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Synthesis of some new heterobicyclic nitrogen systems bearing the 1,2,4-triazine moiety as anti-HIV and anti-cancer drugs, part II

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Some new heterobicyclic nitrogen systems **5**–**18** and/or thioethers **20**, **22** bearing the 1,2,4-triazine moiety have been synthesized via condensation of 3-formylamino-1,2,4-triazine **3** with nitrogen compounds followed by heterocyclization with oxygen reagents. Thioether analogs **20**, **22** have been obtained from fusion of compound **19** with 4-chlorothiophenol. The structure of the products have been established by elemental analysis and spectral data. The anti-HIV and anticancer activities of some products have also been investigated where compounds **20a**, **c** and **22b** exhibited a moderate activity. The biocidal-structures activity correlation was also studied.

1. Introduction

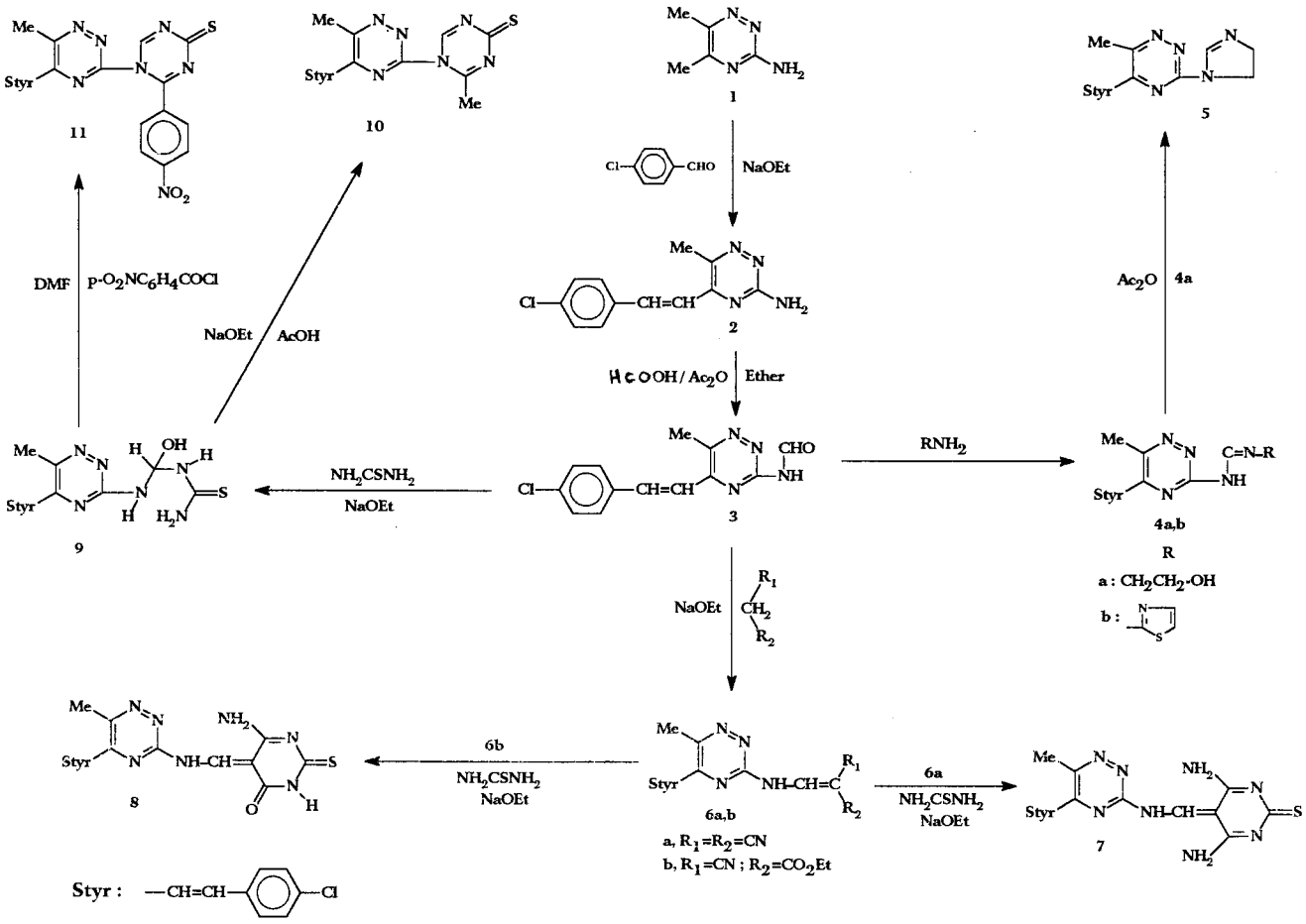
1,2,4-Triazines play a vital role in many biological processes and as synthetic drugs [1–4]. Furthermore, many heterocyclic systems bearing 1,2,4-triazines are found to exhibit remarkable pharmacological effects [5–8]. In search for new anti-HIV and anticancer agents, some additional heterocyclic moieties were incorporated in the 1,2,4-triazine nucleus via the interaction between formylamino-1,2,4-triazine **3** with nitrogen and oxygen reagents.

