

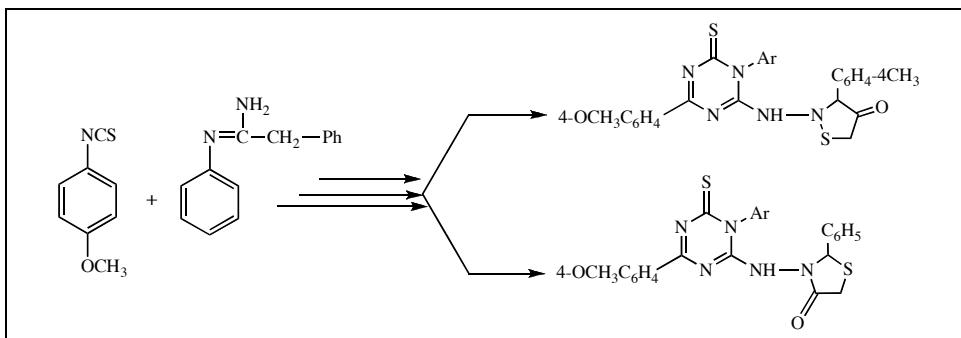
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A series of 4-thiazolidinones having triazinethione moieties have been synthesized by the systematic chemical modification of S-benzylmercapto-1-aryl-4-(4-methoxyphenyl)-1,6-dihydro-1,3,5-triazine-6-thione.

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INTRODUCTION

4-Thiazolidinone derivatives have been known for their antibacterial [1-5], antifungal [6-8], anti HIV [9], antituberculosis [10,11], anti-inflammatory [12,13], anti cancer [14,15], antioxidant [16] properties and as follicle stimulating hormone (FSH) agonists [17]. The 1,3,5-triazine cores posses an important position in the field of drug research due to the presence of three symmetrically positioned N-atoms, which may be substituted by different medicinally relevant substituents [18]. Furthermore, triazine-5-ones have been synthesized by several workers for their screening as anti cancer and anti HIV agents [19-21].

Hence, it was thought worthwhile to couple thiazolidinone as well as triazinethione in order to synthesize some new potential candidates from the view point of pharmaceuticals. The overall synthesis can be summarized through Scheme 1.

