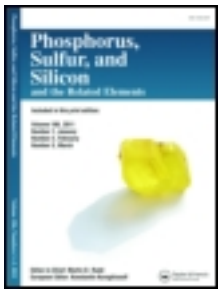

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Synthesis and Antimicrobial Activities of Some 6-Methyl-3-Thioxo-2,3-Dihydro-1,2,4-Triazine Derivatives

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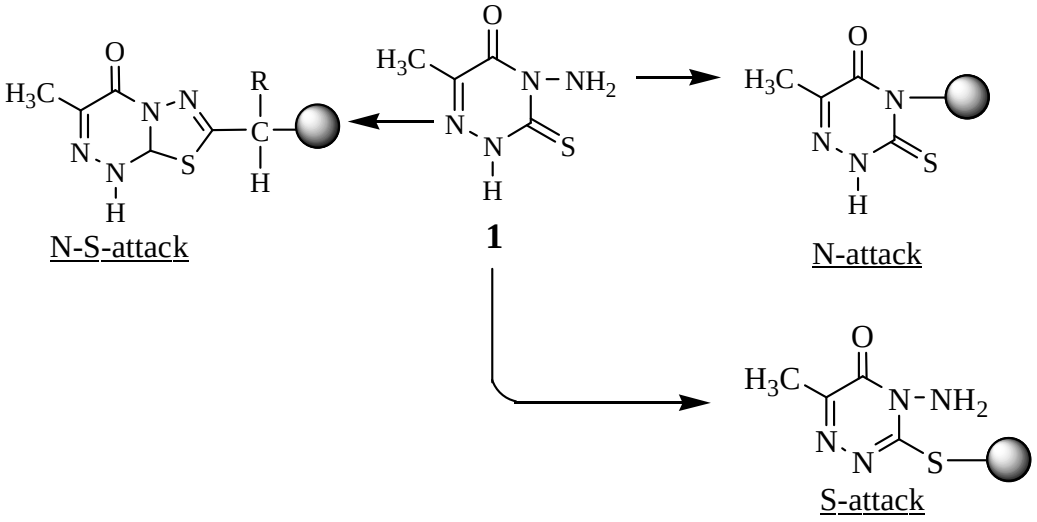
Graphical Abstract



*4-Arylidene-imidazole derivatives (**4a**,**b**) were readily prepared by reacting 4-amino-6-methyl-3–thioxo-2,3–dihydro[1,2,4]triazin-5(4H)-one (**1**) with 4-arylidene-2-phenyl-4H-oxazol-5-one (**2**). Reaction of **1** with some aromatic aldehydes in presence of*

*triethylphosphite exclusively afforded the corresponding aminophosphonates **5a**-**c**. Reaction of **1** with 3-phenyl-1H-quinazoline-2,4-dione (**6a**) and/or 3-phenyl-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (**6b**) gave 2-(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3H-[1,2,4]triazin-4-ylimino)-3-phenyl-2,3-dihydro-1H-quinazolin-4-one (**7**). Moreover, on treating **1** with 2-phenylbenzo[d][1,3]thiazine-4-thione (**8**), 6-methyl-4-(2-phenyl-4-thioxo-4H-quinazolin-3-yl)-3-thioxo-3,4-dihydro -2H-[1,2,4]triazine-5-one (**9**) was obtained in 65% yield. Reaction of **1** with 4-sulfonylaminoacetic acid derivatives (**10a**,**b**) afforded the corresponding sulfonamides (**11a**,**b**), respectively. Acid hydrolysis of **11a** afforded 7-aminomethyl-3-methyl[1,3,4]thiadiazole[2,3-c][1,2,4]triazin-4-one (**12**). 4-Amino-6-methyl-3-(morpholine-4-ylsulfanyl)-4H-[1,2,4]triazin-5-one (**14**) was prepared by reacting compound **1** with morpholine in presence of KI/I_2, while 3,3'-bis(4-amino-6-methyl-5-oxo-triazinyl)disulfide (**16**) was obtained by oxidation of **1** with lead tetraacetate. The antimicrobial activity of the products was evaluated against Gram-positive and Gram-negative bacteria, as well as the fungus Candida albicans.*

Keywords: 1,2,4-Triazines, Imidazoles, Phosphonic acid ester, Quinazonlines, Antimicrobial activity.

