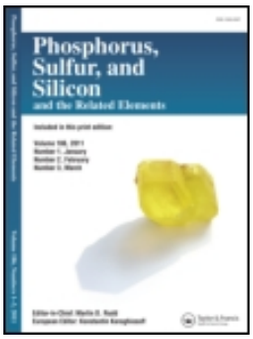

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SYNTHESIS OF 4,9-DIMETHYL-8- (6-ARYL-2-THIOXO-1,2,3,6-TETRAHYDRO PYRIMIDIN-4-YL)-FURO[2,3-H]CHROMEN-2-ONES AS ANTIMICROBIAL AGENTS UNDER MICROWAVE IRRADIATION

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SYNTHESIS OF 4,9-DIMETHYL-8-(6-ARYL-2-THIOXO-1,2,3,6-TETRAHYDRO PYRIMIDIN-4-YL)-FURO[2,3-H]CHROMEN-2-ONES AS ANTIMICROBIAL AGENTS UNDER MICROWAVE IRRADIATION

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*Acrolyl furochromen-2-ones (**3a–i**) obtained in good yields on microwave irradiation of furochromen-2-one (**1**) with various simple and substituted aromatic aldehydes (**2a–i**). **3a–g** on cyclo dehydration with thiourea in domestic microwave oven furnished tetrahydro thiaxopyrimidine furochromen-2-ones **4a–i** in high yields. The structures of the newly synthesized compounds were established on the basis of analytical and spectral data, IR, and ^1H NMR.*

Keywords: Aryl acrolyl furochromen-2-ones; furochromen-2-one; tetrahydro thiaxopyrimidine furo chromen-2-ones

INTRODUCTION

Literature survey reveals that thiopyrimidine derivatives have been found to posses a number of pharmacological activities.[1–7] However, there is no literature report about furochromen-2-one-substituted thioxopyrimidine derivatives. In continuation of our studies on the synthesis of several new compounds under microwave irradiation,[8] we attempted the synthesis of thioxopyrimidines containing furochromen-2-ones. Chromen-2-ones possess marked biological activities;[9] the

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introduction of thioxopyrimidines into chromen-2-one may alter the biocidal activity to some extent.

ANTIMICROBIAL ACTIVITY

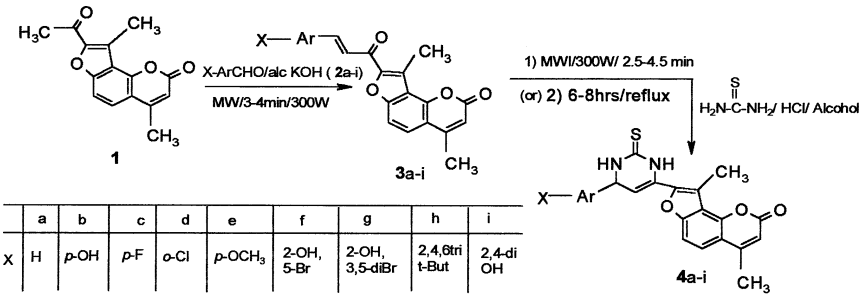
All the newly synthesized compounds were screened for their antibacterial activity against both Gram-positive and Gram-negative bacteria *Staphylococus aureus 209p* and *Escherichia coli Ess 2231* by cup plate method[10] using *Ampicillin* as standard. The compounds were tested at the dose of 1 mg/ml solution in dimethyl formamide (DMF). The activity was reported by measuring the area of inhibition zone in millimeters after 24 h of incubation at 37°C. Compounds **4d** and **4e** show maximum activity against *S. aureus 209p* but other compounds were inactive. None of the compounds are active against *E. coli Ess 2231*.

