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Synthesis, antimicrobial and DFT studies of novel fused thiazolopyrimidine derivatives

Abstract: The reaction of dihydropyrimidine-2(1*H*)-thione **4**, obtained by the condensation of chalcone **3** with thiourea, with chloroacetic acid and 1,2-dibromoethane furnished compounds **5** and **6** and not their respective isomers **8** and **9**. The regiochemistry of the cyclized products and their structure was established by elemental analysis, ^1H NMR, ^{13}C NMR, IR and mass spectral data. Density functional theory (DFT) calculations have been carried out for compound **5a** and its isomer **8a** with Jaguar version 6.5112 using B3LYP density functional method and 6–31G** basis set. ^1H and ^{13}C NMR spectra of compound **5a** and its possible isomer **8a** have been calculated and correlated with experimental results. 2-Arylidene derivatives of **5** were obtained by two routes and their structure was established by spectral data. Compounds **4–7** were screened for their antimicrobial activities.

Keywords: antimicrobial activities; arylidene derivatives; chalcone; DFT studies; spectral data; 4-thiazolidinone.

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Introduction

Heterocyclic compounds are highly ranked among pharmaceutically important natural and synthetic materials. The remarkable ability of heterocyclic nuclei to serve as both biomimetics and active pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs. The thiazolidinone system frequently appears in the structure of various natural products, notably thiamine, compounds possessing cardiac and glycemic benefits such as troglitazone [1] and many metabolic products of fungi and primitive marine animals. Pioglitazone [2] and rosiglitazone are therapeutic agents for the treatment of diabetes [3].

The 4-thiazolidinone system is a core structure in many synthetic compounds exhibiting broad pharmacological spectrum and affinity for various biotargets [4, 5]. Some derivatives are peroxisome proliferator-activated receptor γ (PPAR- γ) agonists showing hypoglycemic activity [6], aldose reductase inhibitors guarding against diabetic complications [7] and cartilage degradation inhibitors [8]. Additionally, 4-thiazolidinone derivatives are reported as anticancer [9, 10], antibacterial [11], anti-HIV [12], anticonvulsant [13], antidiabetic [14] and anti-inflammatory [15] agents.

In continuation of our research program on the synthesis of condensed 4-thiazolidinines [16–18], we report in this paper a novel condensed thiazolo-pyrimidine system. Both thiazole and pyrimidine are bioactive nuclei and it is thought that the condensed system may exhibit enhanced biological activity due to possible synergistic effects. Two novel thiazolo[3,2-*a*]pyrimidin-3(5*H*)-one **5** and dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine **6** systems are reported. Arylidene derivatives **7** of compounds **5** were also synthesized.

Computational studies

The molecular geometry optimization and ^1H and ^{13}C NMR spectra calculations were performed with the Jaguar software package version 6.5112 by using density functional theory (DFT) methods with B3LYP (Becke three parameter Lee-Yang-Parr) exchange correlation functional, which combines the hybrid exchange functional of Becke [19], with the gradient-correlation functional of Lee et al. [20]. The 6–31G** basis set was used for calculations in the gas phase of the structure **5a** and its isomer **8a**, respectively.

As the crystal structures of the molecules are not available, DFT calculations were carried out to predict the geometry of the molecules. The optimized bond lengths and bond angles obtained by geometry optimization at B3LYP/6–31G** level of theory for structure **5a** are reported in Table 1. For structure **5a**, the optimized bond lengths of C=O and S-C in thiazolidinone ring fall in the range of 1.208 Å and 1.856 Å. The optimized bond angles for N-C-O and N-C-S were observed at 122.6° and 126°, respectively. The optimized configurations of structure **5a** and its isomer **8a** with atom numbering schemes are shown in Figure 1.

