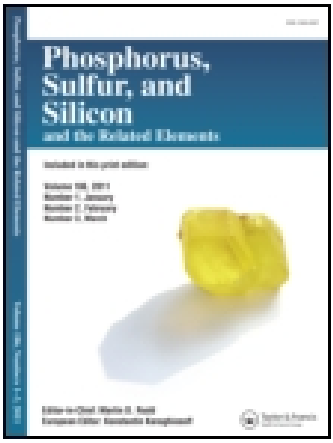

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Synthetic and Biological Studies on 4-Aryloxymethyl Coumarinyl Thiazolidinones

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*A series of new thiazolidinonyl-4-aryloxymethylcoumarins (**4a–h**) have been synthesized from 4-Bromomethylcoumarins (**1a–b**) and 4-aryliminomethyl-phenols (**2a–d**). Structures of all the new compounds are elucidated by elemental analyses, IR, ^{1}H NMR, and mass spectral data. All these compounds have been subjected to in-vitro antimicrobial and in-vivo anti-inflammatory screening.*

Keywords Coumarins; thiazolidinone; 4-bromomethylcoumarins; antimicrobial; anti-inflammatory

INTRODUCTION

Thiazolidinones possessing aryl groups at C-2 and N-3 positions have been found to exhibit anti-tubercular[1] and HIV protease inhibiting[2] activities. Their potential to inhibit inflammation caused by phlogistic agents has been well supported by in-vivo studies in animal models.[3–5] The ability of coumarins to prevent the formation of 5-HETE and 5-HHE in the Arachidonic acid metabolism and their role in inhibiting inflammation has been well established.[6,7] Our earlier work has revealed that linking biocompatible fragments like Vanillin[8] and

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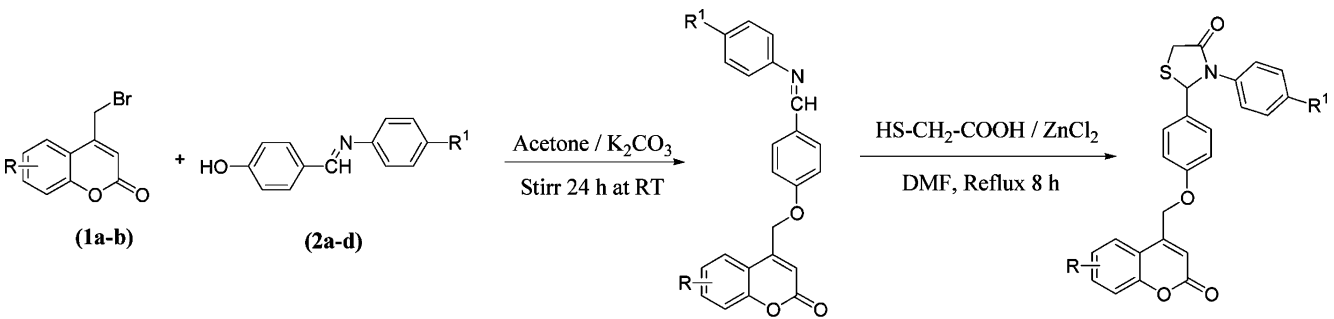
Paracetamol[9] at the allylic position, with respect to the C_3-C_4 double bond, results in 4-aryloxymethylcoumarins with significant inflammation inhibiting and interesting photophysical properties. The introduction of pyrazole ring in the phenoxy moiety was accomplished by using pre-functionalized phenols, leading to a library of pyrazole linked 4-aryloxymethyl coumarins, which were found to be potential anti-inflammatory agents.[10] In view of these reports, it was thought of interest to introduce the thiazolidinone ring at para position in the phenoxy moiety of 4-aryloxymethylcoumarins, by nucleophilic addition and *N*-heterocyclization route (Scheme 1).