2. Investigations and results

2.1. Chemistry

The starting compound 3-formylamino-6-methyl-5-(4-chlorostyryl)-1,2,4-triazine (**3**) was obtained from formylation of 3-amino-6-methyl-5-(4-chlorostyryl)-1,2,4-triazine (**2**) [9] by treatment with Ac_2O-HCO_2H reagent [10].
Condensation of the 3-formylaminotriazine **3** with primary amines, active methylene compounds and/or thiocarbamide was used to form new heterobicyclic systems. Thus, condensation of compound **3** with ethanolamine and 2-aminothiazole refluxing in ethanol, produced **4a**, **b**. Attempts to the cyclization of **4a** using Ac_2O afforded

Scheme 1



4,5-dihydro-1-[6-methyl-5-(4-chlorostyryl)-1,2,4-triazin-3-yl] imidazoline (**5**) (Scheme 1).

On the other hand, condensation of compound **3** with active methylene derivatives such as malononitrile and ethyl cyanoacetate refluxing in glacial acetic acid/fused sodium acetate afforded **6a**, **b** which on cyclocondensation [11] with thiourea on boiling with sodium ethoxide furnished the aminopyrimidinethiones **7** and **8** (Scheme 1).

Also, **3** reacted with thiourea in the presence of sodium ethoxide via addition reaction [12] to give the carbinole derivative **9**. Cyclocondensation reaction of **9** by boiling with glacial acetic acid/fused sodium acetate or 4-nitrobenzoyl chloride in the presence of DMF gave 6-methyl-1-[6-methyl-5-(4-chlorostyryl)-1,2,4-triazin-3-yl]-1,3,5-triazin-4-thione (**10**) and 6-(4-nitrophenyl)-1-[6-methyl-5-(4-chlorostyryl)-1,2,4-triazin-3-yl]-1,3,5-triazin-4-thione (**11**) (Scheme 1).

Condensation of compound **3** with hydrazine hydrate in abs. ethanol produced the amidrazone **12**. Reaction of **12** with glacial acetic acid/fused, sodium acetate and or diethylcarbonate in dioxan [13] afforded 5-methyl-4-[6-methyl-5-(4-chlorostyryl)-1,2,4-triazin-3-yl]-1,2,4-triazole (**13**) and 1 *H*-4-[6-methyl-5-(4-chlorostyryl)-1,2,4-triazin-3-yl]-1,2,4-triazol-5-one (**14**), respectively (Scheme 2).

Some new 1,2,4-triazines bearing other 1,2,4-triazine moieties have been deduced. Thus, 4-[6-methyl-5-(4-chlorostyryl)-1,2,4-triazin-3-yl]-6-(4-chlorostyryl)-1,2,4-triazin-5-one (15) and 5 *H*-4-[6-methyl-5-(4-chlorostyryl)-1,2,4-triazin-3-yl]-5,6-diphenyl-1,2,4-triazine (**16**) have been obtained from cyclocondensation of amidazone **12** with β-(4-chlorostyryl)-α-keto-carboxylic acid or benzoin in the presence of glacial acetic acid/fused sodium acetate, while condensation of compound **12** with isatin in methanol yielded the isatin-3-hydrazone **17** which on reluxing with glacial acetic acid/fused sodium acetate furnished 4-[6-methyl-5-(4-chlorostyryl)-1,2,4-triazin-3-yl]-1,2,4-triazino [6,5-b]indole (**18**) (Scheme 2).

Finally, the target thioethers of the type **20a**–**d** and **22a**, **b** have been obtained from fusion of compound **19** with 4-chlorothiophenol via 1,4-addition reaction [14] (Scheme 3).

