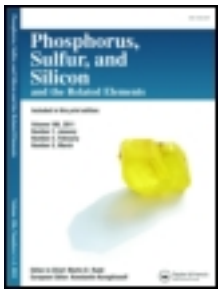

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Synthesis of Heterobicyclic Nitrogen Compounds as Molluscicide Agents Derived from 6-Methyl-5-styryl-1,2,4-triazin-3-thiol: Part I

T. M. Abdel-Rahman [a] , A. A. Shalaby [b] & I. F. Nassar [a]

[a] Faculty of Specific Education, Ain Shams University, Cairo, Egypt

[b] Faculty of Science, Ain Shams University, Cairo, Egypt

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SYNTHESIS OF HETEROBICYCLIC NITROGEN COMPOUNDS AS MOLLUSCICIDE AGENTS DERIVED FROM 6-METHYL-5-STYRYL-1,2,4-TRIAZIN-3-THIOL: PART I

T. M. Abdel-Rahman,[a] *A. A. Shalaby,*[b] *and I. F. Nassar*[a]
Faculty of Specific Education,[a] *Faculty of Science,*[b]
Ain Shams University, Cairo, Egypt

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Some new heterocyclic nitrogen compounds ***1–14*** *have been synthesized from cyclization of 5-styryl-3-mercapto-6-methyl-1,2,4-triazines* ***1*** *with active methylene and/or nitrogen compounds and were evaluated as molluscicidal agents. Significant molluscicidal activities for some of the products towards* Biomophalaria Alexandrina *snails were observed.*

Keywords: Molluscicide activity; substituted 1,2,4-triazines

INTRODUCTION

The structural diversity and biological significance of 1,2,4-triazines have received much attention owing to the wide range of biological activities of these compounds.[1–8] In the present work we describe a convenient one-pot procedure for the synthesis of some new heterobicyclic nitrogen systems bearing a 1,2,4-triazine moiety. The molluscicide activities of some of these compounds also are described.

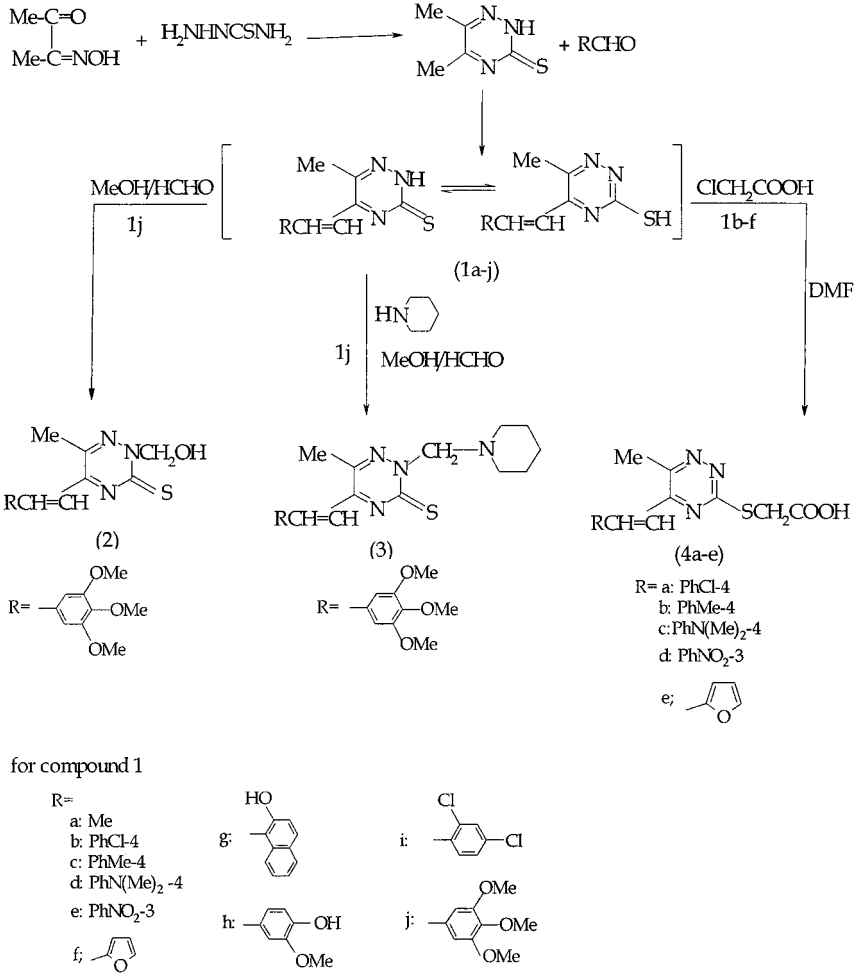
RESULTS AND DISCUSSION

The required 6-methyl-5-[substituted styryl]-2H-[1,2,4]triazine-3-thiones(**1a–j**) were obtained from condensation of 5,6-dimethyl-1,2,4-triazin-3(2H)thione with various aldehydes in glacial acetic acid with fused sodium acetate (Scheme 1).[9,10]

Refluxing compound **1j** with MeOH-HCHO and/or MeOH-HCHO in the presence of piperidine led to the formation of the

Address correspondence to T. M. Abdel-Rahman, Faculty of Specific Education, Ain Shams University, Cairo, Egypt. E-mail: taha_mahmood48@hotmail.com