CHEMISTRY

The present synthetic strategy begins with the generation of the required 4-bromomethylcoumarins[11] (**1a–b**) by the Pechmann cyclisation of *meta* and *para* cresols with 4-bromoethylacetoacetate[12] (Scheme 1). In view of the poor reactivity of the *p*-carbonyl group observed in 4-aryloxymethyl coumarins,[10] pre-functionalized phenols (**2a–d**) (obtained by the reaction of *p*-formyl phenol and aromatic amines) were used for a room temperature allylic S_N reaction under standard acetone-potassium carbonate conditions generating the required precursors (**3a–h**) in high yields. The azomethine group in (**3a–h**) underwent nucleophilic addition with thioglycollic acid followed by dehydration due to N-CO bond formation. The reaction was carried out in dimethyl formamide under refluxing conditions. The products **(4a–h)** were isolated by decomposing the cooled reaction mixture with ice followed by treatment with 10% $NaHCO_3$ to remove excess of thioglycollic acid. The resulting solids were found to be high melting solids and were purified by crystallization from DMF.

RESULTS AND DISCUSSION

The IR spectrum of 4-{4-[(4-chloro-phenylimino)-methyl]-phenoxymethyl}-6-methyl-chromen-2-one (**3c**) (R = 6-CH_3, R^1 = Cl) showed lactone carbonyl stretching frequency at 1699 cm^{-1} and stretching frequency for C=N group at 1624 cm^{-1}. The PMR spectrum of **(3c)** exhibited a singlet due to CH_3 protons at 2.37 δ ppm, C_4-CH_2 at 5.29 δ ppm and C_3-H at 6.56 δ ppm. The aromatic protons resonated in the range of 6.96–8.33 δ ppm. The azomethine proton appeared downfield as a singlet at 9.84 δ ppm. The observed chemical shifts of C_4-CH_2 and C_3-H are in agreement with our earlier work on 4-aryloxymethyl coumarins.[11]



1a, R = 6-CH_3; 1b, R = 7-CH_3

2a, R^1 = H; 2b, R^1 = CH_3; 2c, R^1 = Cl; 2d, R^1 = Br

SCHEME 1

The IR spectrum of 2-[4-(7-methyl-2-oxo-2*H*-chromen-4-ylmethoxy)-phenyl]-3-phenyl-thiazolidin-4-one **(4e)** (R = 7-CH_3, R^1 = H) showed lactone carbonyl stretching at 1715 cm^{-1} and carbonyl of thiazolidinone stretching at 1680 cm^{-1}. The PMR spectrum of 2-[4-(6-methyl-2-oxo-2*H*-chromen-4-ylmethoxy)-phenyl]-3-phenyl-thiazolidin-4-one **(4a)** (R = 6-CH_3, R^1 = H) showed a singlet at 2.45 δ ppm due to C_6-CH_3 protons. A singlet appeared at δ 3.56 was due to methylene protons (S-CH_2) of thiazolidinone ring. Singlets observed at 4.3, 5.24, and 6.64 δ ppm are due to S-CH-N, C_4-CH_2 and C_3-H protons, respectively. The aromatic protons resonated as multiplet in the range of 6.98–7.93 δ ppm. The disappearance of the low field singlet observed in compounds (**3**) and the appearance of an upfield singlet at 4.3 δ ppm, characteristic of thiazolidinones[13] confirmed the addition of thioglycollic acid across the azomethine linkage in compounds (**3**). The EI Mass spectrum of 2-[4-(6-methyl-2-oxo-2*H*-chromen-4-ylmethoxy)-phenyl]-3-phenyl-thiazolidin-4-one **(4a)** (R = 6-CH_3, R^1 = H) showed no molecular ion peak but base peak appeared at *m/z* 145 (100%) due to homolytic cleavage of the allylic CH_2-O bond with the subsequent loss of carbon monoxide, which is in agreement with literature reports.[14]

PHARMACOLOGY

Albino rats of Wister strain of either sex weighing between 150–230 g were selected. The animals were kept on a standard diet and allowed food and water ad libitum. Ibuprofen was used as standard for anti-inflammatory activity administered orally at a dose of 45 mg kg^{-1} body weight in a suspension of 5% gum acacia. Carrageenin (0.1 mL; 1%) suspended in 0.5% carboxymethyl cellulose (CMC). Data were analyzed by one-way ANOVA (F-test) followed by Dunnet multiple comparison test. Differences below the 0.01 level ($P < 0.01$) were considered as statistically significant.

