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Naazneen B. Yaragatti[a]; Manohar V. Kulkarni[a]; Manjunath D. Ghate[b]; Satyanarayan S. Hebbar[c]; Ganesh R. Hegde[c]
[a] Department of Chemistry, Karnatak University, Dharwad, Karnataka, India [b] Department of Pharmaceutical Chemistry, Kripanidhi College of Pharmacy, Bangalore, Karnataka, India [c] Department of Botany, Karnatak University, Dharwad, Karnataka, India

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Synthesis and biological evaluation of some new coumarinyl thiazolopyrimidinones

Naazneen B. Yaragatti[a], Manohar V. Kulkarni[a]*, Manjunath D. Ghate[b], Satyanarayan S. Hebbar[c] and Ganesh R. Hegde[c]

[a]*Department of Chemistry, Karnatak University, Dharwad 580 003, Karnataka, India;* [b]*Department of Pharmaceutical Chemistry, Kripanidhi College of Pharmacy, Bangalore 560 034, Karnataka, India;* [c]*Department of Botany, Karnatak University, Dharwad 580 003, Karnataka, India*

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Two new series of coumarin linked, linear and angularly fused thiazolo-[3,2-a]-pyrimidinones have been synthesized from 3-bromoacetyl coumarins by azole and azine approaches. Regioisomeric 5H and 7H thiazolo-[3,2-a]-pyrimidinones have been clearly distinguished by their IR and UV fluorescence spectral data. All the compounds have been characterized by analytical and spectroscopic methods. Rate and yield enhancements have been achieved using microwave irradiation. The results of *in vivo* diuretic activity indicate that substituents on coumarin do not enhance the activity. *In vitro* antimicrobial activities have shown that the compounds are specifically active against Gram-positive but are inactive against Gram-negative bacterial strains. Moderate fungal activity was observed against *Candida albicans* and *Penicillium chrysogenum* and all the compounds were found to be inactive against *Aspergillus niger*.

Keywords: 3-bromoacetyl coumarins; 4-(3'-coumarinyl)-2-amino thiazole; 2-mercapto uracil; antimicrobial activity; diuretic activity

1. Introduction

Thiazole nucleus is an important component of vitamins, antibiotics and a variety of clinically accepted drugs. Fused thiazolopyrimidines constitute a group of bicyclic heterocyclic systems with the [5,4-d] isomer being isosteric with purines. The [3,2–a] isomers, possessing a bridgehead nitrogen, have received a great deal of attention (*1–3*) in view of their interesting chemical reactivity and wide range of biological properties. A unique feature of thiazolo-[3,2-a]-pyrimidines is their existence in 5H and 7H forms, which have been proposed in very few instances (*4*). Derivatives of thiazolo-[3,2-a]-pyrimidines have been reported to exhibit antibacterial and antifungal (*5*), anti-inflammatory (*6*), antitumor (*7, 8*), antihypertensive (*9*), acetyl cholinesterase inhibitory (*10*) and diuretic activities (*11*). Thiazoles and benzimidazolo thiazoles linked to the C3 position of coumarin have resulted in compounds with potent antimicrobial and anti-inflammatory activities (*12, 13*). The interest in such compounds is due to the fact that biodegradation of coumarins would

*Corresponding author. Email: manohar274@gmail.com

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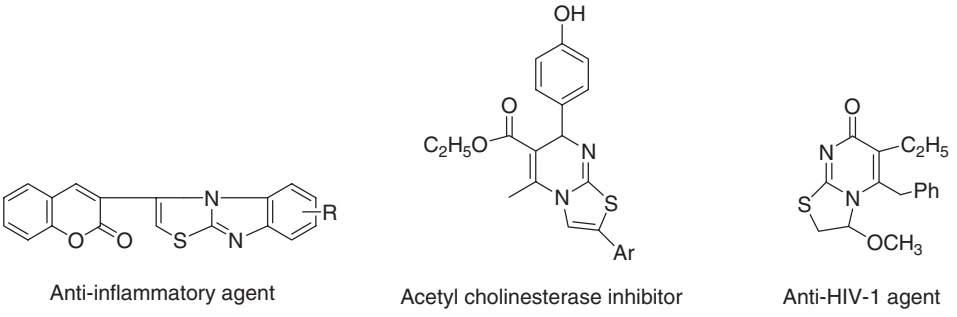


Figure 1. Structurally related bio-active compounds.

lead to *in situ* generation of thiazole-4-acetic acids, useful for the inflammation inhibition process. Further, substituted 3-benzamido coumarins have been found to exhibit promising diuretic activity (*14*). In the light of the above literature reports, it was thought of considerable interest to synthesize 3'-coumarinyl thiazolopyrimidinones. Some of the structurally related compounds are presented (Figure 1).

2. Results and discussion

Thiazolo-[3,2-a]-pyrimidines have been synthesized by the unambiguous azole (3 + 3) approach involving the use of 2-amino thiazoles and β-keto esters leading to exclusive formation of 5H isomers (*15*). A second route involves the construction of a thiazole ring from 2-mercapto uracils and α-halo ketones (*16*), termed as the azine approach, which has the potential of two N-heterocyclizations possible at N3 and N1 leading to the 5H and 7H forms (Figure 2). Derivatives of thiazolopyrimidines have also been synthesized from the retro Diels–Alder reaction (*17*) and these cyclizations have also been achieved under microwave (MW) conditions (*18*).

