KSCN (0.02 mole) and dry acetone (40 mL) was refluxed on water-bath for 4 hr. (TLC monitored). The resulting mixture was cooled, excess of acetone was removed by distillation, and the residue was 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 $C_{12}H_8O_3N_2S$, m.p.165°C, yield 63%; IR: (KBr): 3425 (-NH), 3019, 2923(-CH), 2154 (-CN), 1720(>CO), 1652, 1540, 1391, 1052, 886 cm^{-1}; **3b**: Mol. Formula $C_{13}H_{10}O_3N_2S$; m.p.170 °C, yield 66%; IR: (KBr): 3435 (-NH), 3019, 2945 (-CH), 2157 (-CN), 1725 (>CO), 1660, 1539, 1394, 1050, 882 cm^{-1}.

3c: Mol. Formula $C_{14}H_{12}O_3N_2S$; m.p.174°C yield 68%; IR: (KBr): 3440 (-NH), 3017, 2944 (-CH), 2160 (-CN), 1727 (>CO), 1655, 1538, 1384, 1055, 887 cm^{-1}.

2-imino-3-(2-oxo-2*H*-benzopyran-6-yl) thiazolidin-4-one **4a-c** Finely powdered 1.0 g of 2-thiacyanto-acetamido-amino coumarin **3a-c** was refluxed in 20 mL dimethlyformamide in an oil-bath at 150-60°C for 6 hr. The solvent was removed by distillation under vacuum and the crude product was crystallized from ethanol to give crystals of 2-imino-4-thiazolidinone.

4a: Mol. Formula $C_{12}H_8O_3N_2S$, m.p.158°C; yield 62%; IR: (KBr): 3429 (NH), 3055, 2952 (-CH), 1725 (>CO), 1650, 1554, 1399, 1247, 1092, 1044, 805 cm^{-1} etc. ^1H NMR ($CDCl_3$): δ 4.20 (s, 2H, CH_2), 6.30 (d, 1H, *J* = 8.5Hz, C_3-H), 7.21 (d, 1H, *J* = 8.5Hz, C_8-H), 7.25 (d, 1H, *J* = 8.5Hz, C_7-H), 7.35 (s, 1H, C_5-H), 7.82 (d, 1H, *J* = 8.5Hz, C_4-H), 8.30 (s, 1H, NH, D_2O-exchangable), Calcd. for $C_{12}H_8O_3N_2S$: C, 55.38; H, 3.10; N, 10.76; S, 12.32. Found: C, 55.51; H, 3.12; N, 10.71; S, 12.39%.

4b: Mol. Formula $C_{13}H_{10}O_3N_2S$; m.p.165°C, yield 65%; IR: (KBr): 3432 (NH), 3040, 2950 (-CH), 1721(>CO), 1656, 565, 1400, 1240, 1092, 1041, 890 cm^{-1} ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 4.15 (s, 2H, CH_2), 6.26(d, 1H, *J* = 9Hz, C_3-H), 7.19 (s, 1H, C_8-H), 7.32 (s, 1H, C_5-H), 7.80 (d, 1H, *J* = 8.5Hz, C_4-H), 8.28 (s, 1H, NH, D_2O-exchangable). Calcd. for $C_{13}H_{10}O_3N_2S$: C, 56.92; H, 3.67; N, 10.21; S, 11.69. Found: C, 57.01; H, 3.70; N, 10.18; S, 11.78%.

4c: Mol. Formula $C_{14}H_{12}O_3N_2S$; m.p.168°C yield 68%; IR: (KBr): 3440 (NH), 3045, 2923 (-CH), 1723(>CO), 1652, 1563, 1410, 1230, 1095, 1041, 859 cm^{-1} ^1H NMR ($CDCl_3$): δ 2.27 (s, 3H, CH_3), 2.40(s, 3H, CH_3), 4.10 (s, 2H, CH_2), 6.27 (s, 1H, C_3-H), 7.18 (s, 1H, C_8-H), 7.35 (s, 1H, C_5-H), 8.35 (s, 1H, NH, D_2O-exchangable). MS: *m*/*z* (%): (M+) 288, 214(40), 188(50), 160(25), 170(18), 145(10), 130(30), 91(38), 77(60). Calcd. for $C_{14}H_{12}O_3N_2S$: C, 58.32; H, 4.20; N, 9.72; S, 11.12. Found: C, 58.44; H, 4.24; N, 9.65; S, 11.25%.