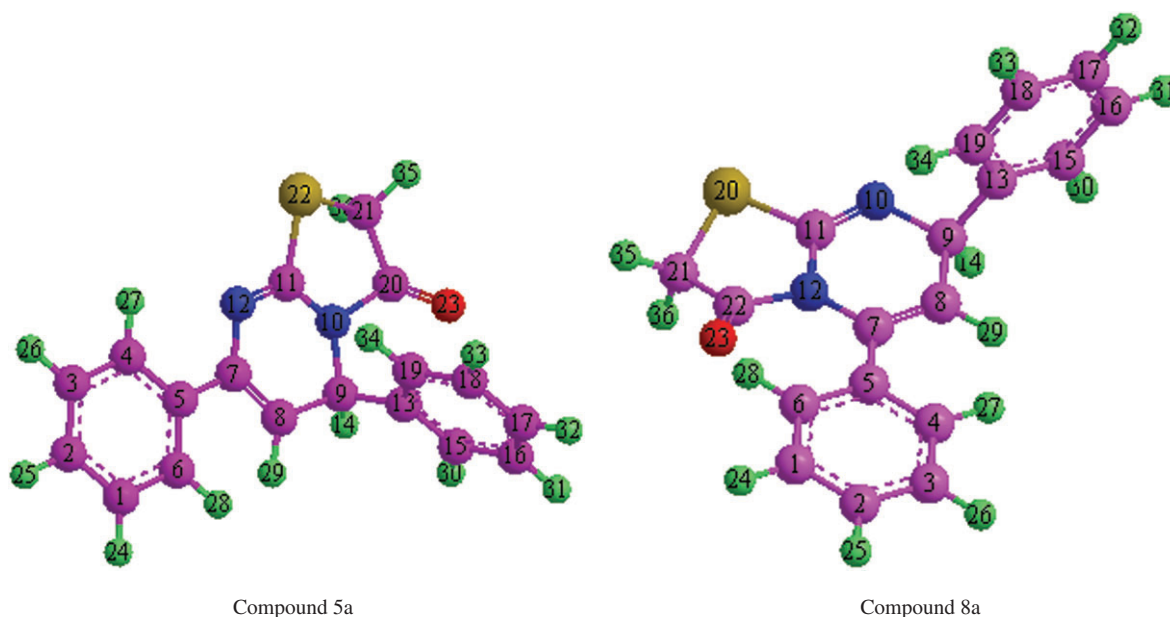


Figure 1 Optimized geometry of compound **5a** and its isomer **8a**.

Shielding tensors of structures **5a** and **8a** were evaluated by using B3LYP functional with basis set given above. To express the chemical shifts in ppm, the geometry of tetramethylsilane (TMS) and chloroform molecules had been optimized and then their ^1H and ^{13}C NMR spectra were calculated by the same method using the same basis set as in the case of the calculations on structures **5a** and **8a**. The shielding of TMS is 32.3379 for ^1H NMR and 202.8593 for ^{13}C NMR. The calculated isotropic shielding constants σ_i were then transformed to chemical shifts relative to TMS by the equation: $\delta_i = \sigma_{\text{TMS}} - \sigma_i$.

Experimental and calculated ^1H and ^{13}C NMR chemical shifts (ppm) of compounds **5a** and its isomer **8a** are reported in Tables 2 and 3. The correlation values of proton chemical shifts are found to be 0.9708 for structure **5a** and 0.8153 for its isomer **8a** (Figure 2). Similarly, the correlation values of carbon chemical shifts of **5a** and **8a** are found to be 0.9973 and 0.9828, respectively (Figure 3). The theoretical and experimental ^1H and ^{13}C data show good correlations for proposed structure **5a** and not for **8a**. Total energies, zero point energies, HOMO and LUMO energies theoretically obtained for structures **5a** and **8a** are reported in Table 4. Spectral correlation and energy values support structure **5a** for the product and are not consistent for the isomeric structure **8a**.

Results and discussion

Treatment of chalcone **3a**, obtained by the reaction of acetophenone and benzaldehyde, with thiourea in alcoholic

KOH gave compound **4a** (Scheme 1). The unsymmetrical thione **4a** on reaction with chloroacetic acid followed by cyclization of the intermediate *in situ* was likely to be transformed into compound **5a** or **8a** or both depending on the mode of cyclization. However, the treatment of thione **4a** with chloroacetic acid in the presence of anhydrous sodium acetate in absolute ethanol afforded a single product (thin layer chromatography, TLC) **5a** or **8a** in 78% yield. The appearance of a band at 1744 cm^{-1} ($\text{C}=\text{O}$) in the IR spectrum, appearance of a peak at $\delta\ 189$ ($\text{C}=\text{O}$) in ^{13}C NMR spectrum and the presence of a molecular ion

Table 1 Selected bond lengths and bond angles of the optimized structure **5a**.