ACUTE TOXICITY STUDIES

For testing the acute toxicity potential of the test compounds, albino mice of either sex weighing 25–50 g were selected, separated in to 10 groups each containing six mice. The dosage was varied from 100 up to 3000 mg kg^{-1} body weight. The mice were continuously observed for 24 h for any signs of increased or decreased motor activity, ataxia, tremors, convulsions, sedation, lacrimation, and so on. After 24 h, the mice were sacrificed; stomach, intestine and liver were inspected under the magnifying lens for any ulcer hemorrhagic spots. The whole experiment on animals was cleared from Institutional Animal Ethics Committee

(IAEC). All the compounds showed good safety profile until the highest dose of 3000 mg kg^{-1} in albino rats. Amongst the behavioral changes no sedation, convulsions and tremors were observed. Post-mortem examination of the stomach and intestine did not reveal any ulcer and hemorrhagic spots. Liver was also examined and showed no necrosis.

ANTI-INFLAMMATORY ACTIVITY (CARRAGEENAN INDUCED RAT PAW OEDEMA METHOD)

Carrageenan induced rat paw oedema inhibition method according to Winter et al.[15] was employed during the present study. Ten groups of rats (six in each group) received Carrageenan (0.1 mL of 1% Carrageenan in 0.5 mL of carboxy methyl cellulose) sub plantarly in the left hind paw. One group was kept as control. Other nine groups received standard and test compounds at a dose of 300 mg kg^{-1} body weight in 0.2 mL of 5% gum acacia only 1 h prior to the sub plantar injection of Carrageenan. The paw edema volume was measured with the help of plethysmograph by mercury displacement method at zero hour immediately after injecting Carrageenan. Then, the edema volume was measured at 1 h interval for 5 h. Control groups received 0.2 mL of 5% gum acacia. Ibuprofen 45 mg kg^{-1} body weight in 0.2 mL of 5% gum acacia was used as the standard. The results indicated that, when compared with the control, compounds (**4b**), (**4d**), and (**4g**) showed significant reduction in edema volume. The results depicting edema volumeand percentage inhibition of inflammation at various time intervals have been summarized in Table I. It can be seen from Table I that all the compounds exhibited a delayed on set of action, which achieved a significant level only at the end of 2 h. Further a steady increase was observed even at the end of 5 h. Compounds (**4d**) and (**4g**) were the best in the present series. Compounds (**4a**), (**4c**), (**4e**), (**4f**), and (**4h**) have not shown significant activity to warrant further investigation.

ANTIMICROBIAL ACTIVITY

The antimicrobial screening for all the compounds was carried out against Gram positive and Gram-negative species with *B. subtilis* and*E. coli* respectively. *A. niger* and *C. albicans* were employed as fungal strains. DMF was used as solvent control. The reference drugs used were *Ciprofloxacin* and *Gresiofulvin*. The tests were carried out by cup plate method[16] at a concentration of 100 μg mL^{-1}. After 48 h of incubation at 37°C, the zone of inhibition was measured in mm. The percent inhibition of the test compounds was related to the standard

TABLE I Results of Antiinflammatory Activity of Compounds (4a–h)

