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Synthesis of heterobicyclic nitrogen systems bearing the 1,2,4-triazine moiety as anti-HIV and anticancer drugs: part I

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Some new heterobicyclic nitrogen systems bearing the 1,2,4-triazine moiety (**3**–**22**) have been achieved by treatment of 3-amino-5,6-disubstituted-1,2,4-triazines **2a**–**h** with some cyclic and acyclic oxygen compounds followed by heterocyclization. Structures of the products have been deduced by elemental analysis and spectral data. Significant anti-HIV and anticancer activities were observed *in vitro* for some members of the series, where compounds **5** and **18** showed a moderate activity.

1. Introduction

1,2,4-Triazines have been reportes as starting compounds for the synthesis of various heterobicyclic systems and posses important biological, pharmacological and medicinal activities [1–3]. In continuation to our earlier work in this area [4–6], the present study deals with the synthesis and chemistry of a series of new heterobicyclic nitrogen compounds starting from 3-amino-5,6-disubstituted-1,2,4-triazines **2a**–**h**. They were evaluated for anti-HIV and anticancer activities in order to establish a correlation between structure and reactivity.

2. Investigations and results

2.1. Chemistry

3-Amino-6-methyl-5-styryl-1,2,4-triazines **2a**–**h** were obtained by warming compound **1** with some aldehydes in the presence of sodium ethoxide (Scheme 1).

A convenient method for the synthesis of the isolated heterobicyclic nitrogen systems **3**, **5**, **7**, **9** was deduced from treatment of compound **2** with the cyclic oxygen compounds **4**, **6**, **8** in dry pyridine [7] (Scheme 2). Thus, compound **2c** underwent condensation with phthalic anhydride in dry pyridine to afford 1-[6-methyl-5-(thiophen-2-yl)ethenyl-1,2,4-triazin-3-yl]phthalimide (**3**) while refluxing **2b** with oxazolone **4** in dry pyridine yielded 1-[6-methyl-5-(4′-dimethylaminostyryl)-1,2,4-triazin-3-yl]-2-(4′-chlorophenyl)-4-arylidienimidazol-5-one (**5**). Similarly, condensation of **2a** with 2-methyl-3,1-benzoxazin-4-one (**6**) in dry pyridine gave 3-[6-methyl-5-(2′,4′-dichlorostyryl)-1,2,4-triazin-3-yl]-2-methylquinazolin-4(*H*)one (**7**). On the other hand, 1 *H*-3-(4′-nitrophenyl)-5,6-diphenyl-4-[6-methyl-5-(2′,4′-dichlorostyryl)-1,2,4-triazin-3-yl]-1,2,4-triazine (**9**) was produced by refluxing compound **2a** with 4 *H*-2-aryl-5,6-diphenyl-1,3,4-oxadiazine (**8**) in dry pyridine (Scheme 2). Interestingly, it was found that compound **2b** on reaction with isothiocyanate derivatives in DMF [8] afforded the N^1,N^2-disubstituted thiourea compounds **10a**, **b**. After heterocyclization with malonic acid and a few drops of acetyl chloride [8], the 5 *H*-1-acetyl/phenyl-3-[5-(4′-dimethylaminostyryl)-6-methyl-1,2,4-triazin-3-yl]-2-thioxopyrimidin-4,6-diones **11a**, **11b** were isolated (Scheme 2).