Bond lengths (Å)		Bond angles (°)	
Entry	Optimized lengths	Entry	Optimized angles
C(21)-H(36)	1.11	H(36)-C(21)-H(35)	109.4
C(8)-H(29)	1.10	H(36)-C(21)-S(22)	112.2
C(11)-N(10)	1.46	H(36)-C(21)-C(20)	108.8
C(20)-N(10)	1.46	N(10)-C(20)-C(21)	118.0
C(9)-N(10)	1.47	N(10)-C(20)-O(23)	122.6
C(8)-C(9)	1.49	C(21)-C(20)-O(23)	122.5
N(12)-C(7)	1.45	C(19)-C(13)-C(9)	121.4
C(11)-N(12)	1.26	C(7)-N(12)-C(11)	115.0
S(22)-C(11)	1.85	N(10)-C(11)-N(12)	126.0
C(21)-S(22)	1.82	N(12)-C(11)-S(22)	126.0
C(20)-C(21)	1.50	C(11)-N(10)-C(20)	124.0
C(20)-O(23)	1.20	C(11)-N(10)-C(9)	108.0
C(9)-H(14)	1.11	N(10)-C(9)-H(14)	107.5
C(5)-C(7)	1.50	C(8)-C(7)-N(12)	120.0

Table 2 Experimental and calculated ^1H NMR chemical shifts (ppm) of compound **5a** and its isomer **8a**.

Structure 5a					Structure 8a			
Entry	Expt. NMR	Calcd shield	Calcd NMR	Averaged NMR	Entry	Calcd shield	Calcd NMR	Averaged NMR
H14	5.59	27.0546	5.66		H14	27.3507	5.34	5.34
H24		24.6816	8.21		H24	24.6120	8.28	
H25		24.7979	8.08		H25	24.8266	8.05	
H26	7.19	24.6245	8.27	8.13	H26	24.5653	8.33	8.22
H27		24.8979	7.97		H27	24.5000	8.40	
H28		24.7466	8.14		H28	24.8359	8.04	
H29	5.86	26.5097	6.25		H29	27.4754	5.21	
H30		24.8402	8.04		H30	24.8266	8.05	
H31		24.6636	8.22		H31	24.6587	8.23	
H32	7.72	24.8466	8.03	8.20	H32	24.8733	8.00	8.18
H33		24.5789	8.32		H33	24.5933	8.30	
H34		24.4682	8.43		H34	24.5374	8.36	
H35	3.95	28.7048	3.89	4.19	H35	28.1817	4.45	4.61
H36		28.1437	4.50		H36	27.8855	4.77	

peak at m/z 307 (63%) in the mass spectrum of the TLC pure product suggested that cyclization had indeed taken place. The IR and mass spectral data were of little help in deciding in favor of either structure **5a** or **8a**. However, the structure **5a** was finally assigned to this cyclization product in preference to structure **8a** on the basis of ^1H NMR spectral data. Similarly, structure **5b** was finally assigned to this cyclization product in preference to structure **8b** on the basis of ^1H NMR spectral data.

The reaction of compound **4a** with 1,2-dibromoethane gave a product which was purified by column chromatography and could be represented by either structure **6a** or **9a**. In either structure (**6a** or **9a**), the singlet at δ 5.32 in its

Table 3 Experimental and calculated ^{13}C NMR chemical shifts (ppm) of compound **5a** and its isomer **8a**.

Compound 5a				Compound 8a		
Entry	Expt. NMR	Calcd shield	Calcd NMR	Entry	Calcd shield	Calcd NMR
C1	132	73.0785	135.64	C1	69.2439	139.65
C3	137	71.5494	137.24	C3	79.3263	129.31
C9	55	151.3189	53.87	C9	145.8602	59.57
C11	161	49.491	160.29	C11	35.2589	175.17
C20	189	26.6823	184.14	C22	5.7554	206.01
C21	39	167.0381	37.44	C21	169.2145	35.16