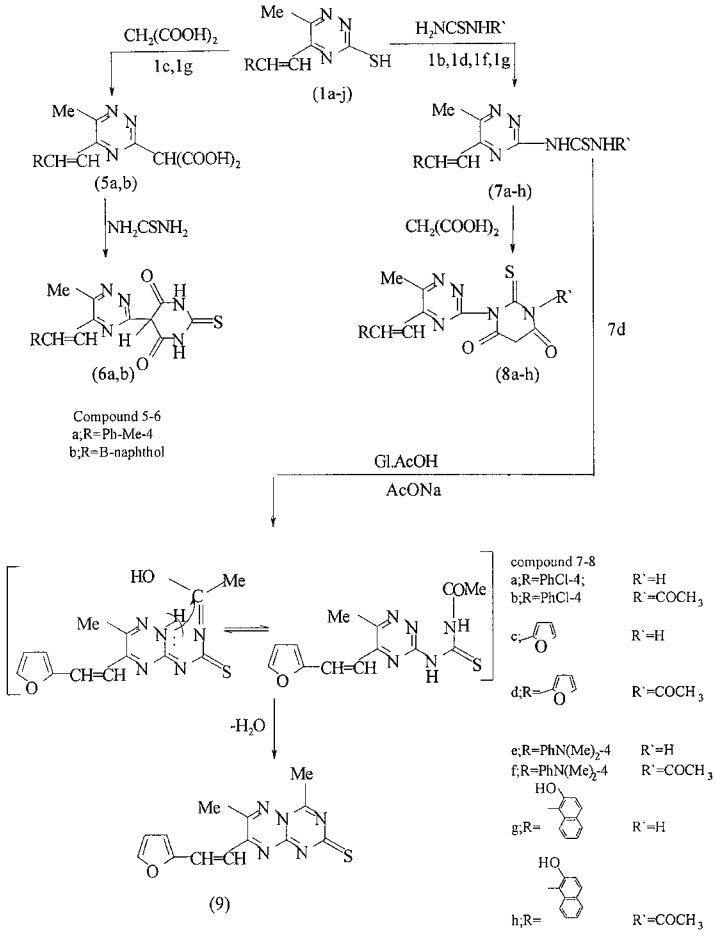
N-hydroxymethylderivative **2** and the N-Mannich's base compound **3** respectively (Scheme 1). On the other hand, refluxing **1b–f** with monochloroacetic acid in DMF produced 3-[Carboxymethylthio]-6-methyl-5-[substituted styryl][1,2,4]triazines (**4a–e**) (Scheme 1).



SCHEME 1

The chemistry of pyrimidines has received much attention in recent years[11–14] due to the unique physical and chemical properties of such derivatives, which have gained wide applications in biological activity. This together with our interest in the synthesis of 1,2,4-triazine derivatives prompted us to investigate the synthesis

of heterobicyclic systems that combind both pyrimidine and 1,2,4-triazines. Thus, the reactions of compounds **1c**,**g** with malonic acid in the presence of sodium ethoxide gave the dibasic acids **5a**,**b** which upon heterocyclization by refluxing with thiourea in methanol furnished 6-methyl-5-[substituted styryl]-3-[4,6-dioxo-2-thioxo-1,3,5-trihydropyrimidin-5-yl][1,2,4]triazines (**6a**,**b**) (Scheme 2).

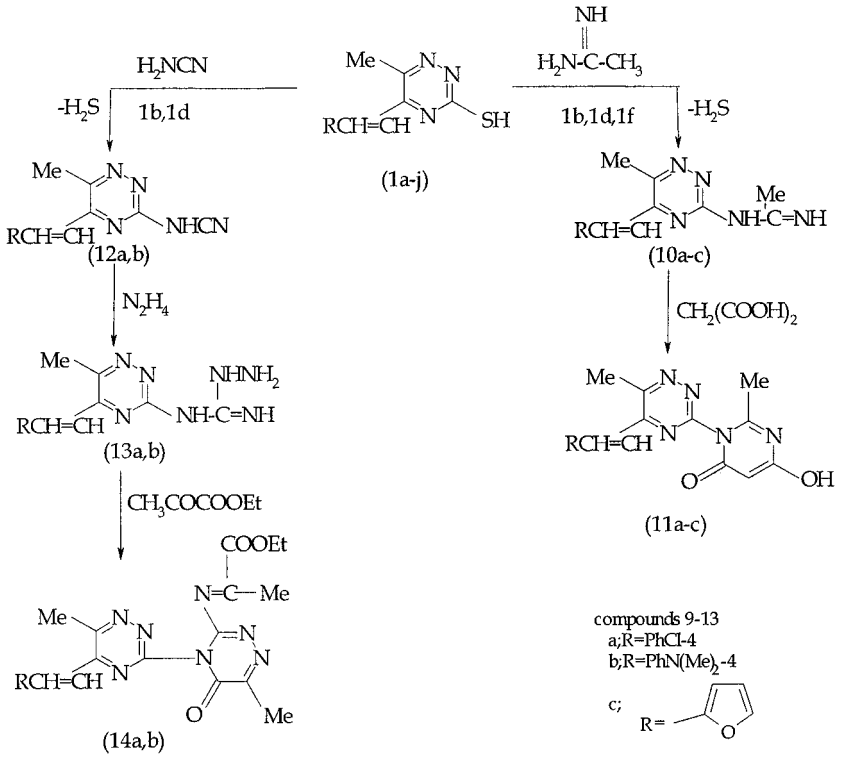


SCHEME 2

The target heterobicyclic nitrogen systems 6-methyl-5-[substituted styryl]-3-[N-substituted thiourea][1,2,4] triazines (**7a–h**) 6-methyl-5-[substituted styryl]-3-[5-dihydro-4,6-dioxo-1-substituted-2-thioxopyrimidin-3-yl][1,2,4]triazines (**8a–h**) and/or 4,7-dimethyl-8-[2-ethenyl