Compd.	R	R^1	Oedema volume at different time intervals* (Percentage Oedema Inhibition)				
			1 h	2 h	3 h	4 h	5 h
Control	—	—	0.876 ± 0.075	1.275 ± 0.055	1.358 ± 0.063	1.565 ± 0.046	1.702 ± 0.036
Ibuprofen	—	—	$0.518 \pm 0.033^{**}$(40.87)	$0.47 \pm 0.027^{**}$ (63.14)	$0.433 \pm 0.028^{**}$ (68.12)	$0.4 \pm 0.044^{**}$ (74.44)	$0.408 \pm 0.064^{**}$ (76.03)
4a	6-CH_3	H	0.81 ± 0.0688^{a}(7.5)	1.15 ± 0.049^{b}(9.80)	1.285 ± 0.051^{c}(5.38)	1.54 ± 0.051^{d} (1.60)	1.531 ± 0.078^{e} (10.05)
4b	6-CH_3	CH_3	$0.701 \pm 0.047^{**}$ (19.98)	$0.74 \pm 0.034^{**}$ (41.96)	$0.641 \pm 0.045^{**}$ (52.80)	$0.613 \pm 0.025^{**}$ (60.83)	$0.603 \pm 0.031^{**}$ (64.57)
4c	6-CH_3	Cl	0.748 ± 0.043^{f} (14.61)	1.203 ± 0.021^{g}(5.64)	1.34 ± 0.04^{h} (1.34)	1.408 ± 0.036^{i}(10.03)	1.535 ± 0.038^{j}(9.8)
4d	6-CH_3	Br	$0.61 \pm 0.046^{**}$ (30.37)	$0.548 \pm 0.023^{**}$ (57.02)	$0.475 \pm 0.039^{**}$ (65.02)	$0.416 \pm 0.037^{**}$ (73.42)	$0.395 \pm 0.038^{**}$ (76.79)
4e	7-CH_3	H	0.77 ± 0.047^{k}(12.10)	1.223 ± 0.118^{l}(4.08)	1.358 ± 0.038^{m}(00)	1.438 ± 0.081^{n} (8.12)	1.426 ± 0.066^{o} (16.22)
4f	7-CH_3	CH_3	0.793 ± 0.061(9.48)	$1.143 \pm 0.093^{**}$ (10.35)	1.33 ± 0.073 (2.06)	$1.388 \pm 0.065^{**}$ (11.31)	$1.456 \pm 0.077^{**}$ (14.45)
4g	7-CH_3	Cl	$0.708 \pm 0.047^{**}$ (19.18)	$0.643 \pm 0.048^{**}$ (49.57)	$0.52 \pm 0.055^{**}$ (61.71)	$0.463 \pm 0.032^{**}$ (70.42)	$0.403 \pm 0.016+^{**}$ (76.32)
4h	7-CH_3	Br	0.796 ± 0.098^{p}(9.48)	1.133 ± 0.063^{q} (11.14)	1.24 ± 0.048^{r} (8.69)	1.368 ± 0.059^{s} (12.59)	1.508 ± 0.064^{t} (11.40)
F value			18.53	183.27	427.07	623.08	627.68
df			9,50	9,50	9,50	9,50	9,50
P			0.4271	0.0041	0.7182	0.3331	0.0582

The data were analyzed by one-way ANOVA followed by Dunnet multiple comparison test. Results are expressed as mean ±S.D, n = 6. $^{**}p < 0.01$ considered as significant. Superscripts^{a-t} have not shown significant activity when compared to control.

whose zone of inhibition was taken as 100%. Among ethers (**3a–d**) and (**3f–h**) showed growth inhibition in the range of 78–94% (Table II) against *B. subtilis* and *E. coli* and the fungal strain *A. niger*. Compound (**3e**) has shown growth inhibition of 78% against *E. coli.* Compound (**3c**), (**3g**), and (**3h**) showed growth inhibition in the range of 78–89% against the *C. albicans.* In the case of thiazolidinonyl coumarins (**4c**), (**4d**), (**4g**) and (**4h**) showed growth inhibition in the range of 78–94% against the bacteria *E. coli,* the fungal strain *A. niger,* and *C. albicans.* Compound (**4b**) showed 78% inhibition against *B. subtilis*. Remaining compounds have been found to be moderately active. Upon (1:1) dilution, the activity observed was reduced and did not warrant further dilution.

EXPERIMENTAL

Melting points were determined using an electric melting point apparatus and are uncorrected. IR spectra were run in KBr pellets on a Nicolet-Impact-410 FT-IR spectrometer (ν_{max} in cm^{-1}). ^1H NMR spectra were recorded in DMSO-d_6 with TMS as an internal standard (Chemical shift in δ, ppm) on a Bruker 300 MHz FT-NMR spectrometer. Mass spectra (EI) were recorded from Indian Institute of Chemical Technology, Hyderabad. Purity of the compounds was checked by TLC. Nomenclature was made using Chem. Draw Ultra version 6.0. All the reagents were of laboratory reagent quality and were purchased from Sd.fine-chem.limited and used after purification. All the new compounds gave satisfactory elemental analyses.