INTRODUCTION

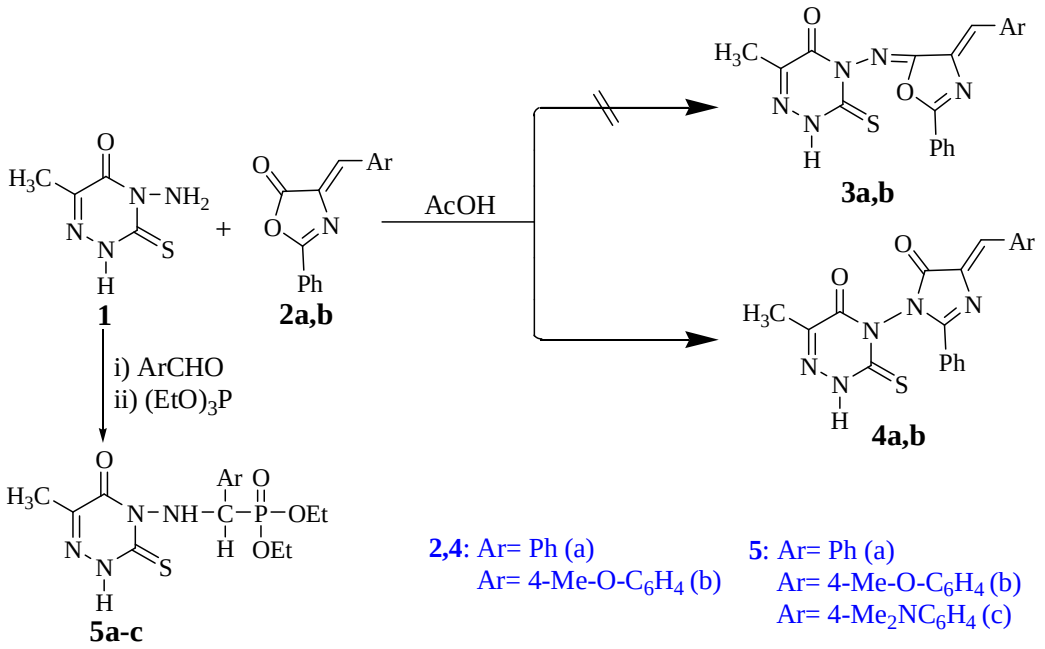
Nitrogen containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activities.[1,2] It is well known that substituted triazines occupied a unique position in medicinal chemistry.[3-6] Triazine derivatives have attracted considerable pharmaceutical interest due to their antiproliferative activity,[7] antiviral agent,[8,9] antihypertensive agent,[10] antitumor and *in vitro* supporting their anti-HIV activity,[11,12] anticonvulsant[13] and antileukemic.[14]

Furthermore, pyrimido-triazines have exhibited antibacterial activity.[15] Antimicrobial activities of 1,2,4-triazines became a subject of interest for researchers.[16-19] The increasing importance of triazine derivatives as intermediates for the synthesis of biologically active compounds has led to continued development of new simple procedures for their synthesis. Thus, we wish to report herein on the synthesis of 4-amino-6-methyl-3-thioxo-5-oxo-3,4-dihydro-1,2,4-triazine and some of its derivatives for evaluating their antimicrobial activities.

RESULTS AND DISCUSSION

4-Amino-6-methyl-3-thioxo-2,3-dihydro[1,2,4]-triazin-5(4*H*)-one (**1**) was prepared according to Dorrnow et al.[20] On refluxing compound **1** with 4-arylidene-2-phenyl-4*H*-oxazol-5-ones (**2a**,**b**), prepared according to recommended method,[21] in glacial acetic acid, the corresponding 4-(4-benzylidene- and 4-(4-methoxybenzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-6-methyl-3-thioxo-3,4-dihydro-2*H*-[1,2,4]triazin-5-ones (**4a**,**b**) derivatives were obtained, instead of the expected products **3a**,**b** (Scheme 1). The structure of

compounds **4a**,**b** were confirmed by each of Infrared (IR), ^{1}H NMR and mass spectral analyses. IR spectra of compounds **4a**,**b** showed broad absorptions at 1631 cm^{-1} (C=O), 1694 cm^{-1} (C=O-imidazolo) and 1641 cm^{-1} (C=O-triazine) and also showed the absence of the absorption due to NH_2 group. Mass spectrum of **4a** showed a low intensity molecular ion peak (M^+, <1%) at m/z = 389. Reacting **1** with some aromatic aldehydes in presence of triethylphosphite in glacial acetic acid at 100^{o}C afforded the corresponding 4-methoxyphenyl- and 4-dimethylaminophenyl[6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-[1,2,4]triazin-4-yl-aminomethyl]phosphonate (**5a-c**)[22] (Scheme 1). IR spectra of compounds **5a-c** showed absorption bands due to the stretching frequency of C=C aromatic at 1511-1614 cm^{-1} and bands of P-O-alkyl at 1024-1058 cm^{-1}. ^{1}H NMR spectrum of **5b** showed signals at 2.18 (s, 3H, CH_3-triazine), a triplet at 2.48-2.50 ppm (CH_3), a quartet at 3.80 ppm (CH_2), 3.90 (s, 1H, NH-*CH*-Ar), 8.50 ppm (s, 1H, NH-triazine), 13.63 ppm (s, 1H, *NH*-CH-Ar). MS spectrum of **5a** showed a low intensity pseudo molecular ion peak (M^++1, <1%) at m/z = 385, which confirmed the postulated structure. ^{31}P NMR spectrum of compound **5a** showed a singlet peak at 68.0 ppm.[23]