The present paper demonstrates the azole and azine approaches to construct coumarinyl thiazolo-[3,2-a]-pyrimidinones and the application of the MW irradiation to these reactions, as well as the results of preliminary biological evaluation studies. The two synthetic routes

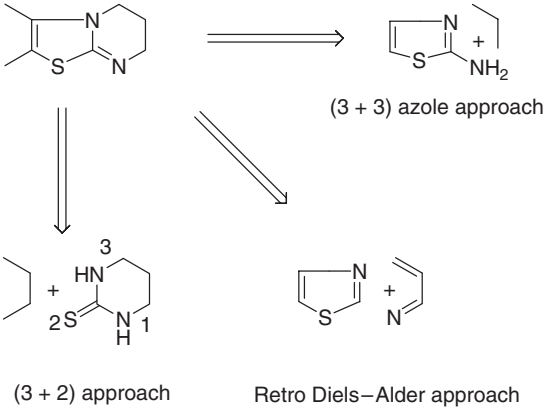
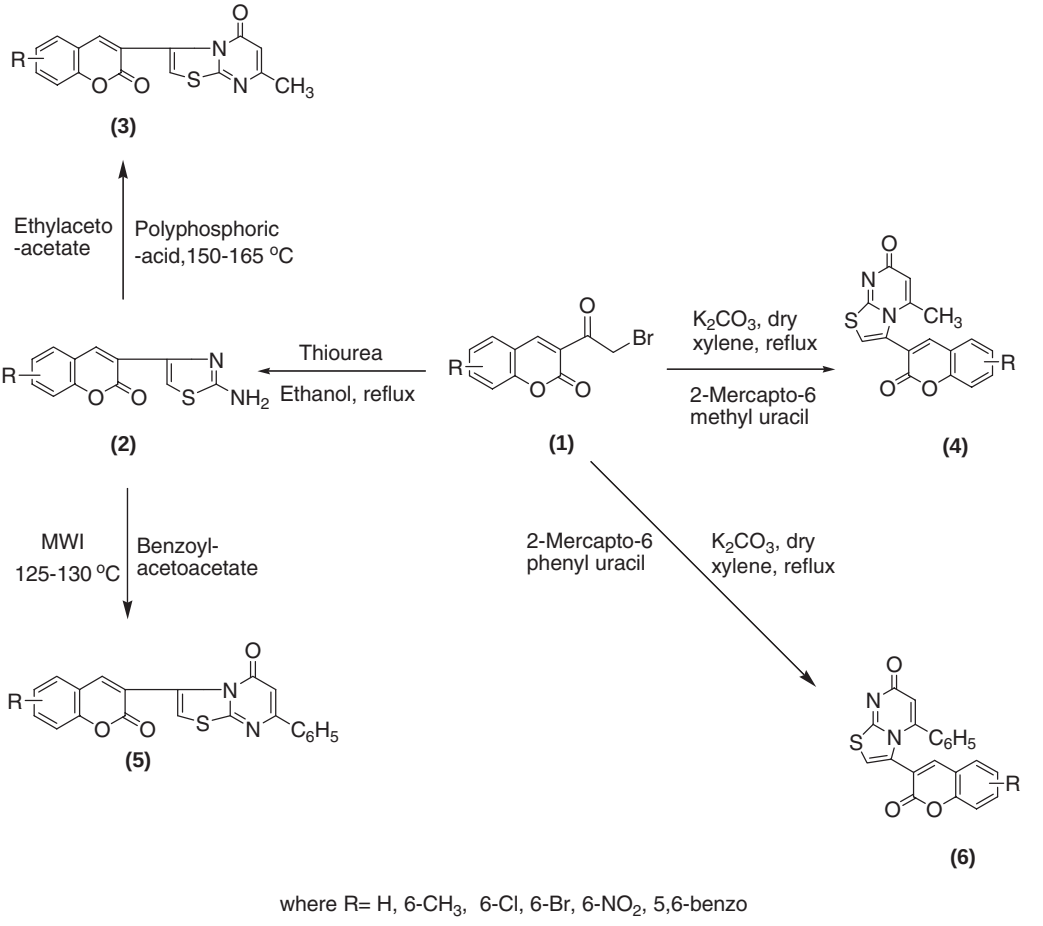


Figure 2. Synthetic routes to thiazolo-[3,2-a]-pyrimidines.



Scheme 1. Synthesis of coumarinyl thiazolo-[3,2-a]-pyrimidines.

employed for the construction of thiazolopyrimidinones linked to the coumarin moiety are outlined in Scheme 1. Various 3-bromoacetyl coumarins (**1**) (*19*) required for both the routes were obtained by the room temperature bromination of 3-acetyl coumarins in chloroform. The corresponding 4-3'-coumarinyl-2-amino thiazoles (**2**) (*20*) which are the precursors for the azole $(3+3)$ approach were in turn isolated as yellow solids by the reaction of (**1**) with thiourea in refluxing ethanol. Reactions of aminothiazoles (**2**) with ethylacetoacetate in polyphosphoric acid at high temperatures lead to thiazolo-[3,2-a]-pyrimidine-5-ones, which is in accordance with the literature reports on the reactions of 2-amino thiazoles with β-keto esters (*21*). Compound **3a**, R=H, exhibited the pyrimidinone carbonyl at 1685 cm^{-1} and the lactone carbonyl at 1716 cm^{-1}. Its UV spectrum DMF showed two intense bands at 280 and 325 nm. The ^{1}H NMR chemical shifts and mass spectral data are consistent with the structure for all of the compounds (**3a**–**3d)**.