Preparation of 4-(4-Phenyliminomethyl-phenoxymethyl)-chromen-2-ones 3(a–h)—General Procedure

4-Phenyliminomethyl-phenols (**2a–d**) (10 mmol) and anhydrous K_2CO_3 (1.38 g, 10 mmol) were stirred in dry acetone (25 mL) for 30 min. 4-Bromomethylcoumarins (**1a–b**) (2.52 g, 10 mmol) was added and stirring was continued for 24 h. The reaction mixture was concentrated and poured into crushed ice (100 g). The solid separated was filtered and washed with 5% HCl (10 mL) to neutralize excess of potassium carbonate. Then, it was washed with 100 mL of cold water and with dilute ethanol. The crude product was dried and recrystallized from DMF.

6-Methyl-4-(4-phenyliminomethyl-phenoxymethyl)-chromen-2-one (3a)

Colorless crystals from DMF. Yield 72%, m.p. 215–217°C; (found; C, 77.89; H, 5.09; N, 3.68. $C_{24}H_{19}O_3N$ (369) requires C, 78.04; H, 5.14;

TABLE II Results of Antimicrobial Assays of Compounds (3a–h) and (4a–h)

			B. subtilis		*E. coli*		*A. niger*		*C. albicans*	
Compd.	R	R′	Zone of inhibition (mm)	Relative inhibition (%)	Zone of inhibition (mm)	Relative inhibition (%)	Zone of inhibition (mm)	Relative inhibition (%)	Zone of inhibition (mm)	Relative inhibition (%)
3a	6-CH_3	H	20	77.7	20	77.7	20	77.7	18	66.6
3b	6-CH_3	CH_3	20	77.7	21	83.33	21	83.33	19	72.2
3c	6-CH_3	Cl	23	94.4	23	94.4	23	94.4	22	88.8
3d	6-CH_3	Br	21	83.33	22	88.8	22	88.8	19	72.2
3e	7-CH_3	H	19	72.2	20	77.7	19	72.2	17	61.1
3f	7-CH_3	CH_3	20	77.7	21	83.33	21	83.33	19	72.2
3g	7-CH_3	Cl	22	88.8	23	94.4	22	88.8	21	83.33
3h	7-CH_3	Br	21	83.33	22	88.8	22	88.8	20	77.7
4a	6-CH_3	H	19	72.2	18	66.6	18	66.6	18	66.6
4b	6-CH_3	CH_3	20	77.7	19	72.2	19	72.2	18	66.6
4c	6-CH_3	Cl	23	94.4	22	88.8	22	88.8	22	88.8
4d	6-CH_3	Br	21	83.33	20	77.7	22	88.8	21	83.33
4e	7-CH_3	H	18	66.6	17	61.1	17	61.1	17	61.1
4f	7-CH_3	CH_3	19	72.2	18	66.6	19	72.2	19	72.2
4g	7-CH_3	Cl	23	94.4	21	83.33	20	77.7	22	88.8
4h	7-CH_3	Br	22	88.8	20	77.7	20	77.7	21	83.33
	DMF		6	—	6	—	6	—	6	—
	Ciprofloxacin		24	100	24	100				
	Gresiofulvin						24	100	24	100

N, 3.79%); IR (KBr): $\nu = 1712$ (C=O, lactone), 1604 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.37$ (s, 3H, C_6-CH_3), 5.35 (s, 2H, CH_2-O), 6.54 (s, 1H, C_3-H), 7.14–8.36 (m, 12H, Ar-H), 9.83(s, 1H, –CH=N) ppm.

6-Methyl-4-[4-(p-tolylimino-methyl)-phenoxymethyl]-chromen-2-one (3b)

Colorless crystals from DMF. Yield 70%, m.p. 209–211°C; (found: C, 78.12; H, 5.26; N 3.49. $C_{25}H_{21}O_3N$ (383) requires C, 78.32; H, 5.48; N, 3.65%); IR (KBr): $\nu = 1709$ (C=O, lactone), 1610 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.37$ (s, 3H, C_6-CH_3), 2.45 (s, 3H, -CH_3), 5.30 (s, 2H, CH_2-O), 6.68 (s, 1H, C_3-H), 6.98–8.42 (m, 11H, Ar-H), 9.93 (s, 1H, –CH=N) ppm.