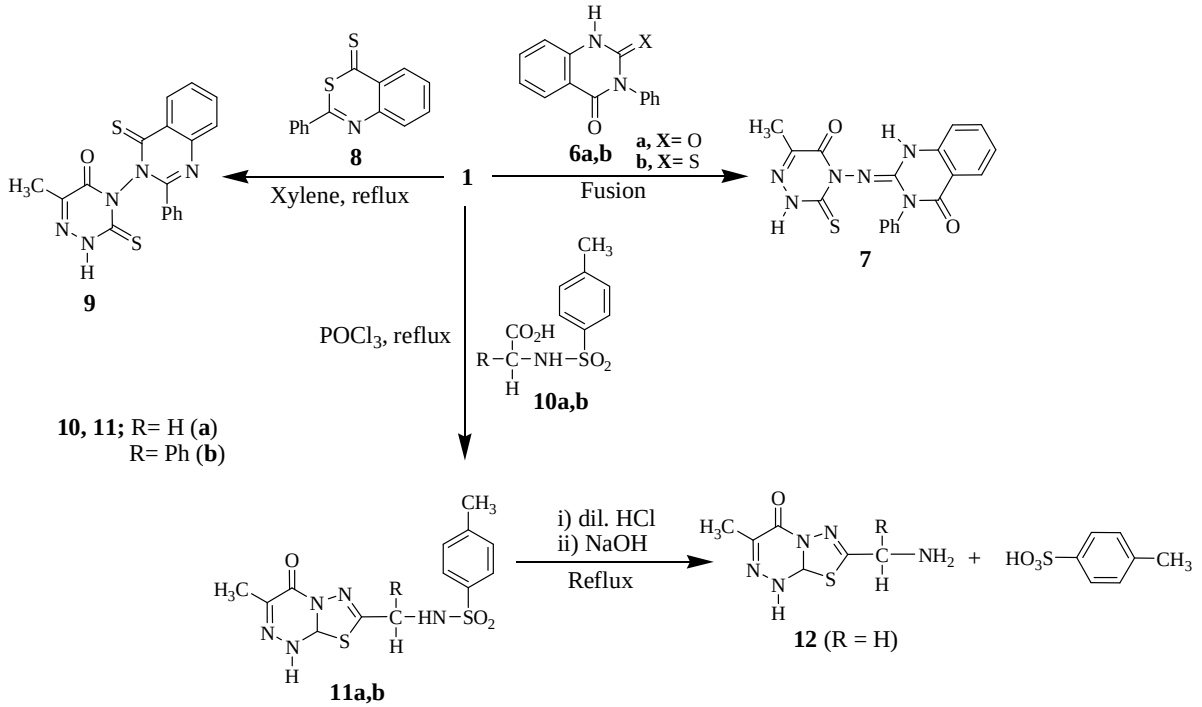


Scheme 1

On heating compound **1** with 3-phenyl-1*H*-quinazoline-2,4-dione (**6a**)[24] at 240°C for 4 h and/or with 3-phenyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**6b**)[24] at 225°C for 3 h, the same product 2-(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-[1,2,4]triazin-4-ylimino)-3-phenyl-2,3-dihydro-1*H*-quinazolin-4-one (**7**) was obtained (Scheme 2). Product **7** seemed to be formed via successive elimination of H_2O and H_2S. Its IR spectrum showed bands at 1616 cm^{-1} (C=O-triazine), 1662 cm^{-1} (C=O-quinazoline), 3214 cm^{-1} (NH-triazine) and 3428 (NH-quinazoline).

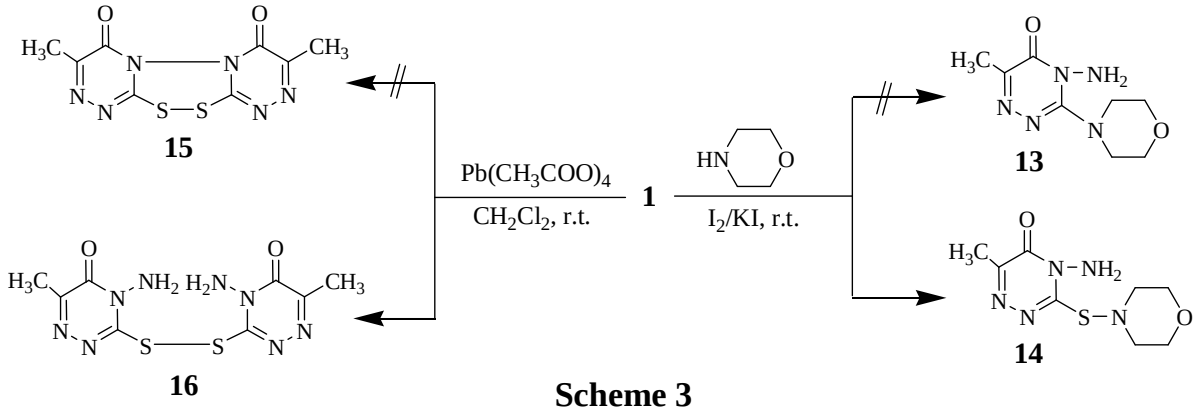
Reacting compound **1** with 2-phenyl benzo[*d*][1,3]thiazine-4-thione (**8**) afforded the corresponding 6-methyl-4-(2-phenyl-4-thioxo-4*H*-quinazolin-3-yl)-3-thioxo-3,4-dihydro-2*H*-[1,2,4]triazin-5-one (**9**) (Scheme 2). IR spectrum of compound **9** showed absorption bands at 1229 cm^{-1} (C=S-triazine) and at 1309 cm^{-1} (C=S-quinazoline). Reaction of **1** with sulfonylaminoacetic acid derivatives **10a**,**b**, prepared according to Okuda et al.[25] in $POCl_3$ at