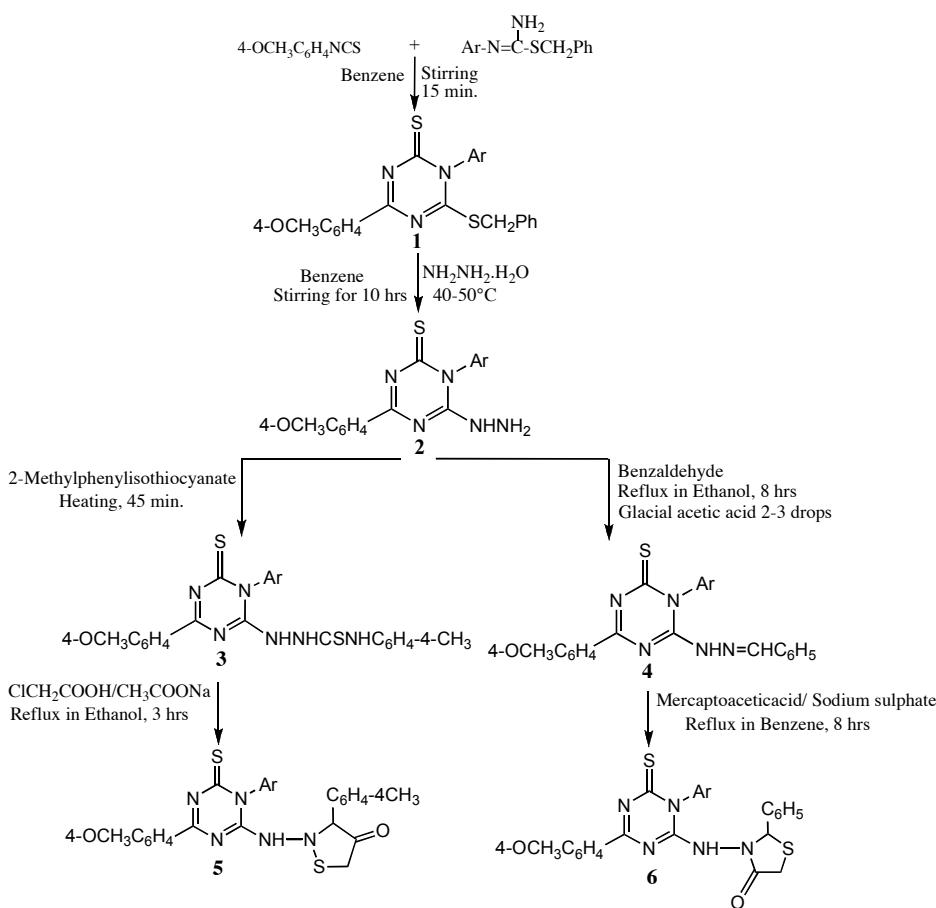
RESULTS AND DISCUSSION

The interaction of 4-methoxybenzoylisothiocyanate and S-benzyl-N-aryl isothiourea afforded the 2-benzylmercapto-1-aryl-4-(methoxyphenyl)-1,6-dihydro-1,3,5-triazine-6-thione **1a-d**. The IR and ¹H NMR spectral studies were used for establishing their structures. The IR spectral band in the region 1645-1540 cm⁻¹ and 1200-1165 cm⁻¹ were assigned as $\nu_{>\text{C}=\text{N}}$ and $\nu_{>\text{C}=\text{S}}$ respectively in accordance with literature reports [22]. It is worth mentioning that triazinethiones with electron releasing substituents like

-OCH₃ and -CH₃ exhibited the $\nu_{>\text{C}=\text{N}}$ and $\nu_{>\text{C}=\text{S}}$ at comparatively lower wave numbers than the triazinethione with electron withdrawing substituents. The NMR spectra of triazinethiones showed signals in the ranges 3.8-2.6 δ ppm (s, 3H, -OCH₃) and 4.9-3.6 δ ppm (s, 2H, -CH₂) in addition to the aromatic protons. The electron releasing/electron withdrawing effects of substituents were observed in NMR spectral pattern on the similar line of IR spectral pattern. Reaction of 2-mercaptophenyl triazinethiones **1a-d** with hydrazine hydrates lead to the formation of hydrazinethiazine **2a-d**. This conversion is clearly reflected in the IR and NMR spectral pattern. IR spectra of compounds **2a-d** showed bands in the region 3390-3330 cm⁻¹ and 3280-3270 cm⁻¹ for $\nu_{\text{N-H}}$ which were absent in IR spectra of triazinethiones. The ¹H NMR spectra showed peaks in δ ppm range of 4.8-4.5 (b, 2H, -NHNH₂) and 5.2-5.0 (b, 1H, -NHNH₂) which disappeared on exchange with deuterium oxide. Hydrazinethiazins **2a-d** on treatment with 2-tolyl isothiocyanates and benzaldehyde afforded corresponding triazinyl thiosemicarbazides **3a-d** and Schiff base **4a-d** respectively.

The formation of the semicarbazides **3a-b** was supported by the enhancement of the integration of aromatic protons as well as appearance of new signal in the range of 2.1-2.4 δ ppm for the -CH₃ group. On the other hand formation of Schiff base **4a-d** was confirmed by the appearance of a signal in the range of 7.9-7.6 δ ppm and disappearance of a signal in the range of 4.8-4.5 δ ppm. At the same time a broad peak in the range of 4.4-4.0 δ ppm was assigned to -NH-. The aromatic protons

Scheme 1



were observed slightly downfield after the Schiff base formation. Formation of thiazolidinones **5a-d**, **6a-d** from corresponding thiosemicarbazides **3a-d** and Schiff bases **4a-d** respectively were confirmed by their corresponding IR and NMR spectral patterns.