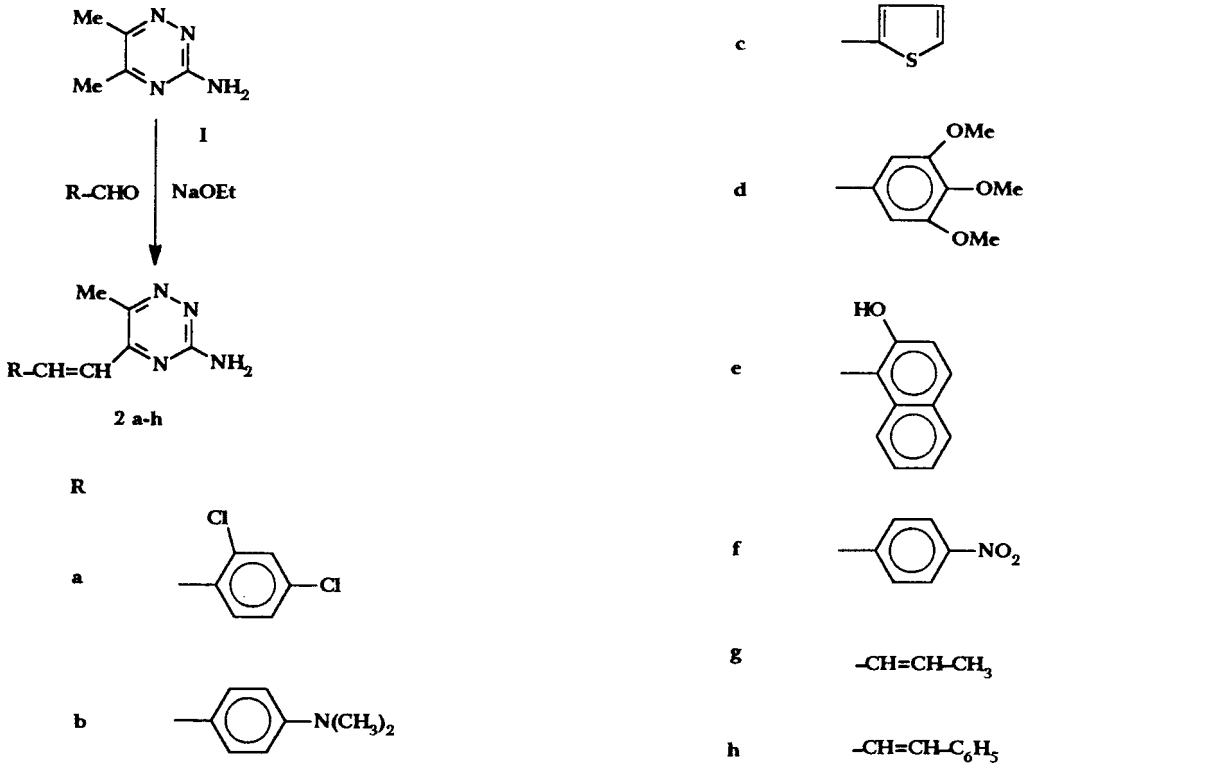
The actual objective of the present work was the formation of fused heterobicyclic nitrogen systems. Thus, cyanoethylation of **2d** using acrylonitrile in pyridine-water yielded 3-cyanoethylamino-5-(3′,4′,5′-trimethoxystyryl)-6-methyl-1,2,4-triazine (**12**) which on boiling with 5% aqueous HCl [9] led to the direct formation of 2 *H*-4-hydroxy-7-methyl-8-(3,4′,5′-trimethoxystyryl)-pyrimido[3,2-*b*][1,2,4]triazine (**13**) (Scheme 3).

The reaction of compound **2** with cyanoesters was also studied. Thus, fusion of **2a** with the ethyl cyanoacetate derivative **14** yielded the acetamide derivative **15**. The latter compound **15** on refluxing with ethanol-piperidine afforded 4-amino-2-oxo-3-substituted-7-methyl-8-(2′,4′-dichlorostyryl)-pyrimido[3,2-*b*][1,2,4]triazine (**16**) while refluxing with 10% aqueous HCl [10] yielded 3 H-2,4-dioxo-3-substituted-7-methyl-8-(2′,4′-dichlorostyryl)-pyrimido-[3,2-*b*][1,2,4]triazine (**17**). Similarly, compound **2b** on reaction with ethyl cyanoacetate in sodium ethoxide gave 3 *H*-4-imino-2-oxo-7-methyl-8-(4′-dimethylaminostyryl)-pyrimido[3,2-*b*][1,2,4]triazine (**18**) (Scheme 3). The target heterobicyclic nitrogen system imidazolo[3,2-*b*][1,2,4]triazine derivatives **19**–**21** have been obtained from the interaction between compound **2a**, and/or **2c** with phenacyl bromide [11], 2-ethoxyethanol or diethyl oxalate in different media [12] (Scheme 3).

Table 1: The anti-HIV-IC_{50} values of some new compounds

Compd.	IC_{50} (μ/ml)	Dose (Molar)	Percent of Protection	Percent of Control	
				Infected	Uninfected
2a	5.84×10^{-8}	6.35×10^{-8}	1.41	6.34	99.38
		2.00×10^{-6}	2.42	7.30	97.29
		2.00×10^{-7}	0.63	5.60	95.12
		6.33×10^{-6}	2.28	7.17	94.77
		2.00×10^{-5}	1.64	6.56	91.65
2b	3.92×10^{-6}	2.00×10^{-7}	2.37	7.25	101.46
		6.00×10^{-7}	3.38	8.64	101.29
		6.35×10^{-8}	0.68	5.65	100.68
2c	7.5×10^{-6}	6.35×10^{-8}	1.52	8.41	95.60
2d	3.58×10^{-6}	2.00×10^{-7}	−0.46	6.57	91.16
2e	2.62×10^{-5}	2.00×10^{-5}	23.94	29.26	65.71
5	1.20×10^{-4}	6.32×10^{-5}	58.24	61.58	89.84
		2.00×10^{-6}	14.10	20.97	93.88
5	9.40×10^{-5}	6.32×10^{-5}	79.18	80.85	71.89
		2.00×10^{-5}	58.08	61.43	78.66
		2.00×10^{-6}	44.37	48.82	89.81
		6.33×10^{-6}	38.89	43.78	91.53
		6.35×10^{-8}	22.04	28.28	94.75
5	9.36×10^{-5}	6.33×10^{-6}	70.32	72.10	85.77
		2.00×10^{-6}	46.87	50.06	96.14
		6.34×10^{-7}	20.63	25.39	92.94
		6.32×10^{-5}	7.07	12.65	66.87
10b	1.26×10^{-5}	2.00×10^{-7}	33.01	41.05	91.42
	1.53×10^{-5}	6.35×10^{-8}	21.56	28.62	99.51
11a	5.64×10^{-6}	1.00×10^{-7}	3.99	10.71	104.85
		3.17×10^{-7}	3.66	10.40	93.56
18	4.31×10^{-6}	2.00×10^{-7}	9.11	15.47	96.30
		6.34×10^{-7}	6.70	13.23	102.42