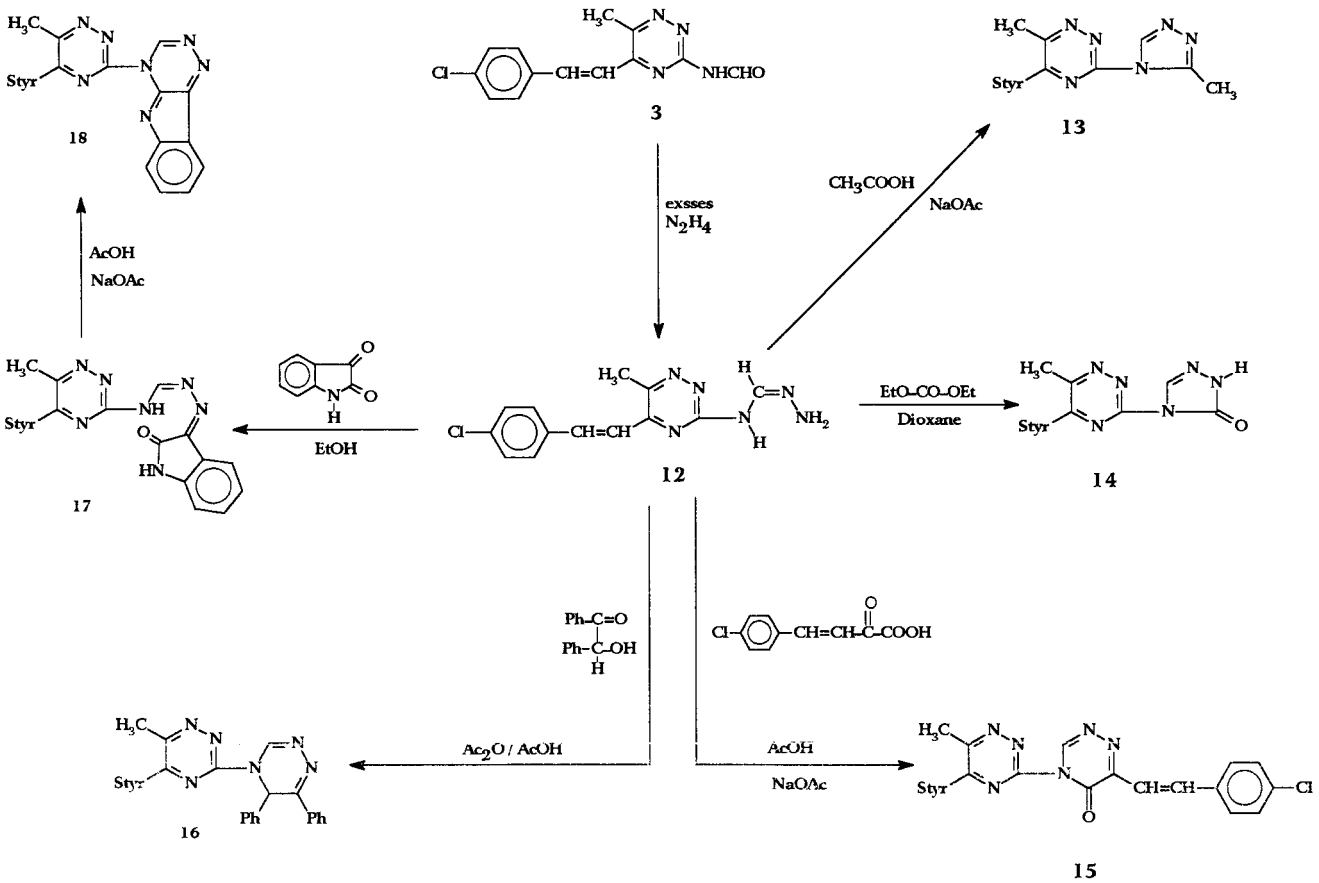
2.2. Pharmacology

In a programme to obtain potent anti-HIV and anticancer agents, the synthesized compounds especially thioethers were tested in view of possible pharmacological activity.