CONCLUSION

The present communication reports new protocol for the synthesis of a series of new thiazolidinones with triazine thione moieties. The compounds reported under present studies may be potential candidates form the view point of pharmacy.

EXPERIMENTAL

Melting Points were determined through open capillary method and are uncorrected. IR spectra were recorded on JASCO/FTIR-5300 spectrophotometer as KBr pellets. ¹H NMR spectra were recorded on JEOL FX 90Q Fourier transform spectrometer using tetramethylsilane (TMS) as an internal standard.

S-Benzyl-N-(4-chlorophenyl)isothiourea. A mixture of (4-chlorophenyl)-2-thiourea (18.6 g, 0.1 mole) and benzyl chloride (12.7 g, 0.1 mole) in 150 mL ethanol was refluxed for 2.5 hrs.

Excess of solvent was removed on flash evaporator and residue thus obtained was neutralized with cold, dilute sodium bicarbonate solution. The free base was extracted with ether and evaporation of ether afforded the desired free base. The other S-benzyl-N-aryl isothioureas were prepared by similar procedure.

General method of preparation of 2-Benzylmercapto-1-(4-chlorophenyl)-4-(4-methoxyphenyl)-1,6-dihydro-1,3,5-triazine-6-thione (1a). A solution of 4-methoxybenzoyl isothiocyanate in benzene (9.6 g, 0.05 mole) was gradually added with vigorous stirring to S-benzyl-4-(4-chlorophenyl) isothiourea (13.8 g, 0.05 mole) in benzene over a period of 15 min. An exothermic reaction took place and a golden yellow solid separated after 20-30 min. It was recrystallized from ethanol-DMF (4:1) mixture.

General method of preparation of 1-(4-chlorophenyl)-2-hydrazino-4-(4-methoxyphenyl)-1,6-dihydro-1,3,5-triazine-6-thione (2a). **1a** (9.0 g, 0.02 mole) was dissolved in excess of benzene (200 mL) hydrazine hydrate (1.0 g, 0.02 mole) was added and the reaction mixture was stirred at 40-50 °C for 10 h. A greenish yellow precipitate thus formed was filtered and washed with excess of petroleum ether and benzene. The resulting hydrazino compound was recrystallized from ethanol-DMF mixture.

1-(4-Chlorophenyl)-2-hydrazino-4-(4-methoxyphenyl)-1,6-dihydro-1,3,5-triazin-6-thione (2a). Yield (56%). m.p 218 °C. IR (KBr): 3290, 1645, 1165 cm⁻¹. ¹H NMR (DMSO-d₆): δ 3.8 (s,

3H, -OCH₃), 4.8 (br, 2H, -NHNH₂), 5.1 (br, 1H, -NHNH₂), 6.9-7.6 (m, 8H, ArH). *Anal.* Calcd. for (C₁₆H₁₄N₅OSCl): C, 53.41; H, 3.92; N, 19.46; S, 8.91; Cl, 9.85. Found: C, 53.62; H, 3.73; N, 19.81; S, 9.64; Cl, 9.48.

1-(4-Methylphenyl)-2-hydrazino-4-(4-methoxyphenyl)-1,6-dihydro-1,3,5-triazin-6-thione (2b). Yield (47%). m.p. 188 °C. IR (KBr): 3290, 1645, 1165 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.1 (s, 3H, -CH₃), 3.8 (s, 3H, -OCH₃), 4.8 (br, 3H, -NHNH₂), 5.1 (br, 1H, -NHNH₂), 6.9-7.6 (m, 8H, ArH). *Anal.* Calcd. for (C₁₇H₁₇N₅OS): C, 60.16; H, 5.05; N, 20.63; S, 9.45. Found: C, 60.52; H, 4.95; N, 20.89; S, 10.35.