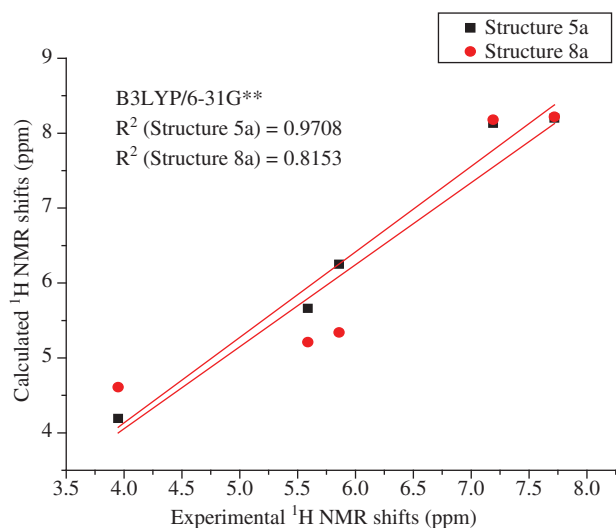
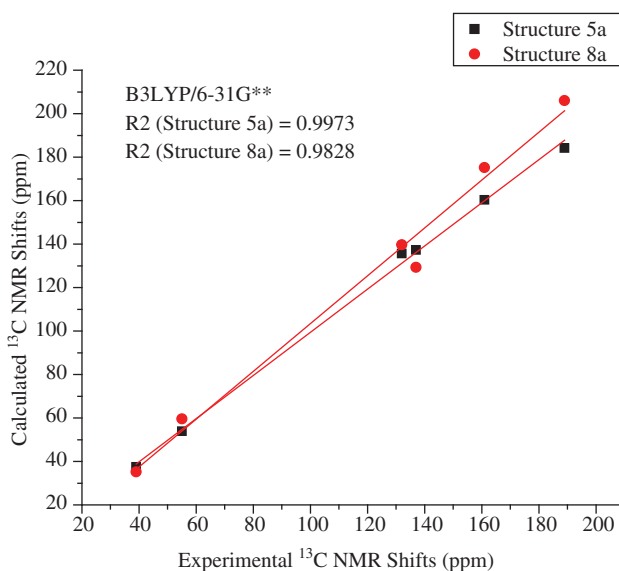
**Figure 2** Plot of the calculated vs. the experimental ^1H NMR chemical shifts (ppm).**Figure 3** Plot of the calculated vs. the experimental ^{13}C NMR chemical shifts (ppm).

Table 4 Theoretically computed energies for compounds **5a** and **8a**.

Parameters	Compound 5a	Compound 8a
HOMO energy (kcal/mol)	-170.01	-165.13
LUMO energy (kcal/mol)	37.88	49.79
Zero point energy (kcal/mol)	186.23	187.71

^1H NMR spectrum integrating for one proton was assignable to H_A . If the structure **8a** is correct for the cyclization product, obtained from thione **4a** and chloroacetic acid, and then H_A would resonate in the same region as that of structure **6a** (or **9a**). By contrast, if structure **5a** is correct, H_A will be deshielded by the thiazolidinone ring and consequently H_A will resonate downfield in comparison to H_A in **6a** (or **9a**). The appearance of a downfield singlet at δ 5.59 for H_A in structure **5a** (or **8a**) as compared with singlet at δ 5.32 for H_A in structure **6a** (or **9a**) supports structure **5a** and is not consistent with structure **8a** for which such a downfield shift would not be expected. The deshielding effect is due to the magnetic anisotropy of the $\text{C}=\text{O}$ group with a minor contribution from the rest of the ring. Similarly, structure **5b** was assigned to the final product (not **8b**). The same structural conclusion is supported by comparing the chemical shifts of H_A of thione **4a** with that of cyclization product **5a**. The H_A proton in thione **4a** resonates at δ 5.12, whereas the

downfield signal at δ 5.59 (1H, s, H_A) in the cyclized product supports structure **5a** in preference to structure **8a**. Also, from DFT studies (Table 4) structure **5a** is preferred over **8a** by energy of 1.48 kcal/mol. Arylidene thiazolidinones **7a–d** were prepared by two routes. In the first approach thiazolidinone **5** was condensed with aldehydes to give arylidene thiazolidinones, whereas in the second approach compound **7a** was obtained directly by heating compound **4a** with chloroacetic acid and benzaldehyde. Structures **7a–d** were established by IR and ^1H NMR spectral data. The parent thiazolidinones **5a** and **5b** exhibit absorption bands at 1744 and 1744 cm^{-1} ($\text{C}=\text{O}$), but unsaturation at the 2-position being conjugated with the carbonyl group at the 3-position as in arylidene thiazolidinones produces a bathochromic shift [21], as expected; the carbonyl absorption band appears at 1728, 1726 cm^{-1} in structures **7a–b** and 1728, 1720 cm^{-1} in structures **7c–d**, respectively. The downfield shift in the position of H_A in ^1H NMR of the product obtained by reaction of **4a** with chloroacetic acid may be due to the presence of the imine group in structure **8a**. If this is the case then in arylidene derivatives **7a–b** H_A proton will not be affected further because of absence of a conjugated carbonyl group. In the case of arylidene derivatives obtained from **5a** the conjugated carbonyl function produces further downfield shift in position of H_A in **7a–b**, that is, δ 6.28 and δ 6.32. This corroborates with structure **5a** and is not consistent with **8a**. Structure **6** (not **9**) for the product, obtained from