In the azine approach, 3-bromoacetylcoumarins (**1**) were reacted with 2-mercapto-6-methyl uracil in refluxing xylene with a view to compare with the azole approach. The product **4a**, R=H, exhibited a band at 1658 cm^{-1} due to pyrimidinone carbonyl, which was significantly less than **3a**. The lactone carbonyl band in **4a** was observed at 1726 cm^{-1}, which is close to the value observed in **3a**. The lower carbonyl stretching frequency is consistent with the values observed in 2- and 4-quinolones and also 2- and 4-pyridones (*22, 23*). The UV spectrum of **4a** in DMF showed two bands at 258 and 290 nm, which is different from **3a**. The ^{1}H-NMR spectrum agrees with the

Table 1. UV–VIS and fluorescence of isomeric coumarinyl thiazolo-[3,2-a]-pyrimidinones (DMF).

	5H isomer			7H isomer	
Compound	Absorption λ_{max} (nm)	Emission λ_{max} (nm)	Compound	Absorption λ_{max} (nm)	Emission λ_{max} (nm)
3a	325	368	**4a**	280	328
3b	352	409	**4b**	309	352
3c	416	477	**4c**	375	422
3d	434	492	**4d**	382	438

Table 2. Preparation of the coumarinyl thiazolo [3,2-a]-pyrimidinones.

Entry	R	R′	Compound	Melting point (°C)	Conventional heating time (h)/yield (%)	MW irradiation time (min)/yield (%)
1	H	$-CH_3$	**3a**	219–221	3.0/70	1.50/90
2	6-CH_3	$-CH_3$	**3b**	231–233	3.0/68	3.00/88
3	6-Cl	$-CH_3$	**3c**	228–230	3.0/67	3.00/84
4	6-Br	$-CH_3$	**3d**	226–228	4.0/69	4.00/89
5	5,6-Benzo	$-CH_3$	**3e**	239–241	4.0/60	4.00/80
6	H	$-CH_3$	**4a**	267–269	24/65	1.30/90
7	6-CH_3	$-CH_3$	**4b**	283–285	24/62	2.00/86
8	6-Cl	$-CH_3$	**4c**	237–239	24/61	2.10/82
9	6-Br	$-CH_3$	**4d**	211–213	24/60	2.50/80
10	5,6-Benzo	$-CH_3$	**4e**	223–225	24/61	2.40/89
11	H	$-C_6H_5$	**5a**	292–294	–	2.00/90
12	6-Cl	$-C_6H_5$	**5b**	299–301	–	3.00/89
13	6-Br	$-C_6H_5$	**5c**	297–299	–	4.20/91
14	6-NO_2	$-C_6H_5$	**5d**	301–303	–	9.00/88
15	H	$-C_6H_5$	**6a**	295–297	24/69	2.20/89
16	6-Cl	$-C_6H_5$	**6b**	297–299	24/67	3.00/84
17	6-Br	$-C_6H_5$	**6c**	307–309	24/65	3.40/82
18	6-NO_2	$-C_6H_5$	**6d**	301–303	27/66	5.00/80

structure and expectedly did not show a significant difference with **3a**. The mass spectral data are consistent with the structures. The UV and fluorescence bands observed for these compounds are listed in Table 1. It can be seen that the longest wavelength band for the angularly fused 7H-ones (**4a**–**4d**) is less than the corresponding 5H-ones (**3a**–**3d**), which is also the case with the emission bands.

Using these two approaches thiazolo-[3,2-a]-pyrimidine-5-ones (**5a**–**5d**) and thiazolo-[3,2-a]-pyrimidine-7-ones (**6a**–**6d**) were obtained using benzoyl acetoacetate and 2-mercapto-6-phenyluracil, respectively. In view of the longer reaction times required for both the approaches, these reactions were also carried out in a Kenstar domestic MW oven at 125 °C (1200 W). It was found that the products were isolated in higher yields and the reaction was completed in a few minutes (Table 2).

2.1. *Pharmacology*

2.1.1. *Antimicrobial assay*

The isomeric coumarinyl thiazolo-[3,2-a]-pyrimidinones were tested for their *in vitro* antibacterial activity against a panel of Gram-positive and Gram-negative reference strains: all microbiological products were purchased from Himedia. Chemicals were of analytical grade from Sigma.

The microorganisms used in this study were *Klebsiella pneumoniae* MTCC109, *Staphylococcus aureus* MTCC737, *Pseudomonas aeruginosa* MTCC1688 and *Proteus vulgaris* MTCC1771. The fungal strains used in the study are *Candida albicans* MTCC183, *Aspergillus niger* and *Penicillium chrysogenum*. DMF was used as a solvent control and the reference drugs used were streptomycin for bacterial strains and nystatin for fungal strains. Antimicrobial activity tests were conducted by using the cup plate method (*24–26*) at a concentration of 25, 50 and 100 μg/mL. The bacteria were grown for 24 h on a nutritive agar medium at 37 °C. The fungal strains were grown on potato dextrose agar medium at 30 °C for 24 h. The zone of inhibition was measured in millimeters. The percentage inhibition of the test compounds was related to the standard, whose zone of inhibition was taken as 100%.