furan]-2-thioxo-1,3,5 triazino[5,6-b][1,2,4]triazine (**9**) have been synthesized from the reaction of **1b**,**d**,**f**,**g** with thiourea or acetyl thiourea[15] to give the N,N′-disubstituted thioureas (**7a–h**). Upon cyclization of these compounds with malonic acid[15] in the presence of glacial acetic acid and/or refluxing compound **7d** with glacial acetic acid with fused sodium acetate, the compounds **8a–h** and **9** were obtained respectively (Scheme 2).

Similarly, reaction of compound **1b**,**d**,**f** with acetamidine hydrochloride via loss of H_2S, afforded the amidines **10a–c** which on refluxing with malonic acid and a few drops of acetyl chloride yielded 6-methyl-5-[substituted styryl]-3-[5-dihydro-4,6-dioxo-2-methylpyrimidin-3-yl][1,2,4]triazines (**11a–c**) (Scheme 3).



SCHEME 3

Amination of compound **1b**,**d** using cyanamide yielded 3-cyanoamino-6-methyl-5-[substituted styryl][1,2,4]triazines (**12a**,**b**), which on addition with hydrazine hydrate produced the N^4-substituted

aminoguanidines (**13a**,**b**). Ring closure of **13a**,**b** with ethyl pyruvate[16] led to the formation of 3-[3-ethylpropionate imino]-6-methyl-5-oxo-[1,2,4]triazin-4-yl)-6-methyl-5-[substituted styryl][1,2,4]triazines (**14a**,**b**) (Scheme 3).

MOLLUSCICIDE EVALUATION

A wide variety of chemical compounds containing –N=C=S moiety have been found to be biologicaly active.[17,18] Cyclic structure containing the –N=C=S group have a range of biological activities.[19–22] On the other hand, several enzymes contain thiol groups, often in the apoenzyme or protein part of the molecule, which is essential for their activity. Consequently any reagent that reacts readily with the thiol group of such systems can destroy their function and may inhibit the reactivity of such enzymes.

The compounds listed in Table I were tested for their effect on some snails, especially *Biomphalaria alexandrina* (average shell diameter 6–8 mm) the intermediate host of *Schistosoma mausoni* in Giza governestate, that were not treated with molluscicides. The snails were adapted to laboratory conditions three weeks before being used in toxicity tests to be sure that they were strong and healthy. Snails were kept in a plastic aguaria filled with dechlorinated tap water at room temperature, 25–27°C. Dried lettuce leaves were added daily and the water was changed weekly.

TABLE I The Molluscicidal Acivity of Some Prepared Compounds Against *Biomphalaria alexandrina* Snails

	Mortality % of snails at concentration		
Compd.	100 ppm	50 ppm	25 ppm
1d	100	100	50
1f	0	0	0
1g	0	0	0
1i	80	20	0
1j	0	0	0
2	0	0	0
3	0	0	0
4b	0	0	0
7b	50	0	0
7g	100	30	0
10b	0	0	0
11c	0	0	0
12b	0	0	0
14a	0	0	0

Stock solutions of the investigated compounds (500 ppm) were dissolved in the least amount of ethanol and diluted with dechlorinated tap water on the basis of weight/volume series of dilutions of each compound were prepared.

The number of snails in each experiment and control was ten. The exposure time was 24 h followed by 24 h as recovery period. Standard procedures were followed according to the methods recommended by WHO.[23,24] Table I indicates that under the employed experimental conditions the quantitative structure activity relationship studies of these compounds showed that:

1. At concentration 25 ppm only one compound **1d** showed an antisnail activity which could be attributed to the p-dimethylaminostyryl moiety.
2. At concentration 50 ppm the compounds **1d**, **1i**, and **7g** showed an antisnail activity in the order **1d** > **7g** > **1i**, which was attributed to the presence of the p-dimethylamino **1d**, β-naphthol (**7g**) and 2,4-dichloro phenyl (**1i**) moieties.
3. At concentration 100 ppm the compounds **1d**, **1i**, **7b** and **7g** showed an antisnail activity in the order **1d** = **7g** > **7b** > **1i**.

Conclusion: Only compounds **1d**, **1i**, **7b**, and **7g** showed antisnail activity.

EXPERIMENTAL

The reported m.p. were uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 293 FT spectrophotometer ($\tilde{\nu}$ in cm^{-1}), UV absorption spectra in DMF were recorded on a Perkin-Elmer, Lambda 4B controlar accessory interface, UV-VIS spectrophotometer (ν in nm), ^{1}H-NMR spectra were recorded on a EM NMR spectrometer 200 MHz PMR using DMSO as a solvent and TMS as an internal reference δ (chemical shifts in ppm), and mass spectra were recorded on a gas chromatographic GCMS qp 1000_{cx} Shimadzu instrument at 70 eV. Compound 5,6-dimethyl-1,2,4-triazin-3(2H) thione was prepared following a reported procedure.[11] The physical data of the synthesized compounds are given in (Table II).