1-(4-Nitrophenyl)-2-hydrazino-4-(4-methoxyphenyl)-1,6-dihydro-1,3,5-triazin-6-thione (2c). Yield (52%). m.p. 182 °C; IR (KBr): 3290, 1645, 1360, 1320, 1165 cm⁻¹. ¹H NMR (DMSO-d₆): δ 3.8 (s, 3H, -OCH₃), 4.8 (br, 2H, -NHNH₂), 5.1 (br, 1H, -NHNH₂), 6.9-7.6 (m, 8H, ArH). *Anal.* Calcd. for (C₁₆H₁₄N₅O₃S): C, 51.88; H, 3.81; N, 22.69; S, 8.66. Found: C, 52.07; H, 3.92; N, 22.51; S, 10.38.

1-(2-Methoxy-5-chlorophenyl)-2-hydrazino-4-(4-methoxyphenyl)-1,6-dihydro-1,3,5-triazin-6-thione (2d). Yield (46%). m.p. 188 °C. IR (KBr): 3290, 1645, 1165 cm⁻¹. ¹H NMR (DMSO-d₆): δ 3.8 (s, 6H, -OCH₃), 4.8 (br, 2H, -NHNH₂), 5.1 (br, 1H, -NHNH₂), 6.9-7.6 (m, 7H, ArH). *Anal.* Calcd. for (C₁₇H₁₆N₅O₂SCl): C, 52.37; H, 4.14; N, 17.96; S, 8.22; Cl, 9.09. Found: C, 52.59; H, 4.36; N, 18.38; S, 8.98; Cl, 8.72.

General method of preparation of N-[2-methylphenyl]-N-1-(4-chlorophenyl)-4-(4-methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazinylthiosemicarbazide (3a). 4-Methyl phenylisothiocyanate (10.0 g, 0.02 mole) was mixed with (2a) (17.0 g, 0.02 mole) and a paste thus formed was heated on a water bath for a period of 45 min. It was then washed with petroleum ether to remove excess of isothiocyanate and recrystallized from benzene.

N-[2-Methylphenyl]-N"-1-[(4-chlorophenyl)-4-(4-methoxyphenyl)]-6-thioxo-1,6-dihydro-1,3,5-triazinylthiosemicarbazide (3a). Yield (39%). m.p. 186 °C. IR (KBr): 3290, 3100, 1540, 1105 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.1 (s, 3H, -CH₃), 3.8 (s, 3H, -OCH₃), 4.6 (br, 1H, -NHNH-), 5.1 (br, 1H, -NHNH-), 6.9-7.2 (m, 12H, ArH). *Anal.* Calcd. for (C₂₄H₂₁N₆OS₂Cl): C, 56.63; H, 4.16; N, 16.51; S, 12.60; Cl, 6.96. Found: C, 56.79; H, 4.01; N, 16.88; S, 13.29; Cl, 7.39.

N-[2-Methylphenyl]-N"-1-[(4-methylphenyl)-4-(4-methoxyphenyl)]-6-thioxo-1,6-dihydro-1,3,5-triazinylthiosemicarbazide (3b). Yield (55%). m.p. 196 °C. IR (KBr): 3290, 3100, 1540, 1105 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.1 (s, 6H, -CH₃), 3.8 (s, 3H, -OCH₃), 4.6 (br, 1H, -NHNH-), 5.1 (br, 1H, -NHNH-), 6.9-7.2 (m, 12H, ArH). *Anal.* Calcd. for (C₂₅H₂₄N₆OS₂): C, 61.45; H, 4.95; N, 17.20, S, 13.12. Found: C, 61.69; H, 5.14; N, 16.92; S, 12.56.

N-[2-Methylphenyl]-N"-1-[(4-nitrophenyl)-4-(4-methoxyphenyl)]-6-thioxo-1,6-dihydro-1,3,5-triazinylthiosemicarbazide (3c). Yield (55%). m.p. 196 °C. IR (KBr): 3290, 3100, 1540, 1360, 1320, 1105 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.1 (s, 3H, -CH₃), 3.8 (s, 3H, -OCH₃), 4.6 (br, 1H, -NHNH-), 5.1 (br, 1H, -NHNH-), 6.9-8.2 (m, 12H, ArH). *Anal.* Calcd. for (C₂₄H₂₁N₇O₃S₂): C, 55.48; H, 4.07; N, 18.87; S, 12.34. Found: C, 55.89; H, 4.41; N, 18.98; S, 11.82.