The results of activity are tabulated in Table 3. Among the thiazolo-[3,2-a]-pyrimidinones, compounds **5c** and **5d** showed moderate to good activity at 100 μg/mL concentration. The same compounds were active even at 25 μg/mL concentration. Similarly, compounds **5c**, **5d**, **6a** and **6b** showed a good activity against *P. vulgaris*, whereas all the compounds (**5a**–**5d** and **6a**–**6d**) showed a very good activity against *Staphylococcus aureus* at all three concentrations. The antibacterial activity demonstrated that all of the compounds were active only against the two Gram-positive strains and had no effect on the Gram-negative strains. The results of antifungal activity demonstrated that they were inactive against *A. niger* and they were more effective against

Table 3. Antimicrobial activity of the selected [3,2-a] pair of isomers.

		Bacterial strain zone of inhibition								Fungal strains zone of inhibition					
		Gram positive				Gram negative									
	Concentration	*P. vulgaris*		*S. aureus*		*K. pneumonia*		*P. aureus*		*C. albicans*		*A. niger*		*P. chrysogenum*	
Compound	(μg/mL)	mm	%	mm	%	mm	%	mm	%	mm	%	mm	%	mm	%
5a	25	–	–	181	82	–	–	–	–	124	62	–	–	–	–
	50	–	–	212	88	–	–	–	–	212	88	–	–	–	–
	100	–	–	258	92	–	–	–	–	266	95	–	–	–	–
5b	25	–	–	159	72	–	–	–	–	136	68	–	–	84	60
	50	–	–	207	86	–	–	–	–	190	79	–	–	130	72
	100	–	–	258	92	–	–	–	–	258	92	–	–	194	88
5c	25	102	85	119	54	–	–	–	–	–	–	–	–	–	–
	50	153	96	144	60	–	–	–	–	142	59	–	–	–	–
	100	197	98.5	180	64	–	–	–	–	202	72	–	–	–	–
5d	25	106	88.3	106	48	–	–	–	–	–	–	–	–	–	–
	50	155	97	135	56	–	–	–	–	–	–	–	–	–	–
	100	198	99	182	65	–	–	–	–	185	66	–	–	–	–
6a	25	–	–	198	90	–		–	–	124	62	–	–	–	–
	50	140	87.5	221	92	–	–	–	–	183	76	–	–	–	–
	100	182	91	266	95	–	–	–	–	247	88	–	–	119	66
6b	25	109	90.1	203	92	–	–	–	–	132	66	–	–	93	52
	50	148	92.5	228	95	–	–	–	–	171	71	–	–	125	69
	100	194	97	271	97	–	–	–	–	230	82	–	–	194	88
6c	25	–	–	150	68	–	–	–	–	–	–	–	–	–	–
	50	–	–	190	79	–	–	–	–	101	42	–	–	–	–
	100	–	–	238	85	–	–	–	–	152	54	–	–	–	–
6d	25	–	–	137	62	–	–	–	–	–	–	–	–	–	–
	50	–	–	178	74	–	–	–	–	–	–	–	–	–	–
	100	–	–	247	88	–	–	–	–	174	62	–	–	–	–
Standard	25	120	100	220	100	80	100	100	100	200	100	100	–	140	100
	50	160	100	240	100	120	100	140	100	240	100	140	–	180	100
	100	200	100	280	100	160	100	180	100	280	100	180	–	220	100
Control		20	–	20	–	20	–	20	–	20	–	20	–	20	–

Notes: Standards used were streptomycin for bacteria and nystatin for fungal strains; control: DMF.

C. albicans and less active against *P. chrysogenum*. In this also, the best results were obtained for compounds **5b** and **6b**, which were active against both *C. albicans* and *P. chrysogenum* at 25 μg/mL concentration. In the thiazolo-[3,2-a]-pyrimidinyl-5-ones, chloro, bromo and nitro substituted was found to be effective and compound **6b** exhibited moderate antifungal activity against *P. chrysogenum*.

2.1.2. *Diuretic activity*

The method of Lipschitz and Kavimani (*27, 28*) was employed for screening the diuretic activity. Adult Wistar rats of either sex weighing 150–200 g were used for the experiment. The animals were caged in standard metal cages provided with food and water *ad libitum*. The animals were divided into six groups (six in each) and deprived of food and water for 18 h prior to the experiment. The first two groups were administered with normal saline (control), furosemide (20 mg/kg, i.p.) and compounds (1 mg/kg body weight, p.o.).

Immediately after administration, animals were placed in metabolic cages (two per cage) specially designed to separate urine and faecal matter and kept at room temperature ($25 \pm 0.5\,^{\circ}C$). During the period of study, no food or water were available to the animals. The total volume of urine was collected and measured from control, standard and compounds after 5 h of administration. The parameters monitored for each individual rat were total urine volume (collected for water intake during the rest period and measured after 24 h of treatment) and urine concentration of Na^+, K^+ and Cl^-. Na^+ and K^+ concentrations were measured by flame photometry and Cl^- concentration was estimated as NaCl by titration with silver nitrate solution (2.096 g/L) using one drop of 5% potassium chromate solution as an indicator (Table 4). All the data are expressed as mean ± SEM and analyzed by ANOVA followed by Dunnet's *t*-test ($n = 6$).