Scheme 1



Scheme 2

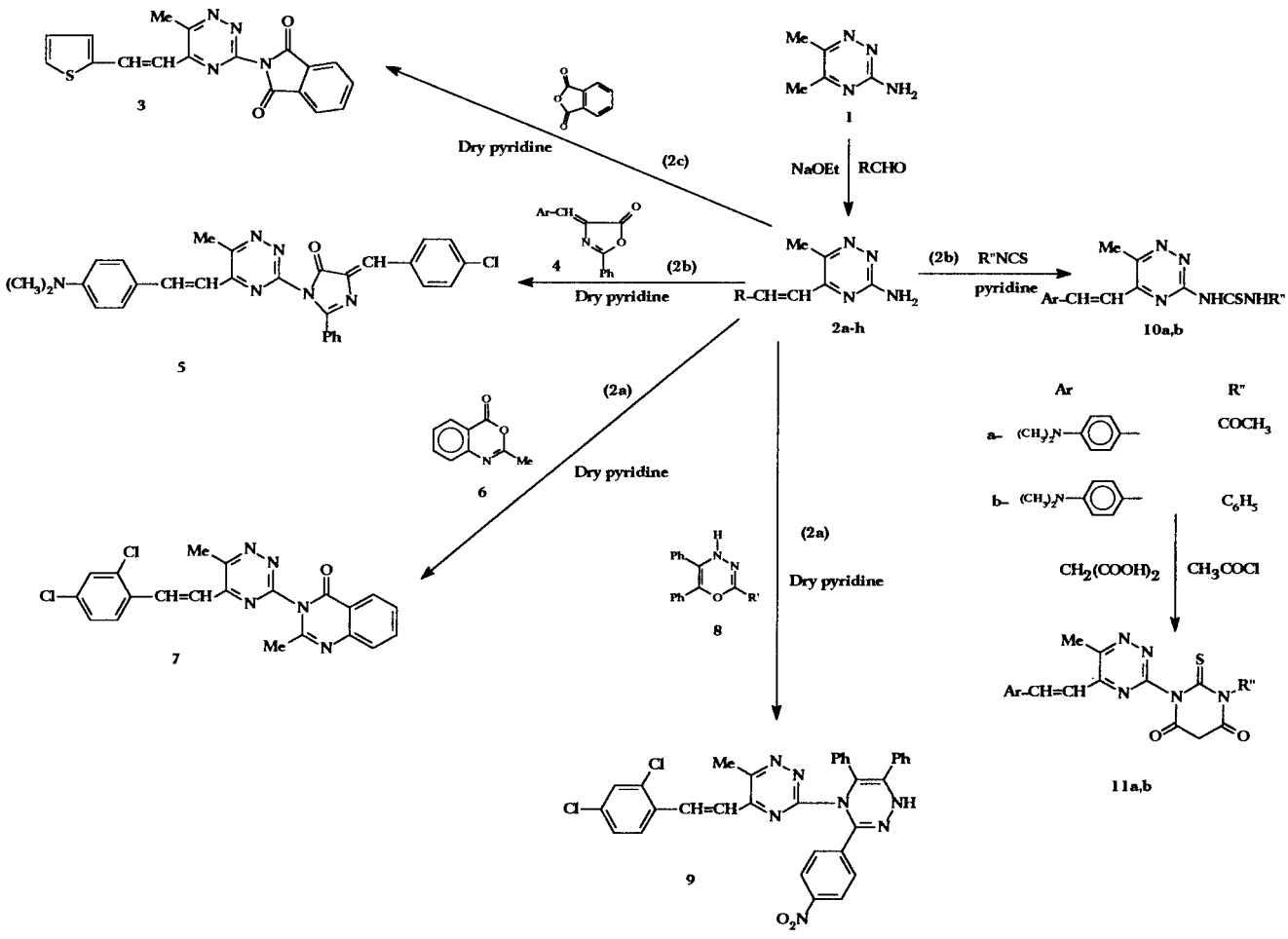


Table 2: *In vitro* antitumor activity data of some new compounds

Compd.	GI_{50}*	Selectivity	
		Differential cellular Sensitivity (Δ^{**})	Differential subpanel Sensitivity
2a	−4.44	0.35	Colon cancer
2b	−4.54	1.11	Leukemia, Colon and Renal Cancer
2b	−5.06	1.20	Non-Small cell Lumg Cancer, Melanoma
2c	−4.69	0.70	Non-Small cell Lung Cancer
2d	−4.85	0.95	Non-Small cell Lung Cancer
2d	−4.69	1.01	Non-Small cell Lung Cancer, Melanoma
2e	−4.56	0.32	Non-Small cell Lung Cancer
5	−4.29	0.28	Renal Cancer
10b	−4.64	0.72	Leukemia, Renal Cacer
11a	−4.92	0.78	Leukemia
11b	−5.04	1.01	Leukemia, Non-Small cell Lung Cancer Colon Cancer, Melanoma, Renal Cancer, Breast Cancer
18	−4.87	3.13	Leukemia, Non-Small cell Lung Cancer, Colon Cancer, Melanoma, Renal Cancer, Breast Cancer

* GI50: 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

Finally, fusion of compound **2b** with ethyl cinnamate led to the direct formation of 3,4-dihydro-4-phenyl-7-methyl-8-(4-dimethylaminostyryl)-pyrimido[3,2-*b*][1,2,4]triazin-2-one (**22**) (Scheme 3).

2.2. Pharmacology

In a programme to obtaine potent anti-HIV and anticancer agents, the new synthesized compounds 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 HIV [13] is designed to detect agents acting at any stage of the virus reproductive cycle. All tested compounds are compared with a positive control (AZT, tetrazolium salt XTT) 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 3