N-[2-Methylphenyl]-N"-1-[(2-methoxy-5-chlorophenyl)-4-(4-methoxyphenyl)]-6-thioxo-1,6-dihydro-1,3,5-triazinylthiosemicarbazide (3d). Yield (55%). m.p. 196 °C. IR (KBr): 3290, 3100, 1540, 1105 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.1 (s, 3H, -CH₃), 3.8 (s, 6H, -OCH₃), 4.6 (br, 1H, -NHNH-), 5.1 (br, 1H, -NHNH-), 6.9-7.2 (m, 11H, ArH). *Anal.* Calcd. for

(C₂₅H₂₃N₆O₂S₂Cl): C, 55.70; H, 4.30; N, 15.59; S, 11.90; Cl, 6.58. Found: C, 55.94; H, 4.62; N, 16.00; S, 12.22; Cl, 6.82.

General method of preparation N-[1-4-chlorophenyl]-4-(4-methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]-N'-benzylidene hydrazine (4a). A mixture of (2a) (7.0 g, 0.02 mole), benzaldehyde (0.2 g, 0.02 mole) and 2-3 drops of glacial acetic acid were taken in ethanol. The reaction mixture was refluxed for about 8 hours. It was then filtered and the filtrate was allowed to cool overnight. The title compound was separated out as fine yellow needles.

N-[1-(4-chlorophenyl)]-4-[4-(4-methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]-N'benzylidene hydrazine (4a). Yield (69%). m.p. 212 °C. IR (KBr): 3340, 1630, 1090 cm⁻¹. ¹H NMR (DMSO-d₆): δ 3.8 (3H, s, -OCH₃), 4.4 (br, 1H, -NH-), 6.9-7.7 (m, 13H, ArH), 7.9 (s, 1H, -N=CH-). *Anal.* Calcd. for (C₂₃H₁₈N₅OSCl): C, 61.67; H, 4.05; N, 15.63; S, 7.16; Cl, 7.91. Found: C, 61.94; H, 4.41; N, 15.95; S, 7.38; Cl, 7.48.

N-[1-(4-Methylphenyl)]-4-[4-(4-methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]-N'-benzylidene hydrazine (4b). Yield (51%). m.p. 260 °C. IR (KBr): 3340, 1630, 1090 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.1 (s, 3H, -CH₃), 3.8 (s, 3H, -OCH₃), 4.4 (br, 1H, -NH-), 6.9-7.7 (m, 13H, ArH), 7.9 (s, 1H, -N=CH-). *Anal.* Calcd. for (C₂₄H₂₁N₅OS): C, 67.43; H, 4.95; N, 16.38. S, 7.50. Found: C, 67.76; H, 5.22; N, 16.64; S, 7.96.

N-[1-(4-Nitrophenyl)]-4-[4-(4-methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]-N'-benzylidene hydrazine (4c). Yield (56%). m.p. 230 °C. IR (KBr): 3340, 1630, 1360, 1320, 1090 cm⁻¹. ¹H NMR (DMSO-d₆): δ 3.8 (s, 3H, -OCH₃), 4.4 (br, 1H, -NH-), 6.9-7.7 (m, 13H, ArH), 7.9 (s, 1H, -N=CH-). *Anal.* Calcd. for (C₂₃H₁₈N₆O₃S): C, 60.25; H, 3.96; N, 18.33; S, 6.99. Found: C, 60.55; H, 4.16; N, 18.67; S, 7.52.