The diuretic activity of the synthesized compounds showed significant activity, except **3d** and **4d**, which are substituted by -Br in the sixth position of the coumarin ring. The remaining tested compounds, unsubstituted and substituted with chloro and methyl groups showed promising activity. Compounds exhibit a high activity compared with standard Furosemide 20. The amount of chlorine in the urine sample of the simple unsubstituted compound is very high (2600 μmol/kg), which is significant compared with Furosemide 20.

Among all of the tested compounds, compounds **3a** and **4a** showed the highest activity in the case of total sodium, potassium and chloride depletion compared with the standard. The 6-bromo-substituted compounds showed lower diuretic activity, and the sodium, potassium and

Table 4. The *in vitro* diuretic activity of selected [3,2-a] pair of isomers against Albino rats (μmol/kg).

Sl. no.	Compound R	Total urine volume (ml/24 h)	Total Na^+ (μmol/kg)	Total K^+ (μmol/kg)	Total Cl^- (μmol/kg)
1	**3a**	32.44 ± 0.4	142.5 ± 4	150 ± 6	2600
2	**3b**	25.72 ± 0.2	119 ± 7	125 ± 5	2048
3	**3c**	28.23 ± 0.5	123 ± 4	145 ± 3	2245
4	**3d**	20.55 ± 0.3	115 ± 2	116 ± 7	1658
5	**4a**	32.34 ± 0.4	146 ± 4	148 ± 6	2630
6	**4b**	27.72 ± 0.1	120 ± 3	120 ± 5	2022
7	**4c**	28.62 ± 0.2	123 ± 5	149 ± 3	2222
8	**4d**	20.62 ± 0.1	118 ± 2	118 ± 9	1652
	Control	18.2 ± 0.3	85 ± 3	82.2 ± 2	685
	Furosemide 20 (standard)	24.18 ± 0.7	113 ± 3	120 ± 9	1945

Notes: The values are expressed as mean ± SEM. The results are analyzed using ANOVA followed by Dunnet's *t*-test ($n = 6$).

chloride depletion was also found to be very low. Thus, the synthesized coumarinyl thiazolo-[3,2-a]-pyrimidinones proved to be promising diuretics that need further in-depth investigation.

3. Conclusion

3-Bromoacetyl coumarins have successfully been used as molecular handles to generate isomeric thiazolo-[3,2-a]-pyrimidinones, and this method has the potential to be applied for other heterocycles which would lead to a large number of biologically potent biheterocyclic compounds. To the best of our knowledge, this is the first report in this direction.

4. Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra (KBr) were run on a Nicolet impact 410 FT-IR spectrometer (υ_{max} in cm^{-1}). ^1H NMR spectra were recorded in DMSO-d_6 with TMS as an internal standard (chemical shift δ in ppm and J values in Hz) on a Bruker 300 MHz FTNMR spectrometer. Mass spectra were recorded on a Finnignan MAT (Model MAT8200) spectrometer. The UV fluorescence spectrum was recorded on a U-3310 UV–VIS, F-7000 spectrophotometer. Elemental analysis was carried out on a Heraus CHN rapid analyser. Nomenclature was created using ChemDraw software. The purity of the compounds was checked by thin layer chromatography on silica gel plates using ethyl acetate and a benzene solvent system. All the reagents were of laboratory reagent quality and were used after purification.

4.1. *General procedure for the synthesis of 7-methyl-3-[(3′-coumarinyl)]-5H-[1,3]-thiazolo-[3,2-a]-pyrimidine-5-ones (3a–3e)*

A mixture of substituted coumarinylaminothiazole (**2**) (0.0025 mol), ethylacetoacetate (0.0025 mol) and polyphosphoric acid (2.0 g) was heated to 150–165 °C for 3–4 h. The reaction mixture was cooled and poured into ice-cold water, and the separated solid was filtered off. It was washed several times with ethanol, dried and recrystallized from ethanol/dioxane (1:1) to yield a crystalline solid.

4.1.1. *7-Methyl-3-[(3′-coumarinyl)]-5H-[1,3]-thiazolo-[3,2-a]-pyrimidine-5-one* ***(3a)***

IR (KBr) cm^{-1}: 1685, 1716; ^1H NMR (300 MHz, DMSO) δ: 2.29 (s, 3H, C_6-H of pyrimidine), 7.36 (d, 1H, $J = 7.4$ Hz, C_5H), 7.42 (t, 1H, $J = 7.6$ Hz, C_6-H), 7.62 (s, 1H, C_5-H of pyrimidine), 7.68 (t, 1H, $J = 7.3$ Hz, C_7-H), 7.78 (d, 1H, $J = 7.6$ Hz, C_8H), 8.15 (s, 1H, C_5-H of thiazole), 8.50 (s, 1H, C_4-H of coumarin); LC-MS 310.9 (M^+, 100%). Anal. Calcd. for $C_{16}H_{10}N_2O_3S$: C, 61.93; H, 3.25; N, 9.03%. Found: C, 61.88; H, 3.27; N, 9.05.