2.2.1. In vitro anti-HIV testing

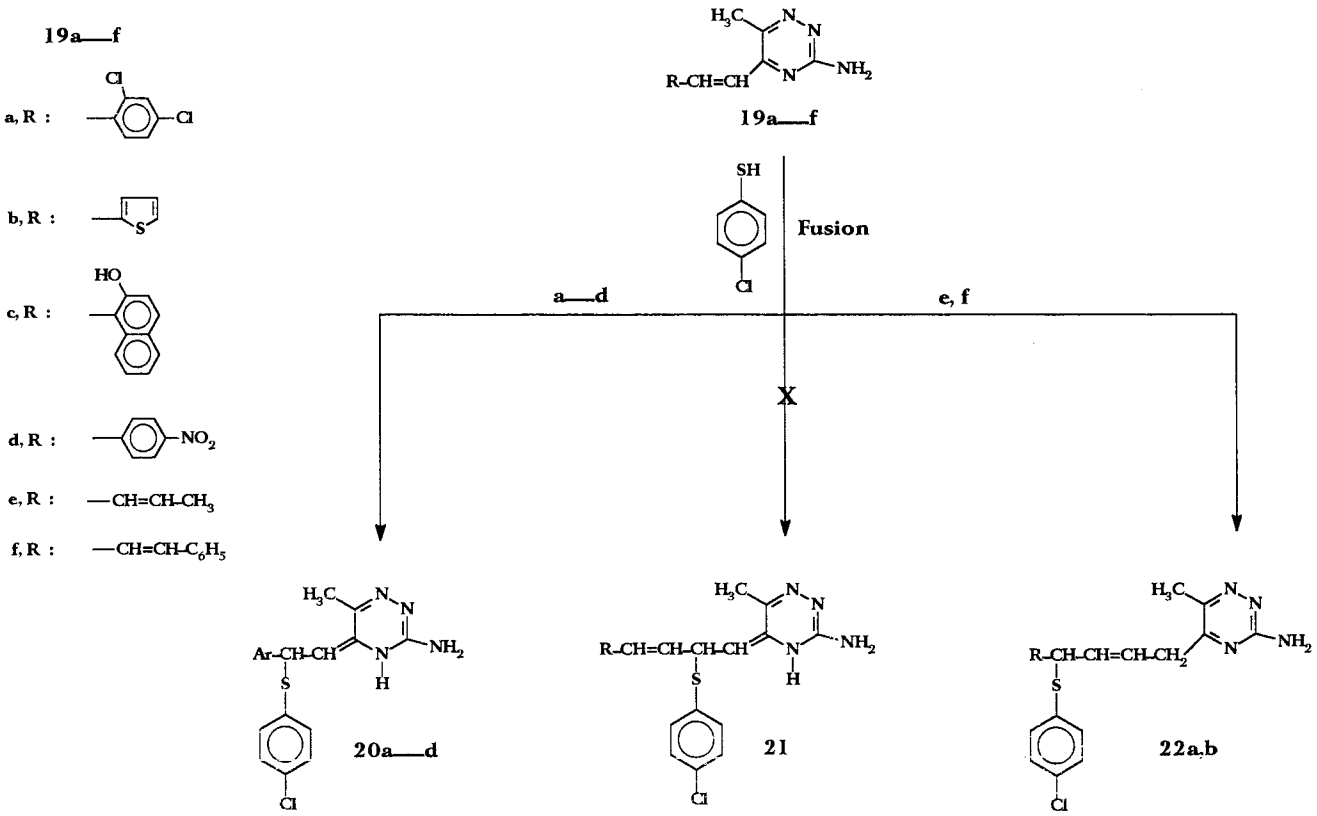
The procedure used in the National Cancer Institute, Bethesda, Maryland, USA for agents against HIV [15] is designed to detect agents acting at any stage of the virus reproductive cycle. All tested compounds are compared with a positive (AZT, tetrazolium salt XTT) control done at the same time under identical conditions. The results of anti-HIV activity for the synthesized compounds have been recorded in Table 1.

Scheme 2



Scheme 2

Scheme 3



2.2.2. In vitro antitumor testing

Most of the newly synthesized compounds have been evaluated *in vitro* for antitumor activity according to a described method [16] in different concentrations, a sulforhodamine β (SRB) protein assay was used to estimate cell viability or growth. The results obtained for the tested compounds were outlined in Table 2. The tests were carried out in the National Cancer Institute, Bethesda, Maryland, USA.