4-{4-[(4-Chloro-phenylimino)-methyl]-phenoxymethyl}-6-methyl-chromen-2-one (3c)

Colorless crystals from DMF. Yield 62%, m.p. 244–246°C; (found; C, 71.11; H, 4.27; N, 3.31. $C_{24}H_{18}O_3NCl$ (403) requires C, 71.37; H, 4.46; N, 3.46%); IR (KBr): $\nu = 1699$ (C=O, lactone), 1624 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.37$ (s, 3H, C_6-CH_3), 5.29 (s, 2H, CH_2-O), 6.56 (s, 1H, C_3-H), 6.96–8.33 (m, 11H, Ar-H), 9.84 (s, 1H, –CH=N) ppm.

4-{4-[(4-Bromo-phenylimino)-methyl]-phenoxymethyl}-6-methyl-chromen-2-one (3d)

Colorless crystals from DMF. Yield 66%, m.p. 242–244°C; (found; C, 64.12; H, 3.83; N, 3.01. $C_{24}H_{18}O_3NBr$ (447) requires C, 64.28; H, 4.01; N, 3.12%); IR (KBr): $\nu = 1738$ (C=O, lactone), 1617 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.46$ (s, 3H, C_6-CH_3), 5.34 (s, 2H, CH_2-O), 6.66 (s, 1H, C_3-H), 7.13–7.93 (m, 11H, Ar-H), 9.94 (s, 1H, –CH=N) ppm.

7-Methyl-4-(4-phenyliminomethyl-phenoxymethyl)-chromen-2-one (3e)

Colorless crystals from DMF. Yield 70%, m.p. 252–254°C; (found; C, 77.88; H, 5.01; N, 3.63. $C_{24}H_{19}O_3N$ (369) requires C, 78.04; H, 5.14; N, 3.79%); IR (KBr): $\nu = 1727$ (C=O, lactone), 1604 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.39$ (s, 3H, C_7-CH_3), 5.27 (s, 2H, CH_2-O), 6.50 (s, 1H, C_3-H), 7.06–7.82 (m, 12H, Ar-H), 9.83 (s, 1H, –CH=N) ppm.

7-Methyl-4-[4-(p-tolylimino-methyl)-phenoxymethyl]-chromen-2-one (3f)

Colorless crystals from DMF. Yield 68%, m.p. 262–264°C; (found; C, 78.17; H, 5.29; N, 3.51. $C_{25}H_{21}O_3N$ (383) requires C, 78.32; H, 5.48; N, 3.65%); IR (KBr): $\nu = 1736$ (C=O, lactone), 1611 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.40$ (s, 3H, C_7-CH_3), 2.50 (s, 3H, -CH_3), 5.32 (s, 2H, CH_2-O), 6.49 (s, 1H, C_3-H), 7.10–7.91 (m, 11H, Ar-H), 9.83 (s, 1H, –CH=N) ppm.

4-{4-[(4-Chloro-phenylimino)-methyl]-phenoxymethyl}-7-methyl-chromen-2-one (3g)

Colorless crystals from DMF. Yield 60%, m.p. 260–262°C; (found; C, 71.19; H, 4.31; N, 3.29. $C_{24}H_{18}O_3NCl$ (403) requires C, 71.37; H, 4.46; N, 3.46%); IR (KBr): $\nu = 1724$ (C=O, lactone), 1621 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.40$ (s, 3H, C_7-CH_3), 5.21 (s, 2H, CH_2-O), 6.49 (s, 1H, C_3-H), 7.11–7.83 (m, 11H, Ar-H), 9.83 (s, 1H, –CH=N) ppm.