6-Methyl-5-propenyl-2H-[1,2,4]triazin-3-thione (1a)

A mixture of 5,6-dimethyl-1,2,4-triazin-3(2H) thione (0.01 mmol) and acetaldehyde (0.01 mmol) in AcOH (20 ml)-AcONa (5 g) was refluxed for 2 h and poured onto ice. The solid obtained was filtered and crystallized to give **1a** (Table II).

TABLE II Characterizing Data of the Prepared Compounds

Compd.	Solvent	m.p. °C (yield)	Molecular formula (mol. wt.)	Analysis % calculated (found)				
				C	H	Cl	N	S
1a	AcOH	115–116 (55)	$C_7H_9N_3S$ (167.24)	50.28 (50.04)	5.42 (5.38)		25.13 (24.96)	19.17 (18.81)
1b	EtOH	276–277 (40)	$C_{12}H_{10}N_3ClS$ (263.75)	54.65 (54.37)	3.82 (3.66)	13.44 (13.08)	15.93 (15.48)	12.16 (11.87)
1c	MeOH	190–191 (50)	$C_{13}H_{13}N_3S$ (243.33)	64.17 (65.09)	5.38 (5.17)		17.27 (17.08)	13.18 (13.51)
1d	Pet. Ether	172–173 (55)	$C_{14}H_{16}N_4S$ (272.38)	61.74 (61.88)	5.92 (6.01)		20.57 (20.83)	11.77 (11.47)
1e	Benzene	180–181 (52)	$C_{12}H_{10}N_4O_2S$ (274.31)	52.55 (52.98)	3.68 (3.64)		20.42 (20.61)	11.69 (11.52)
1f	Benzene	207–208 (45)	$C_{10}H_9N_3OS$ (219.92)	54.62 (54.47)	4.42 (4.38)		19.11 (19.23)	14.58 (14.52)
1g	AcOH	276–278 (40)	$C_{16}H_{13}N_3OS$ (295.97)	64.93 (64.91)	4.43 (4.28)		14.20 (14.17)	10.83 (10.70)
1h	EtOH	213–215 (50)	$C_{13}H_{13}N_3O_2S$ (275.34)	56.71 (56.45)	4.76 (4.81)		15.26 (15.09)	11.65 (11.51)
1i	EtOH	175–176 (55)	$C_{12}H_9N_3Cl_2S$ (298.85)	48.23 (48.20)	3.25 (3.38)	23.97 (23.73)	14.20 (13.33)	10.84 (10.71)
1j	EtOH	214–215 (48)	$C_{15}H_{17}N_3O_3S$ (319.39)	56.41 (56.25)	5.37 (5.42)		13.16 (13.27)	10.04 (9.92)
2	EtOH	180–181 (30)	$C_{16}H_{19}N_3O_4S$ (349.42)	55.00 (54.83)	5.48 (5.35)		12.03 (11.97)	9.18 (8.96)
3	EtOH	196–198 (22)	$C_{21}H_{28}N_4O_3S$ (416.55)	60.55 (60.72)	6.78 (6.65)		13.45 (13.23)	7.70 (7.33)
4a	AcOH	270–271 (28)	$C_{14}H_{12}N_3O_2ClS$ (321.79)	52.26 (52.17)	3.76 (3.87)	11.02 (10.90)	13.06 (12.89)	9.96 (10.01)
4b	EtOH	256–258 (25)	$C_{15}H_{15}N_3O_2S$ (301.38)	59.78 (59.66)	5.02 (4.96)		13.94 (13.88)	10.64 (10.50)
4c	AcOH	280–281 (30)	$C_{16}H_{18}N_4O_2S$ (330.42)	58.16 (58.22)	5.49 (5.37)		16.99 (17.07)	9.70 (9.53)
4d	AcOH	190–192 (35)	$C_{14}H_{12}N_4O_4S$ (332.35)	50.60 (50.54)	3.64 (3.56)		16.86 (16.78)	9.65 (9.55)
4e	AcOH	230–231 (33)	$C_{12}H_{11}N_3O_3S$ (277.31)	51.98 (51.87)	4.00 (4.11)		15.15 (15.22)	11.56 (11.73)
5a	Pet. Eter	220–222 (32)	$C_{16}H_{15}N_3O_4$ (313.32)	61.34 (61.76)	4.83 (4.72)		13.41 (13.33)	
5b	EtOH	271–272 (22)	$C_{19}H_{15}N_3O_5$ (365.36)	62.46 (62.35)	4.14 (3.97)		11.50 (11.69)	
6a	Pet. Ether	210–212 (21)	$C_{17}H_{15}N_5O_2S$ (353.41)	57.78 (57.66)	4.28 (4.17)		19.82 (20.01)	9.07 (8.93)
6b	Benzene	260–261 (31)	$C_{20}H_{15}N_5O_3S$ (405.45)	59.25 (59.15)	3.73 (3.81)		17.27 (16.96)	7.91 (7.87)
7a	EtOH	190–192 (33)	$C_{13}H_{12}N_5ClS$ (305.80)	51.06 (50.98)	3.96 (4.03)	11.59 (11.52)	22.90 (23.07)	10.49 (10.33)

(Continued on next page)