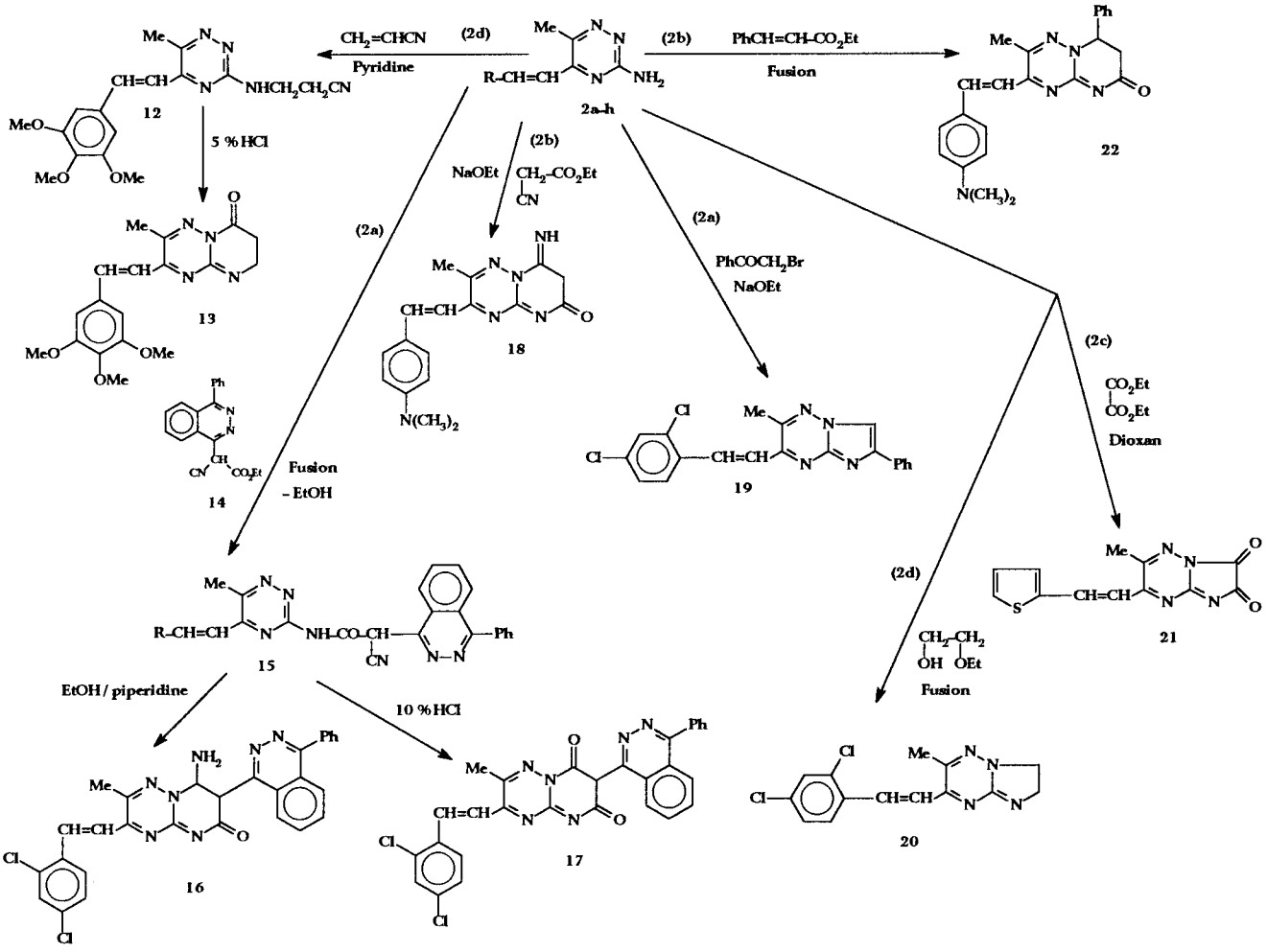


Table 3: Physical data of the heterobicyclic nitrogen systems 2-22

Compd.	R	crystallized from	M.p. (C°)	Yield (%)	Mol. Formula*	M. Wt.	(M^+)
2a	2,4-$Cl_2-C_6H_4$-	Toluene	190–192	60	$C_{12}H_{10}Cl_2N_4$	281	M + 2
2b	4-$(Me_2N)C_6H_4$-	Dioxan	250–252	60	$C_{14}H_{17}N_5$	255	M + 1
2c	2-Thienyl-	Toluene	181–182	85	$C_{10}H_{10}N_4S$	218	M + 1
2d	3,4,5-$(OMe)_3C_6H_2$-	Chloroform	172–174	75	$C_{15}H_{18}N_4O_3$	302	M + 3
2e	2-$OHC_{10}H_6$-	Toluene	79–80	50	$C_{16}H_{14}N_4O$	278	M + 1
2f	4-$NO_2C_6H_4$-	THF	above 300	80	$C_{12}H_{11}N_5O_2$	257	M + 1
2g	$CH_3-CH=CH$-	Dil. EtOH	222–223	60	$C_9H_{12}N_4$	176	M
2h	Ph–CH=CH-	Dil. EtOH	214–215	75	$C_{14}H_{14}N_4$	238	M
3	2-Thienyl-	Toluene	218–220	80	$C_{18}H_{12}N_4O_2S$	352	M + 2
5	4-$(Me_2N)C_6H_4$-	Pet. ether	225–226	60	$C_{30}H_{24}Cl_2N_6O$	555	M + 3
7	2,4-$Cl_2C_6H_4$-	Dioxan	182–183	78	$C_{21}H_{15}Cl_2N_5O$	424	M + 3
9	2,4-$Cl_2C_6H_4$-	Pet. ether	120–121	75	$C_{33}H_{23}Cl_2N_7O_2$	620	M + 3
10a	4-$(Me_2N)C_6H_4$-	DMF	226–227	68	$C_{17}H_{20}N_6OS$	356	M + 2
10b	4-$(Me_2N)C_6H_4$-	MeOH	192–193	79	$C_{21}H_{22}N_6S$	390	M + 2
11a	4-$(Me_2N)C_6H_4$-	MeOH	189–190	80	$C_{20}H_{20}N_6O_3S$	424	M + 2