5-arylidene-2-imino-3-(2-oxo-2*H*-benzopyran-6-yl)-4-thiazolidinone **5a-i** A mixture of **4a-c** (0.01 mole), aryl aldehydes (0.01 mole) and fused sodium acetate (0.015 mole) in gl. 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 **5a-i**.

5a: Mol. Formula $C_{19}H_{12}O_3N_2S$; m.p. 185°C yield 60%; IR: (KBr): 3356 (-NH), 1705 (>C=O), 1670, 1551, 1435, 1223, 1131, 1025, 834 cm^{-1}; ^1H NMR ($CDCl_3$): 6.23 (d, 1H, *J* = 9.3Hz, C_3-H), 6.80-7.30 (m, 3H, C_8-H, C_7-H, C_5-H), 7.55 (m, 4H, Ar-H), 7.65 (d, 1H, *J* = 9Hz, C_4-H), 8.05 (s, 1H, C=CH-Ar), 8.32 (s, 1H, NH, D_2O-exchangable).

5b: Mol. Formula $C_{20}H_{14}O_3N_2S$; m.p.168°C yield 68%; IR: (KBr): 3342 (-NH), 1725 (>C=O), 1668, 1552, 1421, 1248, 1030, 869 cm^{-1}; ^1H NMR ($CDCl_3$): 2.40 (s, 3H, CH_3), 6.24 (d, 1H, *J* = 9Hz, C_3-H), 6.85 (s, 1H, C_8-H), 7.20 (s, 1H, C_5-H), 7.58 (m, 4H, Ar-H), 7.70 (d, 1H, *J* = 9Hz, C_4-H), 8.08 (s, 1H, C=CH-Ar), 8.29 (s, 1H, NH, D_2O-exchangable).

5c: Mol. Formula $C_{21}H_{16}O_3N_2S$; m.p. 210°C yield 68%; IR: (KBr): 3354 (-NH), 1710 (>C=O), 1650, 1557, 1425, 1233, 1123, 824 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.26 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.25 (s, 1H, C_3-H), 6.88 (s, 1H, C_8-H), 7.23 (s, 1H, C_5-H), 7.50 (m, 4H, Ar-H), 8.03 (s, 1H, C=CH-Ar), 8.32 (s, 1H, NH, D_2O-exchangable).

5d: Mol. Formula $C_{20}H_{14}O_4N_2S$; m.p. 182°C, yield 55%; IR: (KBr): 3329 (NH), 3045, 2950 (-CH), 1721 (>CO), 1655 (>C=O), 1550, 1400, 1032, 805 cm^{-1} ^1H NMR ($CDCl_3$): δ 3.65 (s, 3H, OCH_3), 6.25 (d, 1H, *J* = 8.7Hz, C_3-H), 6.85-7.30 (m, 3H, C_8-H, C_7-H,C_5-H), 7.35 (d, 2H, *J* = 7.5Hz, 2′-6′-H), 7.40 (d, 2H, *J* = 7.5Hz, 3′-5′-H), 7.68 (d,1H, *J* = 9Hz, C_4-H), 8.05 (s, 1H, C=CH-Ar), 8.34 (s, 1H, NH, D_2O-exchangable);

5e: Mol. Formula $C_{21}H_{16}O_4N_2S$; m.p. 188°C yield 58%; IR: (KBr): 3340 (-NH), 3016, 2934 (-CH), 1723 (>CO), 1655, 1538, 1384, 1050, 897 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 6.20 (d, 1H, *J* = 9Hz, C_3-H), 6.80 (s, 1H, C_8-H), 7.10 (s, 1H, C_5-H), 7.30 (d, 2H, *J* = 7.5Hz, 2′-6′-H), 7.50 (d, 2H, *J* = 7.5Hz, 3′-5′-H), 7.68 (d, 1H, *J* = 9.3Hz, C_4-H), 8.03 (s, 1H, C=CH-Ar), 8.30 (s, 1H, NH, D_2O-exchangable).