TABLE II Characterizing Data of the Prepared Compounds *(Continued)*

Compd.	Solvent	m.p. °C (yield)	Molecular formula (mol. wt.)	Analysis % calculated (found)				
				C	H	Cl	N	S
7b	Benzene	240–242 (30)	$C_{15}H_{14}N_5OSCI$ (347.834)	51.80 (51.66)	4.06 (4.21)	10.19 (10.44)	20.13 (20.33)	9.22 (9.04)
7c	EtOH	236–238 (37)	$C_{11}H_{11}N_5OS$ (261.311)	50.56 (51.00)	4.24 (4.06)		26.80 (26.72)	12.27 (11.97)
7d	EtOH	265–266 (35)	$C_{13}H_{13}N_5O_2S$ (303.35)	51.48 (51.33)	4.32 (4.27)		23.09 (22.95)	10.57 (10.5)
7e	Benzene	280–281 (20)	$C_{15}H_{18}N_6S$ (314.421)	57.30 (57.09)	5.77 (5.56)		26.73 (26.61)	10.20 (10.03)
7f	DMF	285–286 (20)	$C_{17}H_{20}N_6OS$ (356.46)	57.28 (57.17)	5.66 (5.71)		23.58 (23.42)	9.00 (8.94)
7g	Benzene	260–261 (24)	$C_{17}H_{15}N_5OS$ (337.412)	60.52 (60.34)	4.48 (4.38)		20.76 (21.00)	9.50 (9.41)
7h	Pet. Ether	220–221 (32)	$C_{19}H_{17}N_5O_2S$ (379.45)	60.15 (60.28)	4.52 (4.43)		18.46 (18.40)	8.45 (8.32)
8a	EtOH	250–252 (30)	$C_{16}H_{12}N_5O_2ClS$ (373.83)	51.41 (51.52)	3.24 (3.13)	9.48 (9.27)	18.73 (18.87)	8.58 (8.32)
8b	Benzene	286–287 (31)	$C_{18}H_{14}N_5O_3ClS$ (416.17)	51.95 (51.79)	3.39 (3.23)	8.52 (8.37)	16.90 (16.67)	7.71 (7.63)
8c	EtOH	275–277 (24)	$C_{14}H_{11}N_5O_3S$ (329.35)	51.06 (51.56)	3.37 (3.52)		21.26 (21.38)	9.74 (9.47)
8d	EtOH	270–272 (48)	$C_{16}H_{13}N_5O_4S$ (371.382)	51.75 (52.00)	3.53 (3.48)		18.86 (18.71)	8.63 (8.59)
8e	Pet. Ether	265–266 (25)	$C_{18}H_{18}N_6O_2S$ (382.45)	56.53 (56.46)	4.74 (4.87)		21.97 (22.12)	8.38 (8.25)
8f	Pet. Ether	210–212 (22)	$C_{20}H_{20}N_6O_3S$ (424.49)	56.59 (59.32)	4.75 (4.67)		19.80 (20.03)	7.55 (7.32)
8g	EtOH	286–287 (32)	$C_{22}H_{17}N_5O_4S$ (447.48)	59.05 (58.89)	3.83 (3.72)		15.65 (15.44)	7.17 (6.92)
8h	EtOH	246–248 (36)	$C_{20}H_{15}N_5O_3S$ (405.45)	59.25 (59.06)	3.73 (3.62)		17.27 (17.03)	7.91 (8.01)
9	EtOH	260–261 (21)	$C_{13}H_{11}N_5OS$ (285.34)	54.72 (54.38)	3.89 (4.01)		24.54 (24.35)	11.24 (11.43)
10a	EtOH	270–271 (45)	$C_{14}H_{14}N_5Cl$ (287.76)	58.44 (58.63)	4.90 (4.72)	12.32 (11.92)	24.34 (24.55)	
10b	Pet. Ether	255–257 (40)	$C_{16}H_{20}N_6$ (296.38)	64.84 (64.72)	6.80 (6.88)		28.36 (28.17)	
10c	AcOH	296–297 (31)	$C_{12}H_{13}N_5O$ (243.28)	59.25 (59.12)	5.39 (5.23)		28.79 (28.64)	
11a	MeOH	230–231 (32)	$C_{17}H_{14}N_5O_2Cl$ (355.79)	57.39 (57.22)	3.97 (3.81)	9.97 (9.53)	19.68 (19.52)	
11b	Pet. Ether	133–135 (50)	$C_{19}H_{20}N_6O_2$ (364.42)	62.63 (62.70)	5.53 (5.38)		23.06 (23.30)	
11c	AcOH	280–282 (55)	$C_{15}H_{13}N_5O_3$ (311.31)	57.88 (57.75)	4.21 (4.09)		22.50 (22.38)	

(Continued)

TABLE II Characterizing Data of the Prepared Compounds *(Continued)*

Compd.	Solvent	m.p. °C (yield)	Molecular formula (mol. wt.)	Analysis % calculated (found)				
				C	H	Cl	N	S
12a	DMF	235–236 (53)	$C_{13}H_{10}N_5Cl$ (271.72)	57.47 (57.29)	3.71 (3.58)	13.05 (12.86)	25.77 (25.91)	
12b	Pet. Ether	230–231 (54)	$C_{15}H_{16}N_6$ (280.34)	64.27 (63.89)	5.75 (5.81)		29.98 (29.59)	
13a	DMF	247–249 (55)	$C_{13}H_{14}N_7Cl$ (303.76)	51.41 (51.50)	4.65 (4.54)	11.67 (11.43)	32.28 (32.09)	
13b	EtOH	185–186 (53)	$C_{15}H_{20}N_8$ (312.39)	57.68 (57.57)	6.45 (6.53)		35.87 (35.78)	
14a	DMF	230–231 (35)	$C_{21}H_{20}N_7O_3Cl$ (454.91)	55.45 (55.72)	4.65 (4.51)	7.79 (7.70)	21.55 (21.95)	
14b	Pet. Ether	190–191 (33)	$C_{23}H_{26}N_8O_3$ (462.52)	59.73 (60.01)	5.67 (5.59)		24.23 (24.18)	