Table 1: Anti-HIV-IC_{50} values of the some new compounds

Compd.	IC_{50} (μg/ml)	Dose (molar)	Percent of protection	Percent of control	
				Infected	Uninfected
20a	1.79×10^{-5}	3.57×10^{-8}	16.25	25.46	99.24
20a	1.92×10^{-5}	3.57×10^{-7}	7.86	14.31	97.33
20b	7.93×10^{-6}	6.34×10^{-7}	5.68	17.00	91.64
20b	7.77×10^{-6}	6.35×10^{-8}	9.41	17.56	96.78
20c	1.15×10^{-5}	6.33×10^{-6}	10.37	20.23	80.00
20c	1.10×10^{-5}	6.33×10^{-6}	12.77	18.88	83.08
20d	3.52×10^{-5}	2.00×10^{-7}	5.32	11.95	100.89
20d	3.59×10^{-5}	6.34×10^{-7}	−0.78	8.29	91.63
20d	2.51×10^{-5}	2.00×10^{-5}	37.58	49.44	62.11
20d	2.29×10^{-5}	2.00×10^{-5}	43.31	48.98	56.19
22a	7.72×10^{-6}	6.33×10^{-6}	36.33	42.70	60.65
22a	5.6×10^{-6}	6.33×10^{-6}	24.58	32.12	46.17
22b	5.35×10^{-6}	6.34×10^{-7}	52.24	57.02	101.37
22b	5.35×10^{-6}	2.00×10^{-7}	52.06	56.85	111.33
22b	3.73×10^{-7}	2.00×10^{-7}	16.93	25.24	102.30
22b	3.71×10^{-6}	6.34×10^{-7}	12.53	18.65	96.00
22b	3.29×10^{-6}	2.00×10^{-6}	79.86	81.87	80.33
22b	3.29×10^{-6}	6.34×10^{-6}	17.06	25.35	100.43

3. Discussion

Generaly, the HIV activity for the tested compounds lies between high, moderate to letheal activity were compound **22b** > **20d** > **22a** > **20a** > **20b** > **20c**. Also, the introduction of a thioetherbutylene moiety to the aminotriazine **22b** and a nitro group at the thioether moiety to the aminotriazine **20d** results in an enhancement of the HIV activity. The anticancer activity for the tested compounds lies between moderate and letheal activity in the following

Table 2: *In vitro* antitumor activity data of some new compounds

Compd.	GI_{50}* Log^{10}	Selectivity analysis	
		Differential cellular sensitivity (Δ)**	Differential subpanel sensitivity
20a	−4.87	1.02	Leukemia, colon cancer
20b	−4.87	0.61	Leukemia
20c	−4.90	1.00	Leukemia, non-small cell lung cancer, CNS Cancer, melanoma, Renal cancer, breast Cancer
20d	−4.13	0.55	Leukemia, non-small cell lung cancer
22a	−5.10	0.61	Leukemia, non-small cell lung cancer, CNS cancer, Breast cancer
22b	−5.39	1.23	Leukemia, CNS cancer, renal cancer

* GI_{50}: Concentration giving 50% inhibition
** The reported data represent the logarlithmic difference between the parameter value referred to the most sensible cell line and the same mean parameter
Δ is considered low if <1, moderate if >1 and <3, high if >3

Table 3: Physical data of the new heterobicyclic nitrogen systems

Compd.	Crystallized from	M.p. (°C)	Yield (%)	Mol. formula	M. wt.	(M^+)
2	MeOH	220–221	70	$C_{12}H_{11}ClN_4$	246.5	M+1
3	MeOH	178–180	50	$C_{13}H_{11}ClN_4O$	274.5	M+1
4a	$CHCl_3$	222–223	85	$C_{15}H_{16}ClN_5O$	317.5	M+1
4b	dil MeOH	175–177	80	$C_{16}H_{13}ClN_6S$	356.5	M+2
5	petr. ether	124–125	60	$C_{15}H_{14}ClN_5$	299.5	M+1
6a	C_6H_6	109–110	90	$C_{16}H_{11}ClN_6$	322.5	M+1
6b	dil MeOH	220–221	75	$C_{18}H_{16}ClN_5O_2$	369.5	M+1
7	dil MeOH	243–244	55	$C_{17}H_{15}ClN_8S$	398.5	M+2
8	THF	246–248	50	$C_{17}H_{14}ClN_7S$	383.5	M+2
9	dil MeOH	214–215	40	$C_{14}H_{15}ClN_6SO$	350.5	M+2
10	petr. ether	168–170	50	$C_{16}H_{13}ClN_6S$	356.5	M+2
11	$CHCl_3$	154–155	60	$C_{21}H_{14}ClN_7SO_2$	463.5	M+2
12	EtOH	237–238	75	$C_{13}H_{13}ClN_6$	288.5	M+1
13	C_6H_6	195–196	80	$C_{15}H_{13}ClN_6$	312.5	M+1
14	THF	246–247	60	$C_{14}H_{11}ClN_6O$	314.5	M+1
15	dil EtOH	209–210	78	$C_{23}H_{16}Cl_2N_6O$	463	M+2
16	dil MeOH	85–87	90	$C_{27}H_{21}ClN_6$	464.5	M+1
17	dil MeOH	200–201	85	$C_{21}H_{16}ClN_7O$	417.5	M+1
18	$CHCl_3$	above 280	55	$C_{21}H_{14}ClN_7$	400	M+1
20a	C_6H_6	140–141	50	$C_{18}H_{15}Cl_3N_4S$	425.5	M+4
20b	C_6H_6	99–100	55	$C_{16}H_{15}ClN_4S_2$	362.5	M+3
20c	petr. ether	95–97	60	$C_{22}H_{19}ClN_4SO$	422.5	M+2
20d	petr. ether	232–234	70	$C_{18}H_{16}ClN_5SO_2$	401.5	M+2
22a	C_6H_6	80–82	65	$C_{15}H_{17}ClN_4S$	320.5	M+2
22b	C_6H_6	76–78	78	$C_{20}H_{19}ClN_4S$	382.5	M+2