85°C gave the corresponding 4-methyl-*N*-[(3-methyl-4-oxo-4*H*-[1,3,4]thiadiazolo[2,3-*c*]triazin-7-ylmethyl]benzenesulfonamide and 4-methyl-*N*-[(3-methyl-4-oxo-4*H*-[1,3,4]thiadiazolo[2,3-*c*]triazin-7-ylphenylmethyl]benzenesulfonamide derivatives (**11a**,**b**), respectively, were obtained. Hydrolysis of compound **11a** with dilute hydrochloric acid afforded 7-aminomethyl-3-methyl-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-one (**12**)[26] and 4-toluenesulfonic acid[27] (Scheme 3). IR spectra of compounds **11a**,**b** showed the characteristic absorption peaks of NH groups at 3284 and 3422 cm^{-1} and SO_2 group at 1160 cm^{-1}, respectively. Moreover, their IR spectra showed the absence of C=S group. ^1H NMR of compound **11b** showed singlet signals at 4.9 ppm (s, 1H, CH-Ph) and 2.2 ppm (s, 3H, CH_3-Ar). IR spectrum of compound **12** showed the existence of NH_2 at 3248, (sym.) and 3171 cm^{-1}, (antisym.).



Scheme 2

Treating **1** with morpholine in presence of potassium iodide and iodine at room temperature afforded 4-amino-6-methyl-3-(morpholin-4-ylsulfanyl)-4*H*-[1,2,4]triazin-5-one (**14**)[28] in a low yield instead of the expected structure **13** (Scheme 3). Although iodine is not very soluble in pure water, it can dissolve in water that contains I^- (aq) ion.[29] In aqueous solution, iodine has the tendency to react with excess iodide anions to form the tri-iodide anion. The tri-iodide ion can react with another iodine molecule to form the linear penta-iodide anion.[30] The reduction of water in the presence of K^+ proceeds through the reductive formation of alkali metal which brought about a decrease in yield of product **14**.[31] ^{1}H and ^{13}C NMR spectra of compound **14** could not be obtained due to its insolubility in hot DMSO. IR spectrum of compound **14** showed band at 3426 cm^{-1} due to NH_2 group and the absence of C=S group. Oxidation of **1** with lead tetraacetate (LTA) in methylene chloride at room temperature afforded unexpectedly *bis*(4-amino-6-methyl-5-oxo-1,2,4-triazinyl)disulfide (**16**) instead of the proposed structure **15** (Scheme 3). IR spectrum of compound **16** showed the existence of NH_2 at 3202 cm^{-1} (sym.) and 3292 cm^{-1} (antisym.) and the absence of C=S group. MS spectrum of compound **16** showed a molecular ion peak (M^+, <1%) at m/z = 314.



Scheme 3

The antimicrobial activity of the products was evaluated against Gram-positive and Gram-negative bacteria, as well as the fungus Candida albicans. The results showed that compound **1** has antimicrobial activities against *Escherichia coli* and *Candida albicans* but failed to show any activity against other tested organisms (*Pseudomonas aeruginosa, Aeromonas sp, Klebsiella sp, Bacillus subtilis and Staphylococcus aureus*). Compound **1** was added to the liquid media containing the sensitive organisms to obtain different concentrations (0.2-1.6 mg/mL). The results that are represented in Figures S 1 and S 2 (Supplemental Materials) indicated that increase of sensitivity of the selected organisms was enhanced by increasing the concentration of the compound [as indicated by the ratio of surviving cell number (M/C)] till 0.5 mg/mL. It was noticed that the sensitivity was nearly stable above 0.5 mg/mL with no further inhibition growth. Thus 0.5 mg/mL of this compound could be considered the minimum inhibitory concentration (MIC) against the tested sensitive organisms[32].