The antifungal activity of these compounds were evaluated against *Aspergillus fumigatus, Candida albicans C. albicans, ATCC 10231, Candida krusei Go3, and Candida glabrata HO5* at a concentration of 1 mg/ml using *Fluconazole* as standard. The antifungal activity was reported by measuring the area of inhibition zone in millimeters after 48 h of incubation at 37°C. Compounds **4d**, **4e** exhibited highest activity against *C. albicans* and *C. albicans ATCC* 10231, and they show moderate activity against *C. krusei GO3, C. glabrata HO5*. They are inactive against *A. fumigatus,* but other compounds are inactive against all these different fungi. The results are shown in Table I.

TABLE I Antimicrobial Activity of Compounds

Sr. no.	*S. aureus 209p*	*E. coli ESS 2231*	*A. fumigatus*	*C. albicans*	*C. albicans ATCC 10231*	*C. krusei GO3*	*C. glabrata HO5*
4a	—	—	—	—	—	—	—
4b	—	—	—	—	—	—	—
4c	—	—	—	—	—	—	—
4d	11	—	—	11	11	9 h	10 h
4e	10	—	—	12	12	9 h	9 h
4f	—	—	—	—	—	—	—
4g							
4h	—	—	—	—	—	—	—
4i	—	—	—	—	—	—	—
Flucanazole	—	—	—	29 h	25 h	19	15

h, hazy zone.
Mean value of area of inhibition in mm.



SCHEME 1

RESULTS AND DISCUSSION

Furochromen-2-one on reaction with simple and substituted aromatic aldehydes in alcoholic KOH in microwave irradiation for 2.5–4.5 min yields acryloyl furochromen-2-ones (**3a–i**). The compounds **3a–i** on cyclodehydration with thiourea furnished the final products **4a–i** (Scheme 1). The synthesis of **4a–i** was carried out in microwave irradiation and conventional methods. Microwave irradiation of organic

TABLE II Physical Data of the Compounds Synthesized

Compound	Molecular formula (mol. wt)	Method A yield (%)	Time (min)	m.p. (°C)	Cal./found (%) C	Cal./found (%) H
3a	$C_{22}H_{16}O_4$ (344)	81.7	3	227	76.73 76.78	4.68 4.66
3b	$C_{22}H_{16}O_5$ (360)	84.6	3	189	73.33 73.31	4.48 4.45
3c	$C_{22}H_{15}FO_4$ (362)	75.7	3	178	72.92 72.91	4.17 4.18
3d	$C_{22}H_{15}ClO_4$ (378)	76	3.5	198	69.76 69.77	3.99 3.97
3e	$C_{23}H_{18}O_5$ (374)	77.5	3.5	215	73.79 73.77	4.85 4.88
3f	$C_{22}H_{15}BrO_5$ (439)	76	3.5	185	60.16 60.15	3.44 3.45
3g	$C_{22}H_{14}Br_2O_5$ (518)	69.7	3.5	226	51.00 51.10	2.72 2.73
3h	$C_{34}H_{40}O_4$ (512)	67.8	3.5	169	79.65 79.66	7.86 7.85
3i	$C_{22}H_{16}O_6$ (376)	82.7	3.5	210	70.21 70.23	4.29 4.26

TABLE III IR (Cm^{-1}) and ^1H NMR (δ *ppm*) of the Compounds (**3a–i**)