4-{4-[(4-Bromo-phenylimino)-methyl]-phenoxymethyl}-7-methyl-chromen-2-one (3h)

Colorless crystals from DMF. Yield 63%, m.p. 244–246 °C; (found; C, 64.10; H, 3.87; N, 3.03. $C_{24}H_{18}O_3NBr$ (447) requires C, 64.28; H, 4.01; N, 3.12%); IR (KBr): $\nu = 1722$ (C=O, lactone), 1609 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.49$ (s, 3H, C_7-CH_3), 5.30 (s, 2H, CH_2-O), 6.56 (s, 1H, C_3-H), 7.08–8.38 (m, 11H, Ar-H), 9.94 (s, 1H, –CH=N) ppm.

Preparation of 2-[4-(2-oxo-2H-chromen-4-ylmethoxy)-phenyl]-3-phenyl-thiazolidin-4-ones 4(a-h)—General Method

To a solution of (**3a–h**) (10 mmol) in DMF (30 mL) was added thioglycollic acid (0.7 mL, 10 mmol) and $ZnCl_2$ (1 g) and the reaction mixture was refluxed for 8 h, cooled and poured onto crushed ice (100 g). The separated solid was filtered and washed with 10% $NaHCO_3$ (10 mL). The crude product was dried and recrystallized from DMF.

2-[4-(6-Methyl-2-oxo-2H-chromen-4-ylmethoxy)-phenyl]-3-phenyl-thiazolidin-4-one (4a)

Colorless crystals from DMF. Yield 62%, m.p. 180–182°C; (found; C, 70.24; H, 4.69; N, 3.04. $C_{26}H_{21}O_4NS$ (443) requires C, 70.42; H, 4.74; N, 3.16%); IR (KBr): $\nu = 1722$ (C=O, lactone), 1699 (C=O, amide) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.45$ (s, 3H, C_6-CH_3), 3.56 (s, 2H, S-CH_2), 4.30 (s, 1H, S-CH-N), 5.24 (s, 2H, CH_2-O), 6.64 (s, 1H, C_3-H), 6.98–7.93 (m, 12H, Ar-H) ppm; ms m/z 145 (Base peak, 100%).

2-[4-(6-Methyl-2-oxo-2H-chromen-4-ylmethoxy)-phenyl]-3-p-tolyl-thiazolidin-4-one (4b)

Colorless crystals from DMF. Yield 59%, m.p. 178–180°C; (found; C, 70.72; H, 4.89; N, 2.91. $C_{27}H_{23}O_4NS$ (457) requires C, 70.89; H, 5.03; N, 3.06%); IR (KBr): $\nu = 1720$ (C=O, lactone), 1688 (C=O, amide) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.19$ (s, 3H, C_6-CH_3), 2.36 (s, 3H, -CH_3), 3.37 (s, 2H, S-CH_2), 4.21 (s, 1H, S-CH-N), 5.19 (s, 2H, CH_2-O), 6.55 (s, 1H, C_3-H), 6.90–8.06 (m, 11H, Ar-H) ppm.

3-(4-Chloro-phenyl)-2-[4-(6-methyl-2-oxo-2H-chromen-4-ylmethoxy)-phenyl]-thiazolidin-4-one (4c)

Colorless crystals from DMF. Yield 35%, m.p. 188–190°C; (found; C, 65.17; H, 4.05; N, 2.81. $C_{26}H_{20}O_4NSCl$ (477) requires C, 65.34; H, 4.18; N, 2.93%); IR (KBr): $\nu = 1720$ (C=O, lactone), 1690 (C=O, amide) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.50$ (s, 3H, C_6-CH_3), 3.60 (s, 2H, S-CH_2), 4.47 (s, 1H, S-CH-N), 5.41 (s, 2H, CH_2-O), 6.54 (s, 1H, C_3-H), 7.14–7.95 (m, 11H, Ar-H) ppm.

3-(4-Bromo-phenyl)-2-[4-(6-methyl-2-oxo-2H-chromen-4-ylmethoxy)-phenyl]-thiazolidin-4-one (4d)

Colorless crystals from DMF. Yield 40%, m.p. 185–187°C; (found; C, 59.61; H, 3.71; N, 2.54. $C_{26}H_{20}O_4NSBr$ (521) requires C, 59.77; H, 3.83; N, 2.68%); IR (KBr): $\nu = 1718$ (C=O, lactone), 1675 (C=O, amide) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.40$ (s, 3H, C_6-CH_3), 3.42 (s, 2H, S-CH_2), 4.39 (s, 1H, S-CH-N), 5.39 (s, 2H, CH_2-O), 6.40 (s, 1H, C_3-H), 7.14–7.94 (m, 11H, Ar-H) ppm.