11b	4-$(Me_2N)C_6H_4$-	Toluene	226–227	90	$C_{24}H_{22}N_6O_2S$	458	M + 2
12	3,4,5-$OMe)_3C_6H_2$-	MeOH	240–241	75	$C_{18}H_{21}N_5O_3$	355	M + 3
13	3,4,5-$(OMe)_3C_6H_2$-	MeOH	232–233	89	$C_{18}H_{20}N_4O_4$	356	M + 4
15	2,4-$Cl_2C_6H_3$-	EtOH	222–223	65	$C_{29}H_{19}Cl_2N_7O$	552	M + 2
16	2,4-$Cl_2C_6H_3$-	dil EtOH	200–201	75	$C_{29}H_{19}Cl_2N_7O$	552	M + 2
17	2,4-$Cl_2C_6H_3$-	dil DMF	224–225	60	$C_{29}H_{18}Cl_2N_6N_6O_2$	567	M + 3
18	4-$(Me_2N)C_6H_4$-	EtOH	241–241	90	$C_{17}H_{18}N_6O$	336	M + 1
19	2,4-$Cl_2C_6H_3$-	Dil. EtOH	174–175	85	$C_{20}H_{14}Cl_2N_4$	381	M + 2
20	2,4-$Cl_2C_6H_3$-	Toluene	228–230	70	$C_{14}H_{12}Cl_2N_4$	307	M + 2
21	2-Thienyl-	Dil. EtOH	190–191	50	$C_{12}H_8N_4O_2S$	272	M + 2
22	4-$(Me_2N)C_6H_4$-	Dil. EtOH	240–241	65	$C_{23}H_{23}N_5O$	385	M + 1

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

2.2.2. In vitro antitumor testing

Most of the newly synthesized compounds have been evaluated *in vitro* for antitumor activity according to the described method [14] in different concentrations; a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth [15]. The results obtained for the tested compounds were outlined in Table 2 and carried out in the National Cancer Institute, Bethesda, Maryland, USA.