Comp.	—C═O str Lactone carbonyl	—C═CO–str Acryloyl	—C═C –str Acryloyl	^1H NMR
3a	1720	1600	1567	7.8 (dd, 1H, $J = 16$ Hz, C-βH), 7.5 (dd, 1H, $J = 16$ Hz, C-αH), 7.4 (dd, 2H, $J = 9$ Hz, C-5, C-6H), 7.20–7.25 (m, 5H, Ar-H), 6.13 (s, 1H, C-3H), 2.83 (s, 3H, C-4CH_3), 2.50 (s, 3H, C-9CH_3)
3b	1718	1602	1565	10.2 (s, 1H, OH), 7.7 (dd, 1H, $J = 16$ Hz, C-βH), 7.5 (dd, 1H, $J = 16$ Hz, C-αH), 7.4 (dd, 2H, $J = 9$ Hz, C-5, C-6H), 7.20–7.25 (m, 4H, Ar-H), 6.13 (s, 1H, C-3H), 2.83 (s, 3H, C-4CH_3), 2.50 (s, 3H, C-9CH_3)
3c	1721	1601	1565	7.8 (dd, 1H, $J = 16$ Hz, C-βH), 7.6 (dd, 1H, $J = 16$ Hz, C-αH) 7.4 (dd, 2H, $J = 9$ Hz, C-5, C-6H), 7.20–7.25 (m, 4H, Ar-H), 6.13 (s, 1H, C-3H), 2.83 (s, 3H, C-4CH_3), 2.50 (s, 3H, C-9CH_3)
3d	1721	1601	1565	7.8 (dd, 1H, $J = 16$ Hz, C-βH), 7.6 (dd, 1H, $J = 16$ Hz, C-αH), 7.4 (dd, 2H, $J = 9$ Hz, C-5, C-6H), 7.20–7.25 (m, 4H, Ar-H), 6.13 (s, 1H, C-3H), 2.83 (s, 3H, C-4CH_3), 2.50 (s, 3H, C-9CH_3)
3e	1720	1604	1563	7.7 (dd, 1H, $J = 16$ Hz, C-βH), 7.6 (dd, 1H, $J = 16$ Hz, C-αH), 7.4 (dd, 2H, $J = 9$ Hz, C-5, C-6H), 7.20–7.25 (m, 4H, Ar-H), 6.13 (s, 1H, C-3H), 3.83 (s, 3H, -OCH_3), 2.83 (s, 3H, C-4CH_3), 2.50 (s, 3H, C-9CH_3)
3f	1719	1605	1566	10.2 (s, 1H, OH), 7.8 (dd, 1H, $J = 16$ Hz, C-βH), 7.6 (dd, 1H, $J = 16$ Hz, C-αH), 7.4 (dd, 2H, $J = 9$ Hz, C-5, C-6H), 7.30 (m, 3H, Ar-H), 6.13 (s, 1H, C-3H), 2.83 (s, 3H, C-4CH_3), 2.50 (s, 3H, C-9CH_3)
3g	1720	1603	1564	10.2 (s, 1H, OH), 7.8 (dd, 1H, $J = 16$ Hz, C-βH), 7.6 (dd, 1H, $J = 16$ Hz, C-αH), 7.4 (dd, 2H, $J = 9$ Hz, C-5, C-6H), 7.30 (s, 1H, C-4′H), 7.25 (s, 1H, C-6′H), 6.13 (s, 1H, C-3H), 2.83 (s, 3H, C-4CH_3), 2.50 (s, 3H, C-9CH_3)
3h	1722	1601	1564	7.8 (dd, 1H, $J = 16$ Hz, C-βH), 7.6 (dd, 1H, $J = 16$ Hz, C-αH), 7.4 (dd, 2H, $J = 9$ Hz, C-5, C-6H), 7.30 (s, 1H, C-3′H), 7.25 (s, 1H, C-5′H), 6.13 (s, 1H, C-3H), 2.83 (s, 3H, C-4CH_3), 2.50 (s, 3H, C-9CH_3), 2.4 (s, 27H, tri-t-But)
3i	1722	1602	1564	10.4 (s, 1H, OH), 10.2 (s, 1H, OH), 7.7 (dd, 1H, $J = 16$ Hz, C-βH), 7.6 (dd, 1H, $J = 16$ Hz, C-αH), 7.4 (dd, 2H, $J = 9$ Hz, C-5, C-6H), 7.30(s, 1H, C-3′H), 7.25 (dd, $J = 8$ Hz, 2H, C-5′, C-6′H), 6.13 (s, 1H, C-3H), 2.83 (s, 3H, C-4CH_3), 2.50 (s, 3H, C-9CH_3)