Compounds **4**, **5**, **7**, **9**, **11a**,**b**, **12**, **14** and **16** were screened for their activities against the test organisms namely *E. coli*, *Ps. aeruginosa, Aeromonas sp, Klebsiella sp, B. subtilis and St. aureus* and *C. albicans*. The results that are listed in Table S 1 (Supplemental Materials) showed that the antimicrobial activity was found to be affected on the structure of the tested derivatives as well as on the tested organisms. However, compounds **5b**, **5c**, **7**, **9**, and **11b** showed no activity towards the tested microorganisms, this may be attributed to the presence of *para*-substituted phenyl and bulky groups which may prevent these compounds to deal with the nature of the pathogen. Other compounds showed variable inhibitory effects. None of the tested compounds showed inhibitory activity against all the test organisms. However, the diameter of

inhibition zone differed also according to the sensitivity of the test organism. It is interesting to show that Bacillus subtilis showed good sensitivity to compounds **4a**, **4b**, **5a**, **14** and **16**. Among the tested derivatives, compound **14** showed the best effect against the majority of the tested organisms (*Klebsiella sp, B. subtilis, E. coli, St. aureus and C. albicans*). This is might be due to the presence of unreacted free amino group beside, the *S*-morpholyl moiety in its structure. *Aeromonas sp* and *Ps. aeruginosa* were resistant to compound.

EXPERIMENTAL

All melting points were uncorrected and performed by the open capillary melting point apparatus. Microanalyses were performed by Microanalysis Unit, National Research Center, Egypt. Infrared spectra were recorded with a Perkin-Elmer 1720 spectrometer. The NMR spectra were recorded on a Bruker AC 200 FT NMR spectrometer at 250 MHz for ^{1}H NMR, and 62.9 MHz for ^{13}C NMR, Bruker 200 MHz and Bruker 90 MHz using TMS as internal standard DMSO as a solvent. ^{31}P NMR spectrum was recorded at 120 MHz on a Varian CFT-20 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). ^{31}P chemical shifts are related to 85% H_3PO_4. Mass spectra (MS) were recorded using electron ionization (EI) on a Varian Mat 311A spectrometer and using fast atom bombardment (FAB) on a Kratos MS 50 spectrometer.

Synthesis of 4a,b

A mixture of compound **1** (1.0 g, 6 mmol) and 4-benzylidene-4*H*-oxazol-5-one (**2a**) (1.4 g, 6 mmol) and/or 4-(4-methoxybenzylidene)-2-phenyl-4*H*-oxazol-5-one (**2b**) (1.6 g, 6 mmol) was refluxed in glacial acetic acid (35 mL) for about 25 h (TLC). The reaction mixture was cooled and poured onto ice and the solid obtained was filtered and crystallized from methanol affording **4a**,**b**.

4-(4-Benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-6-methyl-3-thioxo-3,4-dihydro-2*H*-[1,2,4]triazin-5-one (4a); Ar = Ph; Yield 2 g (75%); m.p. 123-25^{o}C; IR (KBr): υ (cm^{-1}): 3415 (NH), 3059-1565 (H_{arom}), 1631 (C=O), 1477 C=N); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.50 (s, 3H, CH_3), 7.20 (s, 1H, Ph-*CH*=), 7.50-8.10 (m, 10H, H_{arom}), 10.11 (s, 1H, N*H*) ppm; MS (EI): m/z (%) = 389 (M^+, <1), 356 (3), 312 (1), 212 (38), 93 (100); *Anal*. Calcd. for $C_{20}H_{15}N_5O_2S$: C, 61.68; H, 3.88; N, 17.98. Found: C, 61.53; H, 3.69; N, 17.90.

4-(4-(4-Methoxybenzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)-6-methyl-3-thioxo-3,4-dihydro-2*H*-[1,2,4]triazin-5-one (4b); Ar = 4-MeOC_6H_4; Yield 1.5 g (71%); m.p. 158-60^{o}C; IR (KBr): υ (cm^{-1}): 3231 (NH), 1694 (C=O-imidazolo), 1641 (C=O-triazine), 1504 (C=N), 825 (*para*-MeO-aryl); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.49 (s, 3H, CH_3-triazine), 3.80 (s, 3H, OCH_3), 7.09 (s, 1H, Ar-*CH*=), 7.30-8.40 (m, 9H, H_{arom}) ppm; MS (EI): m/z (%) = 419 (M^+, <1), 327 (4), 277 (2), 142 (38); *Anal*. Calcd. for $C_{21}H_{17}N_5O_3S$: C, 60.13; H, 4.09; N, 16.70. Found: C, 60.29; H, 3.90; N, 16.89.