3. Discussion

The discovery and development of novel therapeutic products for the treatment of malignancy and HIV infections is important. This is the reason for our ongoing efforts to develop in cooperation with the NCl effective therapeutic products for patients with aquired immunodeficiency syndrome (AIDS) by structural variations of test compounds. The results of the HIV screening of compounds recently synthesized are recorded in Table 1. Generally, the HIV activity for the tested compounds lies between high moderate to little activity in the following order: **5** > **2e** > **10b** > **18** > **11a** > **26** > **2a**. Also, the introduction of a *p*-dimethylaminostyryl moiety in the 1,2,4-triazine nucleus results in an enhancement of the HIV activity and the imidazolone moiety caused an improved protection (Table 1).

On the other hand, aminopyrimido[3,2-*b*][1,2,4]triazine (**18**), thiobarbituric acid (**11b**) and 3-amino-5-(p-dimethylaminostyryl)-6-methyl-1,2,4-triazine (**2b**), possess reasonable anticancer activity.

Compound **18** has a higher sensitivity than other tested compounds (Table 2).

Compound **5** was found to be more active against HIV, while compound **18** was more active against cancer.

In conclusion, when compounds which contain a 5-*p*-dimethylaminostyryl-1,2,4-triazine moiety were fused with another heterocyclic structure especially imidazolone or aminopyrimidine, the anti HIV and anticancer activities improved.

4. Experimental

M.p.s. are reported uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 293 FT spectrometer (ν_{max} in cm^{-1}), UV absorption spectra in DMF were recorded on a Perkin-Elmer, Lambda 4B Controller Accessory Interface, UV-VIS spectrometer (λ_{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 were recorded on a Gas Chromatographic GCMSqp 1000ex Schimadzu instrument at 70 eV. Compound **1** was prepared following a reported procedure [16]. The physical data of the synthesized compounds are given in Table 3.

4.1. Preparation of 3-amino-5-styryl-6-methyl-1,2,4-triazine (**2a–h**)

A mixture of **1** (0.01 mol) and the appropriate aldehyde (0.01 mol) in NaOEt (0.23 g NA in 50 ml abs. EtOH) was warmed for 10 min, cooled, poured on ice and then neutralized with AcOH. The resultant solid was filtered off and crystallized to give **2a–h** (Table 1); UV (**2h**): $\lambda_{max}(\varepsilon)$: 379 (2.91), 292 (3.03); IR (**2a**): 3300 (NH_2), 3080 (aromatic CH), 2910 (aliphatic CH), 1640 (CH=CH), 1620 (def. NH_2), 1380 (NCN), 820 (aryl group) and 700 (C–Cl); **2c**: 3450 (NH_2), 3010, 2910 (aromatic and aliphatic CH), 1640 (CH=CH), 1620 (def. NH_2), 1100 (C–S). ^1H NMR (**2c**): 1.5 (s, 3H, CH_3), 6,5–6.7 (m, 2 H, CH=CH), 6.8, 7.1–7.3 (thiophene CH), 8 and 8.2 (each s, NH_2 protons). M/z (int. %) (**2c**): 218 (73.19), 190 (1.35), 1.48 (100), 135 (2.23), 134 (3.46), 111 (1.32), 109 (2.09), 97 (3.06), 70 (0.75), 54 (1.05).

4.2. Reaction of **2** *with cyclic oxygen compounds* **4**, **6**, **8***: Formation of the isolated heterobicyclic nitrogen systems* **3**, **5**, **7** *and* **9**

Equimolar amounts of compounds **2** and **4**, **6**, **8** in dry pyridine (100 ml) were refluxed for 12 h, cooled and poured onto ice-Hcl. The formed solid was filtered and crystallized to give the target compounds **3**, **5**, **7** and **9** (Table 1). UV (**5**): $\lambda_{max}(\varepsilon)$: 322 (1.38), 282 (1.94). IR (**3**): 1720, 1680 (2 C=O), 1620 (CH=CH), 1080 (C–S); (**5**): 3030, 2950, 2800 (aromatic and aliphatic CH), 1680–1650 (CO, CH=CH), 1580 (C=N), 1320 (NCN), 850, 780 (aryl groups), 680 (C–Cl); (**7**): 3020, 2980, 2920 (aromatic and aliphatic CH), 1680 (CO), 1630 (CH=CH), 1470 (def. CH_3), 1380 (NCN), 860, 820 (benzo and aryl groups) and 720 (C–Cl); (**9**): 3300–3100 (NH), 3050, 2950 (aromatic and aliphatic CH), 1620 (CH=CH), 1590 (C=N), 1530 (asym. & sym. NO_2), 1220 (C–N), 900, 880, 780 (phenyl and aryl groups) and 690 (C–Cl). M/z (Int. %) (**5**): 554 (2.21), 173 (0.71), 146 (1.98), 124 (2.23), 111 (49.09), 176 (1.60), 158 (45.16), 136 (2.48), 139

(100), 94 (1.57), 80 (3.44), 50 (59.96). ^{1}H NMR (**5**): 1.3 (s, 3 H, CH_3), 1.9, 2.1 (each s, 2 CH_3), 3.3–3.4 (s, 1 H, =CH), 5.99–6.00 (s, 2 H, CH=CH), 7.4–7.6 and 8.1–8.2 (each m. 12 H, aromatic protons).