6-Methyl-5-[substituted styryl]-2H-[1,2,4]triazin-3-thiones (1b–j)

A mixture of 5,6-dimethyl-1,2,4-triazin-3(2H) thione (0.01 mmol) and an aromatic aldehyde such as acetaldehyde, 4-chlorobenzaldehyde, 4-methylbenzaldehyde, 4-(dimethylamino)benzaldehyde, 3-nitrobenzaldehyde, furfural, 2-hydroxynaphthaldehyde, vanilline, 2,4-dichlorobenzaldehyde, and 3,4,5-trimethoxybenzaldehyde (0.01 mmol) in AcOH (20 ml)-AcONa (5 g) was refluxed for 2 h, cooled, and poured onto ice. The resultant solids were filtered and crystallized to give (**1b–j**) (Table II). UV (**1i**): 245 (3.00). IR (**1e**): 3102 (N**H**); 3061 (aromatic C**H**); 2981 (aliphatic CH); 1654 (C**H**=CH); 1593 (C=N); 1526 (assy. NO_2); 1474, 1459 (def. Me); 1166 (C—S); 810, 735 (Phenyl group). (**1j**); 3200 (N**H**); 3050 (aromatic CH); 2880 (aliphatic CH); 1640 (CH=C**H**); 1610 (C=N); 1480 (defm. CH_3); 1350 (NCSN); 1160 (C-S); 1040 (C—O—C); 800 (aryl group). ^{1}H-NMR (**1j**): 1.5 (s, 3**H**, C**H**$_3$); 4.5 (s, 9**H**, 3OC**H**$_3$); 7.1–7.3 (dv, 2**H**, C**H**=C**H**); 7.5–7.7 (m, 2**H**, aromatic protons); 8.7 (s, 1**H**, N**H**). MS (Int.%) (**1a**): m/z 167.24 (8.44); 152 (19.01); 138.9 (100); 124 (11.17); 113 (17.33); 54 (22.05). (**1b**): m/z 263.75; 116 (35.38); 143 (100); (**1f**): m/z 219.916; 132 (7.48); 116 (48.38); 99 (6.67); 60 (100) (**1j**): m/z 319.39; 138 (9.39) 112 (6.11) and 60 (100).

2-Hydroxymethyl-6-methyl-5-[3,4,5-trimethoxystyryl][1,2,4]triazin-3-thione (2)

A mixture of **1j** (0.01 mmol) and formaldehyde (0.01 mmol) in methanol (20 ml) was refluxed for 4 h, cooled, and poured onto ice. The formed

solid was filtered and crystallized to give **2** (Table II). IR: 3450 (OH); 3100–3080 (aromatic CH); 2980 (aliphatic CH); 1610 (CH=C**H**); 1480–1440 (def. CH_3); 1150 (C-S); 1030 (C–O–C); 830 (aryl group). ^{1}H-NMR: 2.5 (s, 2**H**, C$\mathbf{H}_2$); 3.7–4.0 (s, 9**H**, 3OC$\mathbf{H}_3$), 7.35–7.85 (m, 4**H**, styryl and aromatic protons); 8.6 (s, 1**H**, O**H**).

6-Methyl-2-[piperidin-1-ylmethyl]-5-[3,4,5-trimethoxystyryl]-2H-[1,2,4]triazin-3-thione (3)

A mixture of **1j** (0.01 mmol) and formaldehyde (0.01 mmol) in methanol (20 ml) and piperidine (0.01 mmol) was refluxed for 4 h, cooled, and poured onto ice. The resultant solid was filtered and crystallized to give **3** (Table II). ^{1}H-NMR. 1.5 (s, 3**H**, C$\mathbf{H}_3$); 1.9–2.2 (m, 10**H**, piperidine); 2.5 (s, 2**H**, C$\mathbf{H}_2$); 3.5 (s, 3**H**, OC$\mathbf{H}_3$); 7.6–7.9 (m, 2**H**, C**H**=C**H**, 2**H**, aromatic). MS (Int.%): m/z 416.55 (0.04); 390.2 (36.98); 388.2 (100); 373.1 (54.48); 329 (12.87); 195 (11.23).

3-[Carboxymethylthio]-6-methyl-5-[substituted styryl][1,2,4]triazines (4a–e)

A mixture of **1b**, **1c**, **1d**, **1e**, **1f** (0.01 mmol) and monochloroacetic acid (0.01 mmol) in DMF (20 ml) was refluxed for 2 h); cooled, and poured onto ice. The solid obtained was filtered and crystallized to give **4a–e** (Table II). ^{1}H-NMR (**4a**): 1.5 (s, 3**H**, C$\mathbf{H}_3$); 2.2 (s, 2**H**, C$\mathbf{H}_2$); 7.2–7.4 (dv, 2**H**, C**H**=C**H**); 7.6–7.8 (m, 4**H**, aromatic protons); 10.5 (s, 1**H**, O**H**).