Synthesis of 5a-c

General procedure: To a stirred solution of compound **1** (1.0 g, 6 mmol) in glacial acetic acid (30 mL), the desired aromatic aldehydes (benzaldehyde, 4-methoxy benzaldehyde, or 4-

dimethylamino- benzaldehyde; 6 mmol) and triethylphosphite (1 mL, 6 mmol) were added and the reaction mixture was heated under reflux at 100°C for 18-25 h (TLC). The reaction mixture was concentrated to one quarter of its volume and then poured onto ice. The solid product thus formed was filtered, washed by petroleum ether and then crystallized from methanol affording the desired products **5a-c**.[22]

[Phenyl-6-methyl-5-oxo-3-thioxo-2,3-dihydro-3*H*-[1,2,4]triazin-4-ylaminomethyl]phosphonate (5a); Ar = Ph; Yield 1.2 g (55%); m.p. 218-20°C (25 h); IR (KBr): υ (cm^{-1}): 3423 (NH-broad), 1677 (C=O), 1029 (P-O-Et); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.91 (s, 3H, C*H*$_3$-triazine), 1.10-1.12 (t, 6H, 2 x C*H*$_3$-CH$_2$-O, *J* = 5.0 Hz), 2.10 (s, 1H, N-N*H*), 3.90 (s, 1H, Ph-C*H*), 4.10 (q, 4H, 2 x CH$_3$-C*H*$_2$-O), 7.10-7.20 (m, 5H, Ph-), 13.20 (s, 1H, N*H*-triazine) ppm; MS (EI): m/z (%) = 385 (M^++1, <1), 313 (<1), 215 (1), 158 (100), 138 ($C_4H_{11}O_3P$, 23.0); ^{31}P NMR (DMSO-d_6, 120 MHz): δ 68.0 (s, P, sym.) ppm; *Anal*. Calcd. for $C_{15}H_{21}N_4O_4PS$: C, 46.87; H, 5.51; N, 14.58. Found: C, 46.71; H, 5.68; N, 13.78.

[(4-Methoxyphenyl)-6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-[1,2,4]triazin-4-ylaminomethyl]phosphonate (5b); Ar = 4-MeOC_6H_4; Yield 1.8 g (70%); m.p. 247-49°C (20 h); IR (KBr): υ (cm^{-1}): 3212 (NH-amino), 3405 (NH-triazine), 1671 (C=O), 1024 (P-O-Et) 839 (*p*-CH$_3$O-aryl); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.18 (s, 3H, C*H*$_3$-triazine), 2.48-2.50 (t, 6H, 2 x C*H*$_3$, *J* = 5.0 Hz), 3.80 (q, 4H, 2 x C*H*$_2$, *J* = 6.1 Hz), 3.90 (s, 1H, NH-*CH*-Ar), 7.10-7.87 (m, 4H, H$_{arom}$), 8.50 (s, 1H, N*H*-triazine), 13.63 (s, 1H, *NH*-CH-Ar) ppm; MS (EI) m/z (%) = 414 (M^+<1), 307 (11), 277 (14), 107 (8); *Anal*. Calcd. for $C_{16}H_{23}N_4O_5PS$: C, 46.37; H, 5.59; N, 13.52. Found: C, 46.20; H, 5.76; N, 13.72.

[4-(Dimethylamino)phenyl)-6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-[1,2,4]triazin-4-ylaminomethyl] phosphonate (5c); Ar = 4-$Me_2NC_6H_4$; Yield 2.2 g (78%) [MeOH]; m.p. 268-70^oC (18 h); IR (KBr): υ (cm^{-1}): 3183 (NH-amino), 3222 (NH-triazine), 1700 (C=O), 1058 (P-O-Et), 809 (4-aminodimethyl-aryl); ^1H NMR (DMSO-d_6, 250 MHz): δ 0.95 (s, 3H, C*H*$_3$-triazine), 1.10-1.12 (t, 6H, 2 x C*H*$_3$-CH_2-O, *J* = 5.0 Hz), 2.10 (s, 1H, N-N*H*), 2.80 (s, 6H, N-(C*H*$_3$)$_2$), 3.90 (s, 1H, Ph-C*H*), 4.11 (q, 4H, 2 x CH_3-C*H*$_2$-O), 6.60-6.80 (m, 4H, Ph-), 12.50 (s, 1H, N*H*-triazine) ppm; MS (EI) m/z (%) = 427 (M^+, <1), 307 (2), 291 (14), 137 (2); *Anal*. Calcd. for $C_{17}H_{26}N_5O_4PS$: C, 47.77; H, 6.13; N, 16.38. Found: C, 47.87; H, 6.22; N, 16.29.

Synthesis of 2-(6-methyl-5-oxo-3-thioxo-2,5-dihydro-3*H*-[1,2,4]triazin-4-ylimino)-3-phenyl-2,3-dihydro-1*H*-quinazolin-4-one (7)