4.1.2. *7-Methyl-3-[(6′-methyl-(3′-coumarinyl)]-5H-[1,3]-thiazolo-[3,2-a]-pyrimidine-5-one* ***(3b)***

IR (KBr) cm^{-1}: 1680, 1732; ^1H NMR (300 MHz, DMSO) δ: 2.12 (s, 3H, C_6-H of pyrimidine), 2.36 (s, 3H, C_6-H of coumarin), 6.02 (s, 1H, C_5-H of pyrimidine), 6.63 (s, 1H, C_5-H of thiazole), 7.27–7.52 (m, 3H, Ar), 7.60 (s, 1H, C_4-H of coumarin); LC–MS 326 (M^+, 100%). Anal. Calcd. for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64%. Found: C, 62.89; H, 3.70; N, 8.60.

4.1.3. *7-Methyl-3-[(6′-chloro-(3′-coumarinyl)]-5H-[1,3]-thiazolo-[3,2-a]-pyrimidine-5-one* ***(3c)***

IR (KBr) cm^{-1}: 1682, 1738; ^1H NMR (300 MHz, DMSO) δ: 2.36 (s, 3H, C_6-H of pyrimidine), 6.09 (s, 1H, C_5-H of pyrimidine), 6.95 (s, 1H, C_5-H of thiazole), 7.27–7.52 (m, 3H, Ar), 7.63 (s, 1H, C_4-H of coumarin); LC–MS 345 (^{35}Cl, M+1, 100%). Anal. Calcd. for $C_{16}H_9ClN_2O_3S$: C, 55.74; H, 2.63; N, 8.13%. Found: C, 55.52; H, 2.62; N, 8.10.

4.1.4. *7-Methyl-3-[(6′-bromo-(3′-coumarinyl)]-5H-[1,3]-thiazolo-[3,2-a]-pyrimidine-5-one* ***(3d)***

IR (KBr) cm^{-1}: 1636, 1727; ^1H NMR (300 MHz, DMSO) δ: 2.37 (s, 3H, C_6-H of pyrimidine), 6.11 (s, 1H, C_5-H of pyrimidine), 6.95 (s, 1H, C_5-H of thiazole), 7.28–7.67 (m, 3H, Ar), 7.82 (s, 1H, C_4-H of coumarin); LC–MS 390.7 (^{79}Br, M+2, 100%). Anal. Calcd. for $C_{16}H_9BrN_2O_3S$: C, 49.37; H, 2.33; N, 7.20%. Found: C, 49.22; H, 2.22; N, 7.10.

4.1.5. *7-Methyl-3-[(5,6-benzo-(3′-coumarinyl)]-5H-[1,3]-thiazolo-[3,2-a]-pyrimidine-5-one* ***(3e)***

IR (KBr) cm^{-1}: 1624, 1722; ^1H NMR (300 MHz, DMSO) δ: 2.33 (s, 3H, C_6-H of pyrimidine), 6.04 (s, 1H, C_5-H of pyrimidine), 6.17 (s, 1H, C_5-H of thiazole), 7.28–8.22 (m, 6H, Ar), 8.25 (s, 1H, C_4-H of coumarin); LC–MS 360.9. Anal. Calcd. for $C_{20}H_{12}N_2O_3S$: C, 66.65; H, 3.36; N, 7.77%. Found: C, 66.68; H, 3.39; N, 7.66.

4.2. *General procedure for the synthesis of 5-methyl-3-[(3′-coumarinyl)]-7H-[1,3]-thiazolo-[3,2-a]-pyrimidine-7-ones (4a–4e)*

A mixture of substituted 3-bromoacetyl coumarin (**1**) (0.0025 mol), 2-mercapto-6-methyl uracil (0.0025 mol), K_2CO_3(0.0065 mol) was refluxed in 20 mL of dry xylene for 24 h. After completion of reaction, the reaction mixture was filtered off and xylene concentrated on a rotary evaporator. The solid separated was recrystallized from ethanol and dioxane mixture (1:1) to yield a crystalline solid.

4.2.1. *5-Methyl-3-[(3′-coumarinyl)]-7H-[1,3]-thiazolo-[3,2-a]-pyrimidine-7-one-(****4a****)*

IR (KBr) cm^{-1}: 1658, 1726; ^1H NMR (300 MHz, DMSO) δ: 2.15 (s, 3H, C_6-H of pyrimidine), 7.42 (d, 1H, $J = 7.5$ Hz, C_5-H), 7.45 (s, 1H, C_5-H of pyrimidine), 7.65 (t, 1H, $J = 7.1$ Hz, C_6-H), 7.78 (t, 1H, $J = 7.1$ Hz, C_7-H), 7.90 (d, 1H, $J = 7.6$ Hz, C_8H), 8.18 (s, 1H, C_5-H of thiazole), 8.30 (s, 1H, C_4-H of coumarin); LC–MS 310.9 (M^+, 100%). Anal. Calcd. for $C_{16}H_{10}N_2O_3S$: C, 61.93; H, 3.25; N, 9.03. Found: C, 61.88; H, 3.38; N, 9.09.