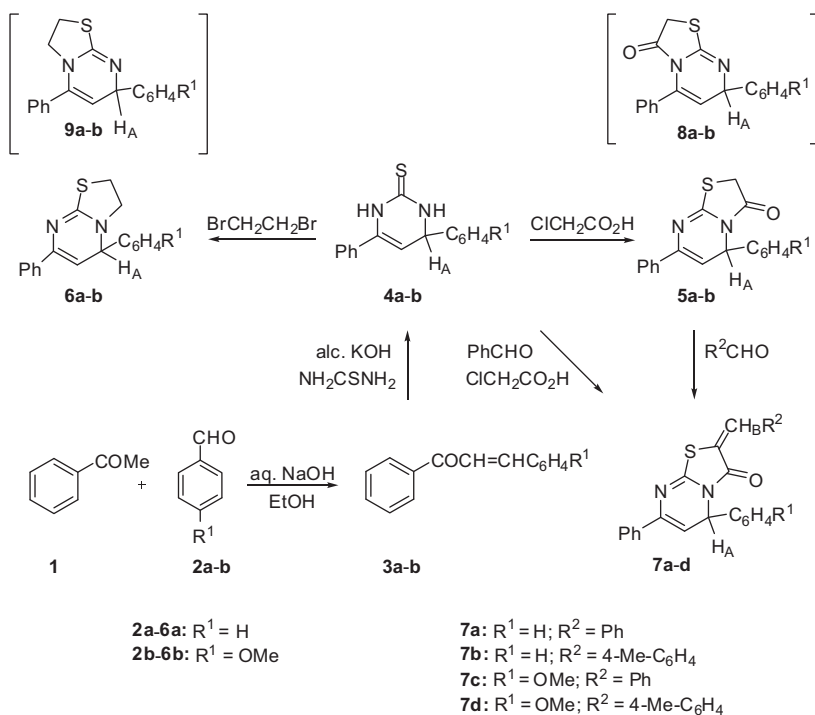
**Scheme 1** Synthesis of condensed 4-thiazolidinones (**5**) and its arylidene derivatives.

Table 5 Antimicrobial activity studies by disc diffusion method of compounds 4–7.

Compound	Zone of inhibition (mm)				
	Antibacterial activity			Antifungal activity	
	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Aspergillus niger</i>	<i>Rhizopus oryzae</i>
4a	3	2	3	3	3
4b	3	3	4	2	2
5a	8	5	6	7	3
5b	9	7	8	6	5
6a	4	3	3	2	5
6b	6	5	2	3	7
7a	6	2	5	3	4
7b	5	4	4	5	4
7c	6	4	3	2	5
7d	7	6	3	4	6
Antibiotic ^a	10	8	9	8	9
DMSO	00	00	00	00	00

^aStreptomycin for bacteria and nystatin for fungi were used at a concentration of 30 µg/mL.

the reaction of compound **4** with 1,2-dibromoethane, was assigned based on the analogy with structure **5**. In a similar way, the structures for compounds **5b** and **7b** were established by spectral data.

Antimicrobial activity

The newly synthesized compounds **4–7** were tested for antibacterial and antifungal activity. The antimicrobial activity of the compounds was assayed by an antimicrobial susceptibility test [22]. In Petri plates, 100 µL of 24 h growth of each microorganism was spread on the surface of nutrient agar for bacteria and fungi. Then, 50 µL compound at a concentration of 100 µg/mL in dimethyl sulfoxide (DMSO) saturated on discs of 6 mm diameter was kept on the agar surface. The plates were refrigerated for 2 h to allow prediffusion of the compounds from the discs into the seeded agar layer and then incubated at 37°C for 24 h for bacteria and 28°C for 48 h for fungi. Zones of inhibition were measured in mm and size of the disc was subtracted from the zone size to measure final activity. DMSO saturated discs served as solvent control or negative control and streptomycin saturated discs (30 µg) for bacteria and nystatin (30 µg) for fungi as a reference or positive control.

All compounds were found to exhibit moderate antibacterial and antifungal activity against different species of bacteria and fungi. From the activity data (Table 5) it was observed that among all the compounds tested, compounds **5a** and **5b** show good activity against all the tested bacteria and fungi. Compound **7d** shows good activity against *Staphylococcus aureus* (inhibition 7 mm, standard showed 10 mm) and *Bacillus subtilis* (inhibition 6 mm,

standard showed 8 mm). Other compounds **4a**, **4b**, **6a**, **6b** and **7a–c** show moderate activity against *Aspergillus niger* and *Rhizopus oryzae* fungi.