TABLE IV Physical Data of the Compounds Synthesized

Compound	Molecular formula (mol. wt.)	Method A yield (%)	Time (min)	Method B yield (%)	Time (h)	M.P (°C)	Cal./found (%) N	S
4a	$C_{23}H_{18}N_2O_3S$ (402)	86	2.5	80	6	240	6.96 6.94	7.97 7.95
4b	$C_{23}H_{18}N_2O_4S$ (418)	77	3	73	6.5	166	6.69 6.70	7.66 7.64
4c	$C_{23}H_{17}FN_2O_3S$ (420)	82	3	78	6.25	192	6.66 6.67	7.63 7.62
4d	$C_{23}H_{17}ClN_2O_3S$ (436)	80	3.5	74	7	215	6.41 6.39	7.34 7.36
4e	$C_{24}H_{20}N_2O_4S$ (432)	68	3.5	63	7	187	6.48 6.45	7.41 7.40
4f	$C_{23}H_{17}BrN_2O_4S$ (497)	74	4	69	7.5	203	5.63 5.66	6.45 6.44
4g	$C_{23}H_{16}Br_2N_2O_4S$ (576)	65	4.5	62	7.5	>300	4.86 4.85	5.56 5.54
4h	$C_{35}H_{42}N_2O_3S$ (570)	71	4.5	65	8	210	6.45 6.45	7.38 7.40
4i	$C_{23}H_{18}N_2O_5S$ (434)	67	4.5	61	8	180	4.91 4.94	5.62 5.60

reactions has rapidly gained popularity as it accelerates variety synthetic transformations.[11] Compared with the conventional reaction, the conditions of this reaction were mild, it was easily executed, and it isolated in high yields in short time. The compounds were fully characterized by IR and ^{1}H NMR (Tables II–V). In IR spectrum the absence of 1610 cm^{-1} indicate the absence of CH═CH─CO-group and the presence of 1249 cm^{-1}, 1710 cm^{-1} indicates C═S and C═O (lactonyl) respectively in the compounds **4a–i**. The appearance of two AB doublets at 7.2 and 7.5 are due to the resonance of C-5, C-6 aromatic protons confirm the angular nature of furo chromen-2-one. Doublet at 4.4 confirms CH proton of thioxo pyrimidine.

EXPERIMENTS

All the melting points are taken in open capillary in liquid paraffin bath and are uncorrected. Purity of all compounds were checked by thin layer chromatography (TLC). IR spectra (KBr) were recorded on Shimadzu FTIR Model 8010 Spectrometer and the ^{1}H NMR spectra in $CDCl_3$on Varian C17-20-ZM-390-200 MH_ZNMR spectrometer using tetramethyl silane (TMS) as an internal standard (Chemical shifts in δ *ppm*). The C, H, N, and S analysis of the compounds was done on a Carlo Erba Model EA1108 C H N and S elemental analyzer.

TABLE V IR (Cm^{-1}) and ^1H NMR (δ *ppm*) of the Compounds (**4a–f**)