4.2.2. *5-Methyl-3-[(6′-methyl-(3′-coumarinyl)]-7H-[1,3]-thiazolo-[3,2-a]-pyrimidine-7-one* ***(4b)***

IR (KBr) cm^{-1}: 1649, 1726; ^1H NMR (300 MHz, DMSO) δ: 2.32 (s, 3H, C_6-H of coumarin), 2.74 (s, 3H, C_6-H of pyrimidine), 7.02 (s, IH, C_5-H of pyrimidine), 7.62 (s, 1H, C_5-H of thiazole), 7.37–8.02 (m, 3H, Ar), 8.49 (s, 1H, C_4-H of coumarin); LC–MS 326 (M^+, 100%). Anal. Calcd. for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64. Found: C, 62.90; H, 3.75; N, 8.62.

4.2.3. *5-Methyl-3-[(6′-chloro-(3′-coumarinyl)]-7H-[1,3]-thiazolo-[3,2-a]-pyrimidine-7-one (**4c**)*

IR (KBr) cm^{-1}: 1642, 1719; ^1H NMR (300 MHz, DMSO) δ: 2.74 (s, 3H, C_6-H of pyrimidine), 7.02 (s, IH, C_5-H of pyrimidine), 7.67 (s, 1H, C_5-H of thiazole), 7.27–8.05 (m, 3H, Ar), 8.52 (s, 1H, C_4-H of coumarin); LC–MS 345 (^{35}Cl, M+1, 100%). Anal. Calcd. for $C_{16}H_9ClN_2O_3S$: C, 55.74; H, 2.63; N, 8.13%. Found: C, 55.72; H, 2.60; N, 8.10.

4.2.4. *5-Methyl-3-[(6′-bromo-(3′-coumarinyl)]-7H-[1,3]-thiazolo-[3,2-a]-pyrimidine-7-one (**4d**)*

IR (KBr) cm^{-1}: 1643, 1728; ^1H NMR (300 MHz, DMSO) δ: 2.73 (s, 3H, C_6-H of pyrimidine), 7.06 (s, 1H, C_5-H of pyrimidine), 7.80 (s, 1H, C_5-H of thiazole), 7.27–7.79 (m, 3H, Ar), 8.42 (s, 1H, C_4-H of coumarin); LC–MS 390.7 (^{79}Br, M+2, 100%). Anal. Calcd. for $C_{16}H_9BrN_2O_3S$: C, 49.37; H, 2.33; N, 7.20. Found: C, 49.32; H, 2.22; N, 7.85.

4.2.5. *5-Methyl-3-[(5,6-benzo-(3′-coumarinyl)]-7H-[1,3]-thiazolo-[3,2-a]-pyrimidine-7-one (**4e**)*

IR (KBr) cm^{-1}: 1644, 1726; ^1H NMR (300 MHz, DMSO) δ: 2.18 (s, 3H, C_6-H of pyrimidine), 6.27 (s, 1H, C_5-H of pyrimidine), 6.56 (s, 1H, C_5-H of thiazole), 7.45–8.05 (m, 6H, Ar), 8.65 (s, 1H, C_4-H of coumarin); LC–MS 360.9. Anal. Calcd. for $C_{20}H_{12}N_2O_3S$: C, 66.65; H, 3.36; N, 7.77%. Found: C, 66.64; H, 3.17; N, 7.36.

4.3. *General procedure for the MW-assisted synthesis of 7-phenyl-3-[(3′-coumarinyl)]-5H-[1, 3]-thiazolo-[3,2-a]-pyrimidine 5-ones (5a–5d)*

A mixture of substituted coumarinyl amino thiazole (**2**) (0.003 mol) and benzoylacetoacetate (0.003 mol) was heated at 125–130 °C in a MW oven for 1–3 min. The crystalline product separated out at room temperature was filtered and washed with water and ether to give a bright yellow-colored solid.

4.3.1. *7-Phenyl-3-[(3′-coumarinyl)]-5H-[1,3]-thiazolo-[3,2-a]-pyrimidine-5-one (**5a**)*

IR (KBr) cm^{-1}: 1632, 1716; ^1H NMR (300 MHz, DMSO) δ: 6.04 (s, 1H, C_5-H of pyrimidine), 6.17 (s, 1H, C_5-H of thiazole), 7.28–8.22 (m, 9H, Ar), 8.25 (s, 1H, C_4-H of coumarin); LC–MS 372.9 (M^+, 100%). Anal. Calcd. for $C_{21}H_{12}N_2O_3S$: C, 67.73; H, 3.25; N, 7.52%. Found: C, 67.52; H, 3.45; N, 7.48.

4.3.2. *7-Phenyl-3-[(6′-chloro-(3′-coumarinyl)]-5H-[1,3]-thiazolo-[3,2-a]-pyrimidine-5-one (**5b**)*

IR (KBr) cm^{-1}: 1666, 1732; ^{1} H NMR (300 MHz, DMSO) δ: 6.17 (s, 1H, C_5-H of pyrimidine), 7.17 (s, 1H, C_5-H of thiazole), 7.43–8.44 (m, 8H, Ar), 8.50 (s, 1H, C_4-H of coumarin); LC–MS 407 (^{35}Cl, M+1, 100%). Anal. Calcd. for $C_{21}H_{11}ClN_2O_3S$: C, 62.00; H, 2.73; N, 6.89%. Found: C, 62.10; H, 2.05; N, 6.74.