Experimental

Melting points (capillary, sulfuric acid bath) are uncorrected. TLC was performed on silica gel G plates using petroleum ether/ethyl acetate (4:1) as eluent and iodine as a visualizing agent. IR spectra were recorded on an ABB FTIR spectrometer. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded in DMSO-*d*₆ on a Bruker Advance II 400 NMR spectrometer. Mass spectra were recorded on a TOF MS ES+ 3.56e4 instrument. The elemental analysis of compounds was performed on a Carlo Erba-1108 elemental analyzer. The structures were optimized by molecular mechanics using the PM3 method based on Hyperchem with version 7.5 packages.

General procedure for the synthesis of chalcones 3

A solution of sodium hydroxide (3.1 g, 0.07 mol) in 28 mL of water and 17 mL of ethanol was stirred at 0°C and treated with 7.43 g (0.06 mol) of acetophenone **1** and then with benzaldehyde (6.57 g, 0.06 mol). Stirring was continued at room temperature for an additional 3–4 h. The mixture was left in ice for approximately 10 h. The resultant solid of **3** was filtered, washed with water and crystallized from ethanol [23].

1,3-Diphenyl-2-propen-1-one (3a) This compound was obtained in 90% yield as a cream colored solid; mp 54–56°C (Lit. mp 42–46°C); IR: ν 1664 (C=O) cm⁻¹; ¹H NMR: δ 7.42 (m, 3H, Ar-H and CH), 7.50 (m, 2H, Ar-H), 7.58 (m, 2H, Ar-H), 7.65 (m, 2H, Ar-H), 7.81 (d, 1H, CH, *J* = 15.7 Hz), 8.03 (m, 2H, Ar-H). Anal. Calcd for C₁₅H₁₂O: C, 86.54; H, 5.77. Found: C, 86.47; H, 5.84.

3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (3b) This compound was obtained in 92% yield as a yellow solid; mp 72–74°C (Lit. mp 69–71°C); IR: ν 1658 (C=O) cm^{-1} ; ^1H NMR: δ 3.85 (s, 3H, OCH_3), 6.93 (m, 2H, Ar-H), 7.41 (d, 1H, CH, $J = 15.6$ Hz), 7.49 (m, 2H, Ar-H), 7.55 (m, 1H, Ar-H), 7.59 (m, 2H, Ar-H), 7.79 (d, 1H, CH, $J = 15.6$ Hz), 8.01 (m, 2H, Ar-H). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{O}_2$: C, 80.67; H, 5.88. Found: C, 80.58; H, 5.94.

General procedure for synthesis of compounds 4

Compound **3** (0.005 mol), and thiourea (0.38 g, 0.005 mol) in ethanolic KOH (1 g in 20 mL ethanol) was heated under reflux for 4 h. The mixture was concentrated to half, and the concentrate was poured into ice-cold water. The resultant solid of **4** was filtered, washed with water and crystallized from ethanol [24].

4,6-Diphenyl-3,4-dihydropyrimidine-2(1H)-thione (4a) This compound was obtained in 82% yield as a yellow solid; mp 160–162°C; IR: ν 1180 (C=S), 1558 (C=C), 3171 (NH) cm^{-1} ; ^1H NMR: δ 5.12 (m, 1H, H_A), 5.31 (m, 1H, CH), 7.28 (m, 1H, Ar-H), 7.37 (m, 7H, Ar-H), 7.47 (m, 2H, Ar-H), 9.08 (br, 1H, NH, exchangeable with D_2O), 9.77 (br, 1H, NH, exchangeable with D_2O). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{S}$: C, 72.18; H, 5.26; N, 10.53; S, 12.03. Found: C, 72.10; H, 5.34; N, 10.45; S, 12.12.

4-(4-Methoxyphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1H)-thione (4b) This compound was obtained in 86% yield as a yellow solid; mp 176–178°C; IR: ν 1250 (C=S), 1558 (C=C), 3202 (NH) cm^{-1} ; ^1H NMR: δ 3.78 (s, 3H, OCH_3), 5.13 (m, 1H, H_A), 5.19 (m, 1H, CH), 6.88 (m, 2H, Ar-H), 7.28 (m, 2H, Ar-H), 7.36 (m, 3H, Ar-H), 7.49 (m, 2H, Ar-H), 8.75 (br, 1H, NH, exchanged with D_2O), 9.05 (br, 1H, NH, exchangeable with D_2O). Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{SO}$: C, 68.92; H, 5.41; N, 9.46; S, 10.81. Found: C, 68.87; H, 5.49; N, 9.54; S, 10.92.