4.3. Addition of isothiocyanate derivatives to 2*: Formation of N,N′-disubstituted thioureas* **10a**, **b**

A mixture of **2** (0.01 mol) and isothiocyanate derivatives (0.01 mol) in DMF (50 ml) was refluxed for 2 h, cooled and poured onto ice. The resultant solid was filtered and crystallized to give **10a**, **b** (Table 3). IR (**10b**): 3210–3110 (NH, NH), 3020, 2900 (aromatic and aliphatic CH), 1620 (CH=CH), 1490 (def. CH_3), 1390 (NCSN), 1160 (C–S), 820, 750, 720 (phenyl and aryl groups).

4.4. Synthesis of 5 H-1-acetyl/phenyl-3-[5-(4′-dimethylaminostyryl)-6-methyl-1,2,4-triazin-3-yl]-2-thioxopyrimidin-4,6-diones **11a** *and* **11b**

A mixture of **10a**, **b** (0.01 mol) and malonic acid (0.01 mol) in acetyl chloride (5 ml) was refluxed for 30 min. The solid obtained was recrystallized to give **11a**, **b** (Table 3). UV (**11b**): $\lambda_{max}(\varepsilon)$: 453.5 (3.41), 393 (3.06), 287.5 (2.99); IR (**11a**): 3020, 2850 (aromatic and aliphatic CH), 1740, 1690, 1650 (3 CO), 1610 (CH=CH), 1550 (C=N), 1470 (def. CH_3), 110 (C–S), 850, 720 (phenyl and aryl groups), M/z (Int. %) (**11b**): 458 (0.01), 381 (0.34), 352 (0.34), 325 (0.42), 284 (1.08), 255 (100), 185 (76.64), 70 (0.49), 54 (6.29). ^{1}H NMR (**11b**): 2.0 (s, 3 H, CH_3), 2.5, 3.0 (each s, 6 H, 2 CH_3), 5.9–6.0 (br. s, 1 H, CH=), 6.8–6.9, 6.95–7.05, 7.2 to 7.3, 7.5–7.7 and 7.9–8.0 (aromatic protons), and 9.0 (s, 1 H, OH).

4.5. Addition of acrylonitrile to 2*: Formation of cyanoethylamine derivative* **12**

A mixture of **2** (0.01 mol) and acrylonitrile (0.012 mol) in pyridine (50 ml) and H_2O (10 ml) was refluxed for 4 h, cooled and acidified with dil. HCl. The appreciptated solid was filtered and crystallized to give **12** (Table 3). IR: 3200–3100 (NH), 3020, 2830 (aromatic and aliphatic CH), 2150 (CN), 1610 (CH=CH), 1480 (def. CH_2, CH_3), 1050 (C–O–C) and 800, 750 (aryl groups). M/z (Int. %): 355 (2.47), 301 (8.33), 302 (100), 286 (4.91), 271 (5.23), 243 (30.87), 217 (85.44). ^{1}H NMR: 1.3–1.4 (br. s, 3 H, CH_3), 2.6–2.8 (m, 4 H, CH_2CN-CH_2N), 3.7, 3.8, 3.9 (each s, 3 OCH_3), 7.2–7.3 (m, 2 H, aromatic protons) and 8.3 (s, 1 H, NH).

4.6. Synthesis of 2,3-dihydro-4-oxo-7-methyl-8-styryl-pyrimido[3,2-b][1,2,4]-triazine (**13**)

Compound **12** (1 g) in HCl (20%, 50 ml) was refluxed for 12 h, cooled and the precipitated solid was filtered and crystallized to give **13** (Table 3). IR: 3050, 2900 (aromatic and aliphatic CH), 1680 (C=O), 1620 (CH=CH), 1580 (C=N), 1480 (def. CH_2, CH_3), 1380 (NCN), 1060 (C–O–C), 810, 730 (aryl group). M/z (Int. %) 356 (0.32), 328 (1.79), 303 (19.05), 302 (100), 287 (3.52), 259 (34.88), 217 (96.69), 202 (10.09), 189 (19.15), 173 (13.39), 145 (26.11), 115 (21.81), 77 (14.76), 70 (8.56), 57 (13.33).

4.7. Fusion of 2 *with ethyl cyanoacetate derivative* **14***: Formation of the cyanoacetamide derivative* **15**

An equimolar mixture of **2** and **14** [17] was fused for 30 min at 150 °C, then cooled. The precipitated solid was recrystallized to give **15** (Table 3). IR: 3200 (NH), 3020, 2900 (aromatic and aliphatic CH), 2200 (CN), 1670 (C=O), 1610 (CH=CH), 1580 (C=N), 1480 (def. CH_3), 870, 780 (aryl groups), 700 (C–Cl).