2-(2,3-Dihydro-6-methyl-5-[substituted styryl][1,2,4]triazin-3-yl)malonic acid (5a,b)

A mixture of **1c**,**1g** (0.01 mmol) and malonic acid (0.01 mmol) in DMF (20 ml) was refluxed for 2 h, cooled, and poured onto ice. The solid obtained was filtered and crystallized to give **5a**,**b** (Table II). IR (**5a**): 3446 (O**H**); 3469 (OH); 3010 (aromatic CH); 2923 (aliphatic CH); 1697 (C=O); 1606 (CH=C**H**); 1456 (def. C$\mathbf{H}_3$); 806 (aryl group). ^{1}H-NMR (**5a**): 1.2 (s, 3**H**, C$\mathbf{H}_3$); 1.5 (s, 3**H**, C$\mathbf{H}_3$); 4.5 (s, 2**H**, C**H**=C**H**); 7.4–7.6 (d, 2**H**, C**H**=C**H**); 7.7–7.9 (m, 4**H**, aromatic protons); 8.5–8.9 (s, 1**H**, O**H**).

6-Methyl-5-[substituted styryl]-3-[4,6-dioxo-2-thioxo-1,3,5-trihydroPyrimidin-5-yl][1,2,4]triazines (6a,b)

Compound **5a** or **5b** (0.01 mmol) and thiourea (0.01 mmol) in AcOH (20 ml) was refluxed for 4 h, cooled, and poured onto ice. The solid

obtained was filtered and crystallized to give **6a** or **b** (Table II). UV (**6b**): 305 (3.0); 290 (3.8) nm. IR (**6b**): 3451, 3444 (OH); 3168 (NH); 3016 (aromatic CH); 2958 (aliphatic C**H**); 1606 (C**H**=CH); 1494 (def. Me); 1338 (NCSN); 1160 (C-S); 804, 767 (aryl group) cm^{-1}. ^{1}H-NMR (**6b**): 2.1 (s, 3**H**, C$\mathbf{H}_3$); 3.5 (s, 1**H**, C**H**); 7.1–7.9 (m, 6**H**, aryl and 2**H**, C**H**=C**H** protons); 9.8 (s, **H**, O**H**) and 12.6 (s, 2**H**, N**H**). MS (Int.%) (**6b**): m/z 405.45; 341.1 (36.58); 340.1 (100); 170 (36.42); 154 (3.02); 115 (9.21).

6-Methyl-5-[substituted styryl]-3-[N-substituted thiourea][1,2,4]triazines (7a–h)

A mixture of **1b**, **1d**, **1f**, or **1g** (0.01 mmol) and thiourea or acetyl thiourea (0.01 mmol) in DMF (20 ml) was refluxed for 2 h, cooled, and poured onto ice. The solid obtained was filtered and crystallized to give **7a–h** (Table II). IR (**7h**) 3450 (OH); 3150 (NH); 3050 (aromatic CH); 2950 aliphatic CH); 1650 (COMe); 1500–1450 (def. Me); 1380 (NCSN); 1160 (C—S); 830, 780 (Phenyl groups). ^{1}H-NMR (**7h**): 1.2 (s, 3**H**, C$\mathbf{H}_3$); 2.5 (s, 3**H**, C$\mathbf{H}_3$CO); 7.5–7.9 (m, 6**H**, aromatic; 2**H**, C**H**=C**H**); 9.5 (s, 1**H**, O**H**); 12.6, 13 (s, 1**H**, N**H**, N**H**).

6-Methyl-5-[substituted styryl]-3-[5-dihydro-4,6,-dioxo-1-substituted-2-thioxo-pyrimidin-3-yl[1,2,4]triazines (8a–h)

A mixture of **7a–h** (0.01 mmol) and malonic acid (0.01 mmol) in AcOH (20 ml) was refluxed for 4 h, cooled, and poured onto ice. The solid was filtered and crystallized to give **8a–h** (Table II). IR (**8b**): 3414 (OH); 3100 (aromatic CH); 2922, 2854 (aliphatic CH); 1725 (C=O); 1609 (C=C); 1463 (def. Me); 1166 (C-S), 780 (aryl group). ^{1}H-NMR (**8b**): 3.2 (s, 3**H**, C$\mathbf{H}_3$CO); 2.4–4.6 (s, 6**H**, 2C$\mathbf{H}_3$); 7.2–7.8 (m, 6**H**, C**H**=C**H**, and aromatic protons); 12.5 (s, 1**H**, O**H**).

4,7-Dimethyl-8-[2-ethenyl furan]-2-thioxo-1,3,5 triazino [5,6-b][1,2,4]triazine (9)

A mixture of **7d** (0.01 mmol) and gl.AcOH (20 ml) fused AcONa (1 g) was refluxed for 2 h, cooled, and poured onto ice. The resultant solid was filtered and crystallized to give **9** (Table II). MS (Int.%): m/z, 285.34; 167 (17.26); 149 (48.03); 93 (8.11); 71 (66.16); 57 (100); 55 (59.01). ^{1}H-NMR 1.1, 1.5 (s, 6**H**, 2C$\mathbf{H}_3$); 7.6–8 (m, 2**H**, C**H**=C**H**, 4**H** furyl protons).