General procedure for synthesis of thiazolidinones 5

A mixture of compound **4** (0.01 mol), chloroacetic acid (0.94 g, 0.01 mol) and anhydrous sodium acetate (0.82 g, 0.01 mol) in absolute ethanol (20 mL) was heated under reflux for 5 h. The mixture was cooled to room temperature and then poured into water. The resultant solid of **5** was filtered, washed with water and crystallized from ethanol.

5,7-Diphenyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (5a) This compound was obtained in 78% yield as a shining white solid; mp 80–84°C; IR: ν 1744 (C=O), 1651 (C=N) cm^{-1} ; ^1H NMR: δ 3.90–4.01 (dd, 2H, SCH_2 , $J = 12.6$, $J = 17.2$ Hz), 5.59 (s, 1H, H_A), 5.86 (s, 1H, CH), 7.12 (m, 1H, Ar-H); 7.22 (m, 1H, Ar-H); 7.28 (m, 2H, Ar-H); 7.35 (m, 5H, Ar-H); 7.82 (d, 1H, Ar-H, $J = 7.5$ Hz); ^{13}C NMR: δ 189, 161, 144, 137, 132, 130, 128, 127, 119, 114, 55, 40, 39; MS: m/z 307 ($\text{M}+\text{H}^+$, 63%). Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{SO}$: C, 70.59; H, 4.58; N, 9.15; S, 10.46. Found: C, 70.65; H, 4.65; N, 9.24; S, 10.52.

5-(4-Methoxyphenyl)-7-phenyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (5b) This compound was obtained in 80% yield as a

white solid; mp 100–102°C; IR: ν 1744 (C=O), 1612 (C=N) cm^{-1} ; ^1H NMR: δ 3.84 (s, 3H, OCH_3), 4.62 (dd, 2H, SCH_2 , $J = 5.7$ Hz, $J = 7.4$ Hz), 6.95 (s, 1H, H_A), 6.97 (s, 1H, CH), 7.52 (t, 2H, Ar-H, $J = 7.4$ Hz), 7.60 (m, 2H, Ar-H), 7.72 (m, 3H, Ar-H), 8.05 (m, 2H, Ar-H); ^{13}C NMR: δ 170, 159, 155, 139, 134, 131, 129, 127, 126, 121, 113, 111, 54, 40, 39, 38, 31, 28, 27; MS: m/z 337 ($\text{M}+\text{H}^+$, 70%). Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{SO}_2$: C, 67.86; H, 4.76; N, 8.33; S, 9.52. Found: C, 67.76; H, 4.85; N, 8.27; S, 9.59.

General procedure for synthesis of compounds 6

A mixture of thione **4** (0.01 mol) and 1,2-dibromoethane (5.0 mL) was stirred at 110°C for 4 h. The crude solid **6** was purified by silica gel column chromatography using petroleum ether/ethyl acetate (4:1) as an eluent.

5,7-Diphenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine (6a) This compound was obtained in 65% yield as a brown solid; mp 140–142°C; IR: ν 1673 (C=N) cm^{-1} ; ^1H NMR: δ 2.42 (t, 2H, SCH_2 , $J = 7.8$ Hz), 3.52 (t, 2H, NCH_2 , $J = 7.9$ Hz), 5.32 (s, 1H, H_A), 5.64 (s, 1H, CH), 7.20 (m, 10H, C_6H_5); ^{13}C NMR: δ 165, 138, 131, 129, 128, 127, 125, 103, 59, 52, 40, 39, 38, 31, 30, 28, 22, 13; MS: m/z 293 ($\text{M}+\text{H}^+$, 100%). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{S}$: C, 73.97; H, 5.48; N, 9.59; S, 10.96. Found: C, 73.88; H, 5.54; N, 9.50; S, 10.88.

5-(4-Methoxyphenyl)-7-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine (6b) This compound was obtained in 62% yield as a yellow solid; mp 160–162°C; IR: ν 1672 (C=N) cm^{-1} ; ^1H NMR: δ 2.84–2.87 (t, 2H, SCH_2 , $J = 6$ Hz), 2.95–2.98 (t, 2H, NCH_2 , $J = 6$ Hz), 3.79 (s, 3H, OCH_3), 5.72 (d, 1H, H_A , $J = 10$ Hz), 5.75–5.77 (d, 1H, CH, $J = 8$ Hz), 6.84–6.87 (m, 2H, Ar-H), 6.91 (d, 2H, Ar-H, $J = 4$ Hz), 7.10–7.14 (m, 1H, Ar-H), 7.25–7.27 (d, 1H, Ar-H, $J = 7$ Hz), 7.47 (m, 3H, Ar-H); ^{13}C NMR: δ 165, 160, 132, 131, 130, 129, 128, 126, 125, 114, 103, 59, 55, 52, 40, 39, 31, 30, 27, 22, 14; MS: m/z 323 ($\text{M}+\text{H}^+$, 100%). Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{SO}$: C, 70.81; H, 5.59; N, 8.70; S, 9.94. Found: C, 70.92; H, 5.67; N, 8.81; S, 9.88.