* All the new compounds gave satisfactory C, H, N, and Cl analysis

order: **22b** > **20a** > **20c** > **20b** > **20d** > **22a**. Only compound **22b** has a higher sensitivity than the other tested compounds. The presence of butylene, chlorine and phenolic moieties in the thioether of amino-1,2,4-triazines caused a moderate activity towards tumour states.

Structure-activity relationships were studied by variations of compound **22b**; compound **22a** had a moderate activity towards HIV with a lower activity towards tumour cases. Also, compound **20d** had a moderate activity towards HIV and a lower activity towards tumour cases which may be due to the 1,2,4-triazine containing sulfur moiety [17]. In conclusion, the skelton of compound **22b** enhanced both the HIV and anticancer activities.

4. Experimental

M.p.'s reported were uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 293 FT spectrophotometer (γ_{max} in cm^{-1}), UV absorption spectra in DMF were recorded on a Perkin-Elmer, Lambda 4B Controller accessory Interface, UV-VIS spectrophotometer (γ_{max} in nm). ^1H NMR spectra were recorded on a EM NMR spectrometer 200 MHz PMR using DMSO as a solvent and TMS as internal reference (chemical shift's in ppm) and MS recorded on a Gas Chromatographic GCMSqp 1000ex Schimadzu instrument at 70 eV. Compounds **2** and **19** were prepared following an reported procedure [18]. The physical data of the synthesized compounds are given in Table 3.

4.1. Preparation of 3-formylamino-5-(4-chlorostyryl)-6-methyl-1,2,4-triazine (3)

A mixture of HCO_2H (3.4 ml) and Ac_2O (8.2 ml) was refluxed for 2 h. The mixture was added dropwise to a solution of compound **2** (0.01 mol) in diethylether (50 ml) to give **3** (Table 3). M/z (Int. %): 274 (0.07), 246 (46.96), 247 (20.90), 248 (18.03), 149 (14.27), 141 (100), 139 (37.34), 115 (38.41); ^1H NMR: 1.9 (s, 3 H, CH_3), 6.8, 7.3 (each s, 1 H, CH=CH), 7.4–7.7, 7.8, 7.9 (4 H, aromatic protons), 8.0 (s, 1 H, NH), 9.9 (s, 1 H, CHO).

4.2. Condensation of 3 with primary amines: Formation of 4a, b

An equimolar mixture of **3** and primary amines, ethanolamine and 2-aminothiazole in abs. EtOH (50 ml) was refluxed for 1 h. The resultant solid was filtered and crystallized to give **4a**, **b** (Table 3). UV (4a): λ_{max} (log ε) 330 (ε 2.27), 275.5 (ε 2.60).

4.3. Synthesis of 1-[5-(4-chlorostyryl)-6-methyl-1,2,4-triazin-3-yl]-4,5-dihydroimidazole (5)

A mixture of **4a** (1 g) and Ac_2O (20 ml) was refluxed for 10 h, cooled and poured onto ice. The solid obtained was filtered and crystallized to give **5** (Table 3); M/z (Int. %): 299.5 (M, 0.28), 177 (12.74), 141 (100), 102 (6.06), 13 (12.64), 69 (0.89), 54 (3.47); ^1H NMR: 1.27 (s, 3 H, CH_3), 2.17 (s, 2 H, CH_2–N), 2.7 (s, 2 H, CH_2–N=), 3.5, 4.2 (each m, CH_2–CH_2), 5.1 (s, 1 H, CH=N), 7.2, 7.3 (s, 2 H, CH=CH), and 7.4–7.6 (m, 4 H, aromatic protons).