A mixture of compound **1** (1.0 g, 6 mmol) and 3-phenyl-1*H*-qunazoline-2,4-dione (**6a**; 1.4 g, 6 mmol) was heated at 240^oC for 4 h (TLC). After cooling, the resulting crude solid product was crystallized from ethanol to give **7**. Yield 1.8 g (65%); m.p. 208-10^oC; IR (KBr): υ (cm^{-1}): 3462 (NH-triazine), 3208 (NH-quinazoline), 2961-2929 (CH-aliphatic), 1660 (C=O-triazine), 1616 (C=O-quinazoline), 1227 (C=S); ^1H NMR (DMSO-d_6, 250 MHz): δ 0.94 (s, 3H, C*H*$_3$-triazine), 3.90 (s, 1H, NH-quinazoline), 6.60-6.70 (m, 4H, Ph-quinazoline), 7.20-7.50 (m, 5H, -Ph), 12.50 (s, 1H, N*H*-triazine) ppm; MS (EI) m/z (%) = 378 (M^+, <1), 364 (5), 236 (15), 156 (6); *Anal*. Calcd. for $C_{18}H_{14}N_6O_2S$: C, 57.13; H, 3.73; N, 22.21. Found: C, 56.92; H, 3.92; N, 21.94.

Similarly, when a mixture of compound **1** and 3-phenyl-2-thioxo-2,3-dihydro-1*H*-quinazoline-4-one (**6b**; 1.5 g, 6 mmol) was heated at 225^oC for 3 h, the same product **7** was obtained in 76% yield (2.4 g); melting point and mixed melting point with **7** gave no depression.

Synthesis of 6-methyl-4-(2-phenyl-4-thioxo-4*H*-quinazolin-3-yl)-3-thioxo-3,4-dihydro-2*H*-[1,2,4]triazine-5-one (9)

A mixture of compound **1** (1.0 g, 6 mmol) and 2-phenylbenzo[*d*][1,3]thiazine-4-thione (**8**; 1.3 g, 6 mmol) in anhydrous xylene (25 mL) was heated under reflux for 13 h (TLC). The reaction solvent was evaporated and the solid residue was crystallized from MeOH/H_2O to give product **9**. Yield 1.1 g (45%), m.p. 163-65^oC; IR (KBr): υ (cm^{-1}): 2961 (CH), 1679 (C=O); ^1H NMR (DMSO-d_6, 250 MHz): δ 2.50 (s, 3H, CH_3-triazine), 7.10-8.11 (m, 9H, H_{arom}), 9.10 (s, 1H, N*H*) ppm; MS (EI) m/z (%) = 379 (M^+, <1), 378 (9), 237 (8), 143 (4); *Anal*. Calcd. for $C_{18}H_{13}N_5OS_2$: C, 56.97; H, 3.45; N, 18.46. Found: C, 57.13; H, 3.61; N, 18.62.

Synthesis of 11a,b

General procedure: To a stirred solution of compound **1** (1.0 g, 6 mmol) in phosphorus oxychloride (15 mL), the desired 4-sulfonylaminoacetic acid derivative [(toluene-4-sulfonylamino)acetic acid (**10a**) or phenyl(toluene-4-sulfonylamino)acetic acid (**10b**)] (6 mmol) was added in small portions. The reaction mixture was heated under reflux at 85^oC for 5 h (TLC). After cooling to room temperature, sodium hydroxide solution (1%, 50 mL) was added and the resulting solid product was filtered, washed with water, dried, and finally recrystallized from MeOH to give **11a**,**b**, respectively.

4-Methyl-*N*-[(3-methyl-4-oxo-4*H*-[1,3,4]thiadiazolo[2,3-*c*]triazin-7-ylmethyl]benzenesulfonamide (11a): R = H; Yield 1.5 g (50%), m.p. 136-38^oC; IR (KBr): υ (cm^{-1}): 3421 (NH), 1628-1597(H_{arom}), 1696 (C=O), 809 (*para*-CH_3-aryl); ^1H NMR (DMSO-d_6, 250 MHz): δ 0.90 (s, 3H,

C*H*$_3$-triazine), 2.30 (s, 3H, C*H*$_3$-Ph), 3.21 (s, 2H, C*H*$_2$-NH), 5.62 (s, 1H, -C*H*$_2$-S), 7.50 (s, 1H, N*H*-triazine), 7.49-7.50 (d, 2H, Ph-, *J* = 2.5 Hz), 7.79-7.80 (d, 2H, Ph-S, *J* = 2.5 Hz), 8.50 (s, 1H, N*H*-CH$_2$) ppm; MS (EI) m/z (%) = 353 (M^+, <1), 199 ($C_6H_9N_5OS$, 2), 198 (11), 170 (7); *Anal.* Calcd. for $C_{13}H_{15}N_5O_3S_2$: C, 44.18; H, 4.28; N, 19.82. Found: C, 44.40; H, 4.11; N, 20.05.