N-[1-(2-Methoxy-5-chlorophenyl)]-4-[4-(4-methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]-N'-benzylidene hydrazine (4d). Yield (52%). m.p. 214 °C. IR (KBr): 3340, 1630, 1090 cm⁻¹. ¹H NMR (DMSO-d₆): δ 3.8 (s, 6H, -OCH₃), 4.4 (br, 1H, -NH-), 6.9-7.7 (m, 12H, ArH), 7.9 (s, 1H, -N=CH-). *Anal.* Calcd. for (C₂₄H₂₀N₅O₂SCl): C, 60.31; H, 4.22; N, 14.65; S, 6.71; Cl, 7.42. Found: C, 60.62; H, 3.98; N, 14.84; S, 7.11; Cl, 7.95.

General method of preparation of 2-[1-(4-chlorophenyl)-4-(4-methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]-hydrazino-3-(2-methylphenyl)thiazolidine (5a). A mixture of (3a) (10.0 g, 0.02 mole), chloroacetic acid (1.0 g, 0.02 mole) and sodium acetate (3.0 g) were taken in ethanol and refluxed for 3 h. It was then poured into crushed ice, filtered and the product was recrystallized from ethanol.

2-[1-(4-Chlorophenyl)]-4-[4-(4-methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]hydrazono-3-(2-methylphenyl)thiazolidinone (5a). Yield (69%). m.p. 212 °C. IR (KBr): 3340, 2900, 1630, 1690, 1090 cm⁻¹. ¹H NMR (DMSO-d₆): δ 4.2 (s, 2H, -CH₂), 3.8 (s, 3H, -OCH₃), 4.4 (br, 1H, -NH-), 6.9-7.7 (m, 13H, ArH). *Anal.* Calcd. for (C₂₅H₂₁N₆O₂S₂Cl): C, 55.91; H, 3.94; N, 15.65; S, 11.94; Cl, 6.60. Found: C, 56.23; H, 4.11; N, 15.94; S, 12.36; Cl, 7.12.

2-[1-(4-Methylphenyl)]-4-[4-(4-methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]hydrazono-3-(2-methylphenyl)thiazolidinone (5b). Yield (51%). m.p. 260 °C. IR (KBr): 3340, 2900, 1690, 1630, 1090 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.1 (s, 3H, -CH₃), 4.2 (s, 2H, -CH₂), 3.8 (s, 3H, -OCH₃), 4.4 (br, 1H, -NH-), 6.9-7.7 (m, 13H, ArH). *Anal.* Calcd. for (C₂₆H₂₄N₆O₂S₂): C, 60.44; H, 4.68; N, 16.27; S, 12.41. Found: C, 60.78; H, 5.01; N, 16.07; S, 12.78.

2-[1-(4-Nitrophenyl)]-4-[(4-methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]hydrazono-3-(2-methyl phenyl)thiazolidinone (5c). Yield (56%). mp 230 °C. IR (KBr): 3340, 2910, 1690, 1630, 1360, 1320, 1090 cm⁻¹. ¹H NMR (DMSO-d₆): δ 3.8 (s, 3H, -OCH₃), 4.2 (s, 2H, -CH₂-), 4.4 (br, 1H, -NH-), 6.9-7.7 (m, 13H, ArH). Anal. Calcd. for (C₂₅H₂₁N₅O₄S₂): C, 54.83; H, 3.87; N, 17.90; S, 11.71. Found: C, 55.15; H, 4.17; N, 18.27; S, 12.19.

2-[1-(2-Methoxy-5-chlorophenyl)]-4-[(4-methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]hydrazono-3-(2-methyl phenyl)methylphenylthiazolidinone (5d). Yield (52%). m.p 214 °C. IR (KBr): 3340, 2910, 1690, 1630, 1090 cm⁻¹. ¹H NMR (DMSO-d₆): δ 3.8 (s, 6H, -OCH₃), 4.2 (s, 2H, -CH₂-), 4.4 (br, 1H, -NH-), 6.9-7.7 (m, 12H, ArH). Anal. Calcd. for (C₂₆H₂₃N₅O₃S₂Cl): C, 55.07; H, 4.09; N, 14.82; S, 11.31; Cl, 6.25. Found: C, 55.46; H, 4.29; N, 14.78; S, 11.65; Cl, 6.62.