4.4. Condensation of compound 3 with active methylene compounds: Formation of 6a, b

A mixture of **3** (0.01 mol) and active methylene compounds like malononitrile, ethyl cyanoacetate (0.01 mol) in sodium ethoxide (0.012 mol Na in 100 ml abs. EtOH) was refluxed for 4 h, cooled and poured onto ice-HCl. The solid produced was filtered and crystallized to give **6a** and/or **6b** (Table 3).

4.5. Synthesis of the 4,6-diaminopyrimidine-2-thione derivative 7

An equimolar mixture of **6a** and thiourea with sodium ethoxide (0.02 mol Na in 100 ml abs. EtOH) was refluxed for 4 h, cooled and poured onto ice-CH_3CO_2H to neutralization. The solid obtained was filtered off and crystallized to give **7** (Table 3); UV: λ_{max} (log ε): 324 (2.26), 283 (2.84); M/z (Int. %): 401 (M+2, 0.55), 399 (0.53), 245 (6.46), 246 (40.56), 141 (100), 142 (30.89), 176 (45.3), 178 (18.41), 139 (27.76), 115 (21.40).

4.6. Synthesis of the 6-amino-2-thioxo-pyrimidin-4(3 H)one derivative 8

A mixture of **6b** (0.01 mol), thiourea (0.01 mol) and sodium ethoxide (0.02 mol Na in 100 ml abs. EtOH) was refluxed for 4 h, cooled and poured onto ice-CH_3CO_2H to neutralization. The solid produced was filtered and crystallized to give **8** (Table 3; IR: 3800–3100 (b, OH, NH_2, NH), 1660–1640 (C=O, NH_2), 1560 (C=N), 820 (aryl group) and 710 cm^{-1} (C–Cl).

4.7. Formation of the carbinolthiocarbamide derivative 9

An equimolar mixture of **3** and thiourea in sodium ethoxide (0.01 mol Na in 100 ml abs. EtOH) was stirred for 2 h at room temperature, then neutralized with dil. CH_3CO_2H to give **9** (Table 3); IR: 3500–3100 (b, OH, NH), 1640 (def. NH_2), 1220 (C=S), 820 (aryl group) and 700 cm^{-1} (C–Cl).

4.8. Synthesis of 1-(heteroaryl)-6-methyl-1,3,5-triazin-4-thione (10)

A mixture of **9** (0.01 mol) and gl. AcOH (50 ml) with fused NaOAc (10 g) was refluxed for 6 h, cooled then poured onto ice. The solid obtained was

filtered and crystallized to give **10** (Table 3); UV: λ_{max} (log ε): 320.5 (2.41), 285.5 (2.53).

4.9. Synthesis of 1-(heteroaryl)-6-(4-nitrophenyl)-1,3,5-triazin-4-thione (**11**)

Equimolar mixture of **9** and 4-nitrobenzoyl chloride in DMF was refluxed for 6 h, cooled and poured onto ice. The resultant solid was filtered and crystallized to give **11** (Table 3); UV: λ_{max} (log ε): 322.5 (2.65), 286 (2.93); IR: 3020, 2800 (aryl and CH_3 group), 1530, 1350 (asym, sym NO_2), 1080 (C=S), and 690 (C−Cl); M/z (Int. %): 466 (0.00), 446 (1.01), 228 (0.14), 177 (34.17), 141 (100), 102 (2.63), 122 (7.37), 76 (4.41), 175 (24.03), 113 (13.25); ^{1}H NMR: 1.96 (s, 1 H, CH_3), 3.73–3.71 (s, 1 H, CH=N), 7.36, 7.26 (each s, 1 H, CH=CH) and 7.4–7.7, 8.2–8.50 (each m, 4 H, aromatic protons).

4.10. Formation of the amidrazone **12**

A mixture of **3** (0.01 mol) and hydrazine hydrate (0.015 mol) in abs. EtOH (50 ml) was refluxed for 30 min, cooled. The solid obtained was filtered and crystallized to give **12** (Table 3); IR: 3300 (NH_2), 3150 (NH), 1630 (CH=CH), 1600–1580 (C=N); ^{1}H NMR: 2.1 (s, 3 H, CH_3), 2.9 (s, 2 H, NH_2), 3.5 (s, 1 H, CH=N), 7.0–7.4 (m, 2 H, CH=CH), 7.6–7.7, 7.8–9.0 (aromatic protons), 10.0 (s, 1 H, NH).