Comp.	C=S	C=O	N–H	^1H NMR
4a	1249	1710	3360	8.12 (bs, 2H, N-H, D_2O exchangeable), 7.68 (d, 1H, $J = 8$ Hz, C-5H), 7.42 (d, 1H, $J = 8$ Hz, C-6H), 7.16 (m, 5H, Ar-H), 6.25 (s, 1H, C-3H), 4.4 (s, 1H, C-5′H), 3.76 (d, 1H, C-4′ H), 2.65 (s, 3H, C-4 CH_3), 2.42 (s, 3H, C-9CH_3)
4b	1240	1705	2960	10.4 (s, 1H, OH, D_2O exchangeable), 8.18 (bs, 2H, N-H, D_2O exchangeable), 7.7 (d, 1H, $J = 8$ Hz, C-5 H), 7.45 (d, 1H, $J = 8$ Hz, C-6H), 7.2 (m, 4H, Ar-H), 6.25 (s, 1H, C-3H), 4.4 (s, 1H, C-5′H), 3.76 (d, 1H, C-4′ H), 2.65 (s, 3H, C-4 CH_3), 2.42 (s, 3H, C-9CH_3)
4c	1245	1710	3100	8.18 (bs, 2H, N-H, D_2O exchangeable), 7.7 (d, 1H, $J = 8$ Hz, C-5 H), 7.45 (d, 1H, $J = 8$ Hz, C-6H), 7.2 (m, 4H, Ar-H), 6.25 (s, 1H, C-3H), 4.4 (s, 1H, C-5′H), 3.76 (d, 1H, C-4′ H), 2.65 (s, 3H, C-4 CH_3), 2.42 (s, 3H, C-9CH_3)
4d	1245	1710	3220	8.18 (bs, 2H, N-H, D_2O exchangeable), 7.7 (d, 1H, $J = 8$ Hz, C-5 H), 7.45 (d, 1H, $J = 8$ Hz, C-6H), 7.2 (m, 4H, Ar-H), 6.25 (s, 1H, C-3H), 4.4 (s, 1H, C-5′H), 3.76 (d, 1H, C-4′ H), 2.65 (s, 3H, C-4 CH_3), 2.42 (s, 3H, C-9CH_3)
4e	1230	1720	3180	8.2 (bs, 2H, N-H, D_2O exchangeable), 7.7 (d, 1H, $J =$ 8 Hz, C-5, H), 7.44 (d, 1H, $J = 8$ Hz, C-6H), 7.2 (m, 4H, Ar-H), 6.25 (s, 1H, C-3H), 4.4 (s, 1H, C-5′H), 3.8 (d, 1H, C-4′ H), 3.7(s, 3H, OCH_3), 2.69 (s, 3H, C-4 CH_3), 2.5 (s, 3H, C-9CH_3)
4f	1235	1680	3310	10.5 (s, 1H, OH, D_2O exchangeable), 8.18 (bs, 2H, N-H, D_2O exchangeable), 7.7 (d, 1H, $J = 8$ Hz, C-5 H), 7.45 (d, 1H, $J = 8$ Hz, C-6H), 7.26–7.28 (m, 3H, Ar-H), 6.25 (s, 1H, C-3H), 4.4 (s, 1H, C-5′H), 3.76 (d, 1H, C-4′ H), 2.65 (s, 3H, C-4 CH_3), 2.42 (s, 3H, C-9CH_3)

Synthesis of 4,9-Dimethyl-8-(3-phenyl-acryloyl)furo[2,3-h]chromen-2-one (3a)

8-Acetyl-4,9-dimethyl-furo[2,3-h]chromen-2-one (0.256 g, 0.001 mol) was mixed with benzaldehyde (0.016 g, 0.001 mol) in 5 ml of 10% alcoholic KOH, and few drops of acetone were added. The reaction mixture was irradiated in microwave at 300 W power level for 3 min. The product was cooled and added to ice-cold water, and the solid obtained was filtered and recrystallized from petroleum ether. **3b–i** were synthesized similarly.

Synthesis of 4,9-Dimethyl-8-(6-phenyl-2thioxo-1,2,3,6-tetrahydro pyrimidin-4-yl)-furo[2,3-h]chromen-2-one (4a)

Method A: Microwave Irradiation

4,9-Dimethyl-8-(3-phenyl-acryloyl)furo[2,3-h]chromen-2-one (0.344 g, 0.001 mol) was mixed with thiourea (0.076 g, 0.001 mol) in 5 ml alcohol, and a few drops of HCl were added to it. The reaction mixture was subjected to microwave irradiation for 2.5 min at 300 W power level. The product was cooled and added to ice-cold water. The solid obtained was filtered and recrystallized from acetic acid as colorless crystals.

Method B: Conventional Heating[12]

4,9-Dimethyl-8-(3-phenyl-acryloyl)furo[2,3-h]chromen-2-one (0.344 g, 0.001 mol) is mixed with thiourea (0.076 g, 0.001 mol) in 30 ml alcohol, and a few drops of HCl were added to it. The reaction mixture was refluxed for 6 h. The product was cooled and added to ice-cold water. The solid obtained was filtered and recrystallized from acetic acid as colorless crystals. Compounds **4a–i** were synthesized similarly.

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