2-[4-(7-Methyl-2-oxo-2H-chromen-4-ylmethoxy)-phenyl]-3-phenyl-thiazolidin-4-one (4e)

Colorless crystals from DMF. Yield 60%, m.p. 168–170°C; (found; C, 70.27; H, 4.61; N, 3.04. $C_{26}H_{21}O_4NS$ (443) requires C, 70.42; H, 4.74; N, 3.16%); IR (KBr): $\nu = 1715$ (C=O, lactone), 1680 (C=O, amide) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.45$ (s, 3H, C_7-CH_3), 3.49 (s, 2H, S-CH_2), 4.29 (s, 1H, S-CH-N), 5.19 (s, 2H, CH_2-O), 6.53 (s, 1H, C_3-H), 6.92–8.02 (m, 12H, Ar-H) ppm.

2-[4-(7-Methyl-2-oxo-2H-chromen-4-ylmethoxy)-phenyl]-3-p-tolyl-thiazolidin-4-one (4f)

Colorless crystals from DMF. Yield 52%, m.p. 204–206°C; (found; C, 70.71; H, 4.89; N, 2.91. $C_{27}H_{23}O_4NS$ (457) requires C, 70.89; H, 5.03; N, 3.06%); IR (KBr): $\nu = 1727$ (C=O, lactone), 1681 (C=O, amide) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.17$ (s, 3H, C_7-CH_3), 2.48 (s, 3H,

-CH_3), 3.42 (s, 2H, S-CH_2), 4.22 (s, 1H, S-CH-N), 5.31 (s, 2H, CH_2-O), 6.59 (s, 1H, C_3-H), 7.14–7.91 (m, 11H, Ar-H) ppm.

3-(4-Chloro-phenyl)-2-[4-(7-methyl-2-oxo-2H-chromen-4-ylmethoxy)-phenyl]-thiazolidin-4-one (4g)

Colorless crystals from DMF. Yield 38%, m.p. 120–122°C; (found; C, 65.17; H, 4.02; N, 2.76. $C_{26}H_{20}O_4NSCl$ (477) requires C, 65.34; H, 4.18; N, 2.93%); IR (KBr): $\nu = 1721$ (C=O, lactone), 1686 (C=O, amide) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.47$ (s, 3H, C_7-CH_3), 3.47 (s, 2H, S-CH_2), 4.49 (s, 1H, S-CH-N), 5.14 (s, 2H, CH_2-O), 6.50 (s, 1H, C_3-H), 6.84–7.90 (m, 11H, Ar-H) ppm.

3-(4-Bromo-phenyl)-2-[4-(7-methyl-2-oxo-2H-chromen-4-ylmethoxy)-phenyl]-thiazolidin-4-one (4h)

Colorless crystals from DMF. Yield 42%, m.p. 80–82°C; (found; C, 59.63; H, 3.65; N, 2.51. $C_{26}H_{20}O_4NSBr$ (521) requires C, 59.77; H, 3.83; N, 2.68%); IR (KBr): $\nu = 1728$ (C=O, lactone), 1671 (C=O, amide) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.50$ (s, 3H, C_7-CH_3), 3.47 (s, 2H, S-CH_2), 4.36 (s, 1H, S-CH-N), 5.41(s, 2H, CH_2-O), 6.54 (s, 1H, C_3-H), 7.14–7.95 (m, 11H, Ar-H) ppm.

CONCLUSION

Thiazolidinone moiety has been found to enhance the anti-inflammatory activity of 4-aryloxymethyl coumarins. Bromo substitution in the arylimino moiety was found to enhance the anti-inflammatory activity. In the antimicrobial activity chloro and bromo substitution were found to be the most favorable for the growth inhibition of *E. coli* and *A. niger*.

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