General procedure for synthesis of arylidene derivatives (7)

These compounds were prepared by two routes. (i) A mixture of thiazolidinone **5** (0.001 mol), aromatic aldehyde (0.001 mol) and anhydrous sodium acetate (0.082 g, 0.001 mol) in glacial acetic acid (10 mL) was heated under reflux for 4 h. The mixture was cooled to room temperature and poured into water. The solid thus obtained was filtered and washed with water and crystallized from dimethylformamide and ethanol mixture (1:1) to give compound **7**. (ii) A mixture of thione **4a** (0.001 mol), chloroacetic acid (0.094 g, 0.001 mol) and aromatic aldehyde (0.001 mol) and anhydrous sodium acetate (0.082 g, 0.001 mol) in glacial acetic acid (10 mL) and acetic anhydride (1 mL) was heated under reflux for 3–4 h. A similar work up as in (i) gave compound **7a**.

(E)-2-Benzylidene-5,7-diphenyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (7a) This compound was obtained in 70% yield as a shining yellow solid; mp 212–214°C; IR: ν 1728 (C=O), 1582 (C=N) cm^{-1} ; ^1H NMR: δ 6.28 (s, 1H, H_A), 6.72 (s, 1H, CH), 7.47 (m, 4H, Ar-H), 7.55 (m,

11H, Ar-H), 7.05 (s, 1H, H_B). Anal. Calcd for C₂₅H₁₈N₂SO: C, 76.14; H, 4.57; N, 7.11; S, 8.12. Found: C, 76.22; H, 4.62; N, 7.06; S, 8.20.

(E)-2-(4-Methylbenzylidene)-5,7-diphenyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (7b) This compound was obtained in 72% yield as yellow needles; mp 202–204°C; IR: ν 1726 (C=O), 1598 (C=N) cm⁻¹; ¹H NMR: δ 2.38 (s, 3H, CH₃), 6.26 (s, 1H, H_A), 6.78 (s, 1H, CH), 7.43 (m, 14H, Ar-H), 7.97 (s, 1H, H_B). Anal. Calcd for C₂₆H₂₀N₂SO: C, 76.47; H, 4.90; N, 6.86; S, 7.84. Found: C, 76.52; H, 4.82; N, 6.92; S, 7.78.

(E)-2-Benzylidene-5-(4-methoxyphenyl)-7-phenyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (7c) This compound was obtained in 66% yield as a light yellow solid; mp 238–240°C; IR: ν 1728 (C=O), 1582 (C=N) cm⁻¹; ¹H NMR: δ 3.71 (s, 3H, OCH₃), 6.32 (s, 1H, H_A), 6.78 (s, 1H, CH), 7.04 (m, 2H, Ar-H), 7.34 (s, 1H, H_B), 7.49 (m, 12H, Ar-H), 7.77 (s). Anal. Calcd for C₂₆H₂₀N₂SO₂: C, 73.58; H, 4.72; N, 6.60; S, 7.55. Found: C, 73.64; H, 4.68; N, 6.69; S, 7.49.

(E)-5-(4-Methoxyphenyl)-2-(4-methylbenzylidene)-7-phenyl-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one (7d) This compound was obtained in 68% yield as a yellow solid; mp 248–250°C; IR: ν 1720 (C=O), 1574 (C=N) cm⁻¹; ¹H NMR: δ 2.37 (s, 3H, CH₃), 3.70 (s, 3H, OCH₃), 6.33 (m, 1H, H_A), 6.83 (s, 1H, CH), 7.04–7.07 (m, 2H, Ar-H), 7.11–7.13 (m, 2H, Ar-H), 7.18–7.20 (m, 3H, Ar-H), 7.43–7.45 (m, 6H, Ar-H), 7.68 (s, 1H, H_B). Anal. Calcd for C₂₇H₂₂N₂SO₂: C, 73.97; H, 5.02; N, 6.39; S, 7.31. Found: C, 73.88; H, 5.10; N, 6.30; S, 7.40.

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