General method of preparation of 2-Phenyl-3-[1-(4-chlorophenyl)-4-(methoxyphenyl)-6-thioxo-1,6-dihydro-1,3,5-triazine-2-yl]amino-thiazolidinone (6a). A mixture of (4a) (9.0 g, 0.02 mole), mercaptoacetic acid (0.80 g, 0.02 mole) and sodium sulphate (5.0 g) were taken in 100 mL of benzene and refluxed for 8 h. It was filtered and the solvent was evaporated in vacuum. The product was then washed with sodium bicarbonate solution to remove unreacted acid and finally recrystallized from ethanol.

2-Phenyl-3-[1-(4-chlorophenyl)]-4-[(4-methoxyphenyl)-6-thioxo-1,6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]aminothiazolidin-4-one (6a). Yield (39%). m.p 262 °C. IR (KBr): 2900, 2140, 1695 cm⁻¹. ¹H NMR (DMSO-d₆) δ 3.8 (s, 3H, -OCH₃), 4.2 (s, 2H, -CH₂-), 5.6 (br, 1H, -NH-), 6.9-7.7 (m, 13H, ArH). Anal. Calcd. for (C₂₅H₂₀N₅O₂S₂Cl): C, 57.52; H, 3.86; N, 13.42; S, 12.28, Cl, 6.79. Found: C, 57.86; H, 4.08; N, 13.66; S, 12.61; Cl, 7.15.

2-Phenyl-3-[1-(4-methylphenyl)]-4-[(4-methoxyphenyl)-6-thioxo-1,6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]aminothiazolidin-4-one (6b). Yield (39%). m.p 262 °C. IR (KBr): 2900, 2140, 1695 cm⁻¹. ¹H NMR (DMSO-d₆) δ 2.1 (s, 3H, -CH₃), 3.8 (s, 3H, -OCH₃), 4.2 (s, 2H, -CH₂-), 5.6 (br, 1H, -NH-), 6.9-7.7 (m, 13H, ArH). Anal. Calcd. for (C₂₆H₂₃N₅O₂S₂): C, 62.25; H, 4.62; N, 13.96; S, 12.78. Found: C, 62.56; H, 4.85; N, 14.22; S, 13.14.

2-Phenyl-3-[1-(4-nitrophenyl)]-4-[(4-methoxyphenyl)-6-thioxo-1,6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]aminothiazolidin-4-one (6c). Yield (46%). m.p 251 °C. IR (KBr): 2900, 2140, 1710, 1360, 1320 cm⁻¹. ¹H NMR (DMSO-d₆): δ 3.8 (s, 3H, -OCH₃), 4.2 (s, 2H, -CH₂-), 5.6 (br, 1H, -NH-), 6.9-7.7 (m, 13H, ArH). Anal. Calcd. for (C₂₅H₂₀N₅O₄S₂): C, 56.38; H, 3.79; N, 15.78; S, 12.04. Found: C, 56.66; H, 3.96; N, 16.14; S, 12.42.

2-Phenyl-3-[1-(2methoxy-5-chlorophenyl)]-4-[(4-ethoxy phenyl)-6-thioxo-1,6-thioxo-1,6-dihydro-1,3,5-triazin-2-yl]amino-thiazolidin-4-one (6d). Yield (48%). m.p 212 °C. IR (KBr): 2900, 2140, 1705 cm⁻¹. ¹H NMR (DMSO-d₆): δ 3.8 (s,

6H, -OCH₃), 4.2 (s, 2H, -CH₂-), 5.6 (br, 1H, -NH-), 6.9-7.7 (m, 12H, ArH). Anal. Calcd. for (C₂₆H₂₂N₅O₃S₂Cl): C, 56.57; H, 4.02; N, 12.69; S, 11.62; Cl, 6.42. Found: C, 56.75; H, 4.37; N, 12.88; S, 11.98; Cl, 6.75.

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