4.3.3. *7-Phenyl-3-[6-bromo-(3′-coumarinyl)]-5H-[1,3]-thiazolo-[3,2-a]-pyrimidine-5-one (**5c**)*

IR (KBr) cm^{-1}: 1658, 1740; ^1H NMR (300 MHz, DMSO) δ: 6.27 (s, 1H, C_5-H of pyrimidine), 7.10 (s, 1H, C_5-H of thiazole), 7.53–8.44 (m, 8H, Ar), 8.40 (s, 1H, C_4-H of coumarin); LC–MS 452.9 (^{79}Br, M+2, 100%). Anal. Calcd. for $C_{21}H_{11}BrN_2O_3S$: C, 55.89; H, 2.46; N, 6.21. Found: C, 55.74; H, 2.47; N, 6.30.

4.3.4. *7-Phenyl-3-[6-nitro-(3′-coumarinyl)]-5H-[1,3]-thiazolo-[3,2-a]-pyrimidine-5-one (**5d**)*

IR (KBr) cm^{-1}: 1642, 1736; ^1H NMR (300 MHz, DMSO) δ: 6.27 (s, 1H, C_5-H of pyrimidine), 7.10 (s, 1H, C_5-H of thiazole), 7.53–8.44 (m, 8H, Ar), 8.40 (s, 1H, C_4-H of coumarin; LC–MS 417.9 (M^+, 100%). Anal. Calcd. for $C_{21}H_{11}N_3O_5S$: C, 60.43; H, 2.66; N, 10.07%. Found: C, 60.22; H, 2.62; N, 9.65.

4.4. *General procedure for the synthesis of 5-phenyl-3-[(3′-coumarinyl)]-7H-[1,3]-thiazolo-[3,2-a]-pyrimidine-7-ones (6a–6d)*

A mixture of substituted 3-bromoacetyl coumarin (0.0026 mol), 2-mercapto 6-phenyl uracil (0.0026 mol), K_2CO_3 (0.0065 mol) was refluxed in 20 mL of dry xylene for 24 h. After completion of reaction, the reaction mixture was filtered off and xylene concentrated on a rotary evaporator. The solid separated was washed with water and ethanol. The solid obtained was crystallized from ethanol/dioxane (1:1).

4.4.1. *5-Phenyl-3-[(3′-coumarinyl)]-7H-[1,3]-thiazolo-[3,2-a]-pyrimidine-7-one (**6a**)*

IR (KBr) cm^{-1}: 1667, 1729; ^1H NMR (300 MHz, DMSO) δ: 6.25 (s, 1H, C_5-H of pyrimidine), 6.30 (s, 1H, C_5-H of thiazole), 7.03–7.66 (m, 9H, Ar), 8.22 (s, 1H, C_4-H of coumarin); LC–MS 372.9 (M^+, 100%). Anal. Calcd. for $C_{21}H_{12}N_2O_3S$: C, 67.73; H, 3.25; N, 7.52%. Found: C, 67.53; H, 3.55; N, 7.13.

4.4.2. *5-Phenyl-3-[(6′-chloro-(3′-coumarinyl)]-7H-[1,3]-thiazolo-[3,2-a]-pyrimidine-7-one (**6b**)*

IR (KBr) cm^{-1}: 1650, 1730; ^1H NMR (300 MHz, DMSO) δ: 6.07 (s, 1H, C_5-H of pyrimidine), 6.50 (s, 1H, C_5-H of thiazole), 8.76 (s, 1H, C_4-H of coumarin), 7.45-8.05 (m, 8H, Ar); LC–MS 407 (^{35}Cl, M+1, 100%). Anal. Calcd. for $C_{21}H_{11}ClN_2O_3S$: C, 62.00; H, 2.73; N, 6.89%. Found: C, 62.12; H, 2.09; N, 6.76.

4.4.3. *5-Phenyl-3-[(6′-bromo-(3′-coumarinyl)]-7H-[1,3]-thiazolo-[3,2-a]-pyrimidine-7-one (**6c**)*

IR (KBr) cm^{-1}: 1654, 1727; ^1H NMR (300 MHz, DMSO) δ: 6.43 (s, 1H, C_5-H of pyrimidine), 6.76 (s, 1H, C_5-H of thiazole), 7.06–8.64 (m, 8H, Ar), 8.68 (s, 1H, C_4-H of coumarin); LC–MS 452.9 (^{79}Br, M+2, 100%). Anal. Calcd. for $C_{21}H_{11}BrN_2O_3S$: C, 55.89; H, 2.46; N, 6.21%. Found: C, 55.80; H, 2.42; N, 6.33.

4.4.4. *5-Phenyl-3-[(6′-nitro-(3′-coumarinyl)]-7H-[1,3]-thiazolo-[3,2-a]-pyrimidine-7-one (**6d**)*

IR (KBr) cm^{-1}: 1660, 1743;^{1}H NMR (300 MHz, DMSO) δ: 6.52 (s, 1H, C_5-H of pyrimidine), 6.73 (s, 1H, C_5-H of thiazole), 6.73–8.58 (m, 8H, Ar), 8.94 (s, 1H, C_4-H of coumarin); LC–MS 417.9 (M^+, 100%). Anal. Calcd. for $C_{21}H_{11}N_3O_5S$: C, 60.43; H, 2.66; N, 10.07%. Found: C, 60.22; H, 2.62; N, 9.65.

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