5f: Mol. Formula $C_{22}H_{18}O_4N_2S$; m.p. 190°C yield 57%. ^1H NMR ($CDCl_3$): 2.21 (s,3H, CH_3), 2.42 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 6.23 (s, 1H, C_3-H), 6.85 (s, 1H, C_8-H), 7.35 (s, 1H, C_5-H), 7.35 (d, 2H, *J* = 7.5Hz, 2′-6′-H), 7.60 (d, 2H, *J* = 7.5Hz, 3′-5′-H), 8.06 (s, 1H, C=CH-Ar), 8.28 (s, 1H, NH, D_2O-exchangable).

5g: Mol. Formula $C_{19}H_{11}O_3N_2SCl$; m.p. 168°C yield 65%; IR: (KBr): 3338 (-NH), 3029, 2940 (CH-arom.), 1727 (>CO), 1655, 1538, 1384, 1055cm^{-1}. ^1H NMR ($CDCl_3$): 6.28 (d, 1H, *J* = 9Hz, C_3-H), 7.05-7.55 (m, 3H, C_8-H, C_7-H, C_5-H), 7.40 (d, 2H, *J* = 7.5Hz, 2′-6′-H), 7.65 (d, 2H, *J* = 7.5Hz, 3′-5′-H), 7.72 (d. 1H, *J* = 9Hz, C_4-H), 8.08 (s, 1H, C=CH-Ar), 8.35 (s, 1H, NH, D_2O-exchangable).

5h: Mol. Formula $C_{20}H_{13}O_3N_2SCl$; m.p. 175°C yield 62%; IR: (KBr): 3320 (-NH), 3018, (-CH), 172 (>CO), 1663 ,1531, 1382, 1065, 887 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.38 (s, 3H, CH_3), 6.25 (d, 1H, *J* = 9Hz, C_3-H), 6.85 (s, 1H, C_8-H), 7.18 (s, 1H, C_5-H), 7.44 (d, 2H, *J* = 7.5Hz, 2′-6′-H), 7.68 (d, 2H, *J* = 7.3Hz, 3′-5′-H), 7.75 (d. 1H, *J* = 9Hz, C_4-H), 8.05 (s, 1H, C=CH-Ar), 8.28 (s, 1H, NH, D_2O-exchangable).

5i: Mol. Formula $C_{21}H_{15}O_3N_2SCl$; m.p. 182°C yield 68%; IR: (KBr): 3340 (-NH), 3011, 2944 (-CH), 1727 (>CO), 1658, 1538, 1394, 1045, 885 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 6.26 (s, 1H, C_3-H), 7.05 (s, 1H, C_8-H), 7.18 (s, 1H, C_5-H), 7.50 (d, 2H, *J* = 7.5Hz, 2′-6′-H), 7.70 (d, 2H, *J* = 7.5Hz, 3′-5′-H), 8.02 (s, 1H, C=CH-Ar), 8.30 (s, 1H, NH, D_2O-exchangable).

3-(2-Oxo-2*H*-benzopyran-6-yl)-thiazolidine-2,4-dione **6c** A mixture of **4c** (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 **6c**. Mol. Formula $C_{14}H_{11}NO_4S$, m.p. 175-77°C, yield: 45%; IR: (KBr): 2966 (-CH), 1725, 1690 (>C=O), 1550, 1440, 1269, 1075, 1020, 893 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 6.26 (s, 1H, C_3-H), 7.33 (s, 1H, C_8-H), 7.35(s, 1H, C_5-H). ^{13}C NMR ($CDCl_3$): 14.6 (CH_3), 18.6 (CH_3), 42.5(CH_2), 114.5(C_3), 115.5-133.5 (5-aromatic carbon), 150(C_{8a}), 151.0(C_4), 160.0(C_2), 165.2(CO), 170.0(N-CO-CH_2).

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