4.8. Formation of 4-amino-2-oxo-3-(4-phenylphthalazin-1-yl)-7-methyl-8-(2′,4′-dichlorostyryl)pyrimido[3.2-b][1,2,4]triazine (**16**)

A mixture of **15** (0.01 mol), EtOH (100 ml) and piperidine (0.5 ml) was refluxed for 12 h, cooled and diluted with ice-acetic acid. The resultant solid was filtered off and recrystallized to give **16** (Table 3), IR: 3400 to 3200 (NH_2), 3050, 2910 (aromatic and aliphatic CH), 1660 (C=O), 1620 (CH=CH), 1570 (C=N), 1470 (def. CH_3), 870, 820 (aryl groups)., 700 (C–Cl).

4.9. Synthesis of 3 H-2,4-dioxo-3-(4-phenylphthalazin-1-yl)-7-methyl-8-(2′,4′-dichlorostyryl)-pyrimido[3,2-b][1,2,4]-triazine (**17**)

A mixture of **15** (1 g) in HCl (25%, 50 ml) was refluxed for 4 h and cooled. The solid obtained was washed with cold H_2O and recrystallized to give **17** (Table 3), IR: 3050, 2890 (aromatic and aliphatic CH), 1680, 1660 (2 C=O), 1600 (CH=CH), 1580 (C=N), 1260 (NCN), 780, 750 (aryl groups), 680, 670 (C–Cl).

4.10. Cycloaddition of 2 *with ethyl cyanoacetate: Formation of the heterobicyclic compound* **18**

A mixture of **2** (0.01 mol) and ethyl cyanoacetate (0.01 mol) in sodium ethoxide (0.02 mol Na in 100 ml abs. EtOH) was refluxed for 4 h, cooled, and then diluted with H_2O/HCl. The solid obtained was filtered off and recrystallized to give **18** (Table 3); UV: $\lambda_{max}(\varepsilon)$: 446 (3.40), 404 shoulder (2.97), 281 (2.01); IR: 3800–3100 (b, NH, OH), 3010, 2900 (aromatic and aliphatic CH), 1670 (C=O), 1610 (CH=CH), 1580 (C=N), 1480 (def. CH_3, CH_2), 1250 (NCN), 850, 800 (aryl groups). ^{1}H NMR: 2.0 (s, 3 H, CH_3), 2.5, 2.7 (each s, 6 H, 2 CH_3), 3.0–3.2 (s, 1 H, cyclic CH), 5.8–6.0 (br., 2 H, CH=CH), 6.7–6.8, 6.9–7.0 (m, 6 H, aromatic and cyclic CH), 7.6–7.7, 7.9–8.0 (m, 4 H, aromatic protons).

4.11. 2-Phenyl-6-methyl-7-(2,4-dichlorostyryl)-imidazo[3,2-b][1,2,4]triazine (**19**)

A mixture of **2** (0.01 mol) and phenacyl bromide (0.01 mol) in sodium ethoxide (0.02 mol Na in 100 ml abs. EtOH) was refluxed for 4 h, cooled, and then diluted with H_2O. The solid obtained was filtered off and recrystallized to give **19** (Table 3); IR: 3020, 2900 (aromatic and aliphatic CH), 1620 (CH=CH), 1560 (C=N), 160 (def. CH_3), 1380 (NCN), 860, 810 (aryl group), 690 (C–Cl). M/z (Int. %): 381 (1.16), 172 (4.97), 173 (15.80), 174 (14.55), 175 (100), 209 (17.6), 210 (75), 133 (2.06), 118 (2.01), 105 (47.74).

4.12. Fusion of 2 *with 2-ethoxyethanol: Formation of 2,3-dihydro-6-methyl-7-(2,4-dichrorostyryl)-imidazo[3,2-b][1,2,4]triazine* (**20**)

A mixture of **2** (0.01 mol) and 2-ethoxyethanol (0.01 mol) was fused for 2 h at 200 °C, then cooled. The resultant solid was filtered and crystallized to give **20** (Table 3): UV: $\lambda_{max}(\varepsilon)$: 434.5 (0.75), 311 shoulder (0.98), 279 (1.03).

4.13. Synthesis of 2,3-dioxo-6-methyl-7-(thiophen-2-yl-styryl)imidazo[3,2-b][1,2,4]triazine (**21**)

A mixture of **2** (0.01 mol) and diethyl oxalate (0.012 mol) in dry dioxan (100 ml) was refluxed for 12 h, then concentrated and diluted with H_2O. The precipitated solid recrystallized to give **21** (Table 3); IR: 1700, 1680 (2 C=O), 1550 (C=N), 1460 (def. CH_3), 820 (aryl group).

4.14. Synthesis of 3,