N-(6-Methyl-5-[substituted styryl][1,2,4]triazin-3yl)acetamidines (10a–c)

A mixture of **1b**, **1d**, or **1f** (0.01 mmol) and acetamidine (0.01 mmol) in DMF (20 ml) was refluxed for 2 h, cooled, and poured onto ice. The solid obtained was filtered and crystallized to give **10a–c** (Table II). IR (**10b**): 3164 (NH); 2926 (aliphatic CH); 1603 (C**H**=C**H**); 1535 (C=N); 1475; 1442 (def. Me); 1364 (NCN); 819; 764 (Phenyl group). ^{1}H-NMR (**10b**): 0.9, 1.2, 1.6 (s, 9**H**, 3C**H**$_3$); 7.4–7.8 (m, 6**H**, 2**H**, C**H**=C**H**, 4**H**, aromatic protons); 8.5, 11.5 (s, 2**H**, N**H**=, N**H**).

6-Methyl-5-[substituted styryl]-3-[5-dihydro-4,6-dioxo-2-methylPyrimidin-3-yl][1,2,4]triazines (11a–c)

A mixture of **10a–c** (0.01 mmol) and malonic acid (0.01 mmol) in AcOH (20 ml) was refluxed for 4 h, cooled, and poured onto ice. The yielded solid was filtered and crystallized to give **11a–c** (Table II). UV (**11a**): 255 (2.0). IR (**11a**): 3364 (OH); 3080 (aromatic CH); 2923 (aliphatic CH); 1740 (C=O); 1609 (C=N); 800 (phenyl group); 700 (C-Cl). ^{1}H-NMR (**11a**): 1.4, 1.6 (s, 6**H**, 2C**H**$_3$); 7.2–8 (m, 7**H**, 1**H**, C**H**=, 2**H**, C**H**=C**H**, 4**H**, aromatic protons); 10.5 (s, 1**H**, OH). MS (Int.%) (**11a**): m/z 355.79; 342.25 (26.95); 167 (40.41); 149 (100).

3-Cyanoamino-6-methyl-5-[substituted styryl]-[1,2,4]triazines (12a,b)

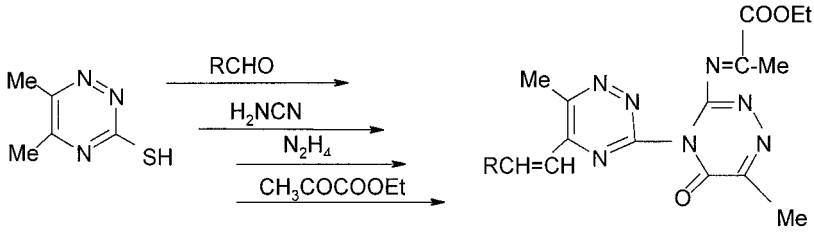
A mixture of **1b**, **1d** (0.01 mmol) and cyanamide (0.01 mmol) in isopropyl alcohol (20 ml) was refluxed for 6 h, cooled, and poured onto ice. The resultant solid was filtered and crystallized to give **12a**,**b** (Table II). IR (**12a**): 3125 (NH); 3050 (aromatic CH); 2922, 2854 (aliphatic CH); 2271 (CN); 1640 (CH=CH); 800 (phenyl group); 720 (C-Cl). ^{1}H-NMR (**12a**): 1.5 (s, 3**H**, C**H**$_3$); 7.5–7.9 (m, 6**H**, 2**H**, C**H**=C**H**, 4**H**, aromatic protons); 8.5 (s, 1**H**, N**H**-CN).

N^4-(6-Methyl-5[substituted styryl][1,2,4]triazin-3-yl)amino Guanidine (13a,b)

A mixture of **12a**,**b** (0.01 mmol) and hydrazine hydrate (0.01 mmol) in isopropyl alcohol (20 ml) was refluxed for 12 h, cooled, and poured onto ice. The solid produced was filtered and crystallized to give **13a**,**b** (Table II). IR (**13a**): 3400 (NH$_2$); 3220–3150 (NH-NH); 1700–1600 (def. NH$_2$, CH=CH); 1520 (N=CH); 780 (phenyl group); 690 (C-Cl). ^{1}H-NMR (**13a**): 1.2 (s, 3**H**, C**H**$_3$); 2.5 (s, 2**H**, N**H**$_2$); 7.4–8 (m, 6**H**, 2**H**, C**H**=C**H**, 4**H**, aromatic protons); 8.5, 11 and 12.2 (each s, 3N**H**).

3-[3-ethyl propionate Imino]-6-methyl-5-oxo-[1,2,4]triazin-4-yl)-6-methyl-5-[substituted Styryl][1,2,4]triazines (14a,b)

A mixture of **13a**,**b** (0.01 mmol) and ethylbyravate (0.01 mmol) in AcOH (20 ml) was refluxed for 4 h, cooled, and poured onto ice. The resultant solid was filtered and crystallized to give **14a**,**b** (Table II). IR (**14b**): 3100 (aromatic CH); 2917 (aliphatic CH); 1678 (C=O); 1606 (C=N); 1437 (def. Me); 817 (phenyl group). ^{1}H-NMR (14b): 0.8–1.5 (m, 15**H**, 5C**H**$_3$); 2.2 (q, 2H, C**H**$_2$); 7.4–7.7 (m, 6**H**, 2**H**, C**H**=C**H**, 4**H**, aromatic protons). M (Int.%): (**14b**): m/z 462 (52); 393 (9.36); 239 (19.42); 148.9 (100) 146 (8.65); 95 (9.36).



a; R=PhCl-4
b; R=PhN(Me)$_2$-4

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