4-Methyl-*N*-[(3-methyl-4-oxo-4*H*-[1,3,4]thiadiazolo[2,3-*c*]triazin-7yl)phenylmethyl]benzenesulfon amide (11b): R = Ph; Yield 3.2 g (80%), m.p. 146-48^{o}C; IR (KBr): υ (cm^{-1}): 3284 (NH), 1721 (C=O), 812 (*para*-CH$_3$-aryl); ^{1}H NMR (DMSO-d$_6$, 250 MHz): δ 2.23 (s, 3H, C*H*$_3$-aryl), 2.50 (s, 3H, C*H*$_3$-triazine), 4.90 (s, 1H, Ph-C*H*-), 7.20-7.60 (m, 9H, H$_{arom)}$, 8.60 (s, 1H, N*H*) ppm; MS (EI) m/z (%) = 429 (M^+, <1), 353 (13), 275 (3), 77 (17); *Anal.* Calcd. for $C_{19}H_{19}N_5O_3S_2$: C, 53.13; H, 4.46; N, 16.31. Found: C, 52.98; H, 4.27; N, 16.23.

Synthesis of 7-aminomethyl-3-methyl-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazin-4-one (12)

A suspension of compound **11b** (0.5 g, 3 mmol) in aqueous HCl (30%, 35 mL) was heated under reflux for 4 h. The reaction mixture was cooled, filtered and the filtrate was neutralized with NaOH solution (10%, 25 mL). The precipitate formed was filtered, dried, and recrystallized from methanol to afford **12**.[25] The filtrate was neutralized by dil. HCl to afford a white precipitate of 4-toluenesulphonic acid (m.p., 108-10^{o}C; yield 45%) (Lit., m.p., 103-5^{o}C).[27]

12: Yield 0.9 g (40%), m.p. 239-40^{o}C; IR (KBr): υ (cm^{-1}): 3248 (NH$_2$, sym.), 3171 (NH$_2$, antisym.), and 1697 (C=O); ^{1}H NMR (DMSO-d$_6$, 250 MHz): δ 0.90 (s, 3H, C*H*$_3$-triazine), 2.60 (s, 2H, C*H*$_2$-NH$_2$), 4.90 (s, 2H, -N*H*$_2$), 5.54 (s, 1H, -C*H*-S), 7.90 (s, 1H, N*H*) ppm; MS (EI) m/z (%) = 199 (M^+, <1), 198 (7), 170 (2), 156 (5); *Anal*. Calcd. for $C_6H_9N_5OS$: C, 36.17; H, 4.55; N, 35.15. Found: C, 36.42; H, 4.67; N, 35.42.

Synthesis of 4-amino-6-methyl-3-(morpholin-4-yl-sulfanyl)-4*H*-[1,2,4]triazin-5-one (14)

To a stirred suspension of compound **1** (1.0 g, 6 mmol) in distilled water (10 mL), a mixture of NaOH solution (0.39 g in 30 mL water, 8 mmol) and morpholine (0.52 g, 6 mmol) was added. A solution of iodine (1.5 g, 6 mmol) and potassium iodide (1.0 g, 6 mmol) in distilled water (20 mL) was then added dropwise to the above reaction mixture and stirred at room temperature for 6 h. The resulting crude solid product thus formed was filtered, dried, and crystallized from DMF to afford **14**.[28] Yield 0.5 g (10%); m.p. 108-10°C; IR (KBr): υ (cm^{-1}): 3426 (NH-broad), 2920-2852 (CH-aliphatic), 1631 (C=O); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.35 (s, 3H, C*H*$_3$-triazine), 2.75-2.81 (t, 2 x C*H*$_2$-N-morpholine, *J* = 12.5 Hz), 3.45-3.50 (t, 4H, 2 x CH$_2$-O-morpholine, *J* = 12.5 Hz), 5.10 (s, 2H, -N-NH$_2$) ppm; MS (EI) m/z (%) = 243 (M^+, <1), 242 (11), 156 (5), 86 (2); *Anal*. Calcd. for $C_8H_{13}N_5O_2S$: C, 39.49; H, 5.39; S, 13.18. Found: C, 39.78, H, 5.68; S, 13.57.

Synthesis of 3,3'-bis(4-amino-6-methyl-5-oxo-triazin-yl)disulfide (16)

To a stirred solution of **1** (1.0 g, 6 mmol) in anhydrous methylene chloride (40 mL), lead tetraacetate (2.6 g, 6 mmol) was added in portions over 15 min. The reaction mixture was stirred at room temperature for 5 h. The lead salts formed were filtered and washed with methylene chloride (10 mL). The filtrate was evaporated and the residual solid was crystallized from ethanol to give **16**. Yield 1.2 g (55%); m.p. 150-52°C; IR (KBr): υ (cm^{-1}): 3292 (NH$_2$, sym.), 3202 (NH$_2$, antisym.), 1666 (C=O), 1499 (C=N); ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.40 (s, 6H, 2 x C*H*$_3$-triazine), 4.93 (s, 4H, 2 x -N-N*H*$_2$) ppm; MS (EI) m/z (%) = 314 (M^+, <1), 281 (2), 249 (49), 160 (<1), 105 (100); *Anal*. Calcd. for $C_8H_{10}N_8O_2S_2$: C, 30.57; H, 3.21; N, 35.65; S, 20.40. Found: C, 30.82; H, 3.33; N, 35.92; S, 20.50.

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