4.11. 4-(Heteroaryl)-5-methyl-1,2,4-triazole (**13**)

A mixture of **12** (0.01 mol) and gl. AcOH (50 ml) with fused NaOAc (5 g) was refluxed for 4 h, cooled and poured onto ice. The solid obtained was filtered and crystallized to give **13** (Table 3); ^{1}H NMR: 1.9 (s, 3 H, CH_3), 2.1 (s, 3 H, CH_3), 4.0 (s, 1 H, CH=N), 6.4, 6.6 (each s, 2 H, CH=CH), 7.1–7.8 (m, 4 H, aromatic protons).

4.12. 4-(Heteroaryl)-1,2,4-triazol-5(1 H)one (**14**)

An equimolar mixture of **12** and diethylcarbonate in dry dioxan (100 ml) was refluxed for 6 h, then concentrated. The solid produced was filtered and crystallized to give **14** (Table 3).

4.13. 4-(Heteroaryl)-6-(4-chlorostyryl)-1,2,4-triazin-5-one (**15**)

A mixture of **12** (0.01 mol) and β-(4-chlorostyryl)-α-oxocarboxylic acid (0.01 mol) in gl. AcOH (50 ml) with NaOAc (5 g) was refluxed for 8 h, cooled and poured onto ice. The solid obtained was filtered and crystallized to given **15** (Table 3); IR: 1675 (C=O), 1630 (CH=CH), 1580 (C=N), 1488 (def. CH_3, CH=CH), 800 (arylgroup), and 700 cm^{-1} (C−Cl); ^{1}H NMR: 2.1 (s, 3 H, CH_3), 3.5 (1 H, endo CH=N), 7.2–7.5 (m, 2 H, CH=CH), 7.6–7.8, 7.9–8.1 (aromatic protons), 8.7 (s, 1 H, exo CH=N).

4.14. 5 H-4-(Heteroaryl)-5,6-diphenyl-1,2,4-triazine (**16**)

An equimolar mixture of **12** and benzoin in Ac_2O/AcOH (1 : 1, 100 ml) was refluxed for 12 h, cooled and poured onto ice. The solid obtained was filtered and crystallized to give **16** (Table 3); M/z (Int. %): 465 (M+1, 0.23), 464 (0.20), 422 (4.06), 420 (19.91), 241 (4.30), 205 (1.04), 178 (1.09), 125 (1.02), 105 (100), 77 (1.76).

4.15. Formation of the isatin-3-hydrazone **17**

A mixture of **12** (0.01 mol) and isatin (0.01 mol) in abs. EtOH (50 ml) was refluxed for 1 h, cooled. The solid obtained was filtered and crystallized to give **17** (Table 3).

4.16. Synthesis of 4-(heteroaryl)-1,2,4-triazino[6,5-b]indole (**18**)

A mixture of **17** (1 g) and gl. AcOH (20 ml) with fused NaOAc (5 g) was refluxed for 4 h, cooled and poured onto ice. The solid produced was filtered and crystallized to give **18** (Table 3); M/z (Int. %): 401 (M+1, 0.0), 399 (0.01), 264 (2.30), 246 (13.6), 195 (1.0), 196 (2.63), 115 (19.23), 94 (10.31), 202 (2.20), 141 (100), 137 (8.51), 102 (8.50); ^{1}H NMR: 1.6 (s, 3 H, CH_3), 3.7 (s, 1 H, CH=N), 5.2–5.5 (m, 2 H, CH=C), 7.2–8.0 (m, 8 H, aromatic protons).

4.17. Synthesis of the thioethers 20 and 22

a) A mixture of **19a–d** (0.01 mol) and 4-chlorothiophenol (0.012 mol) was fused at 200 °C for 2 h, cooled then treated with petr.-ether to give **20a–d** (Table 3).

b) A mixture of **19e**, **f** (0.01 mol) and 4-chlorothiophenol (0.012 mol) was fused at 200 °C for 2 h, cooled then treated with petr.-ether to give **22a**, **b** (Table 3); IR: 3100 (NH), 1650 (C=C), 1600 (def. NH_2), 1580 (C=N), 1070 (C−S−C), 880, 800 (aryl groups) and 720 (C−Cl); M/z (Int. %) (**22a**): 425 (0.48), 282 (12.22), 143 (11.08), 159 (100), 161 (63.0), 123 (10.14), 124 (18.48), 70 (4.68), 45 (6.82), 53 (15.02); UV (**22b**): λ_{max} (log ε): 331.5 (2.67), 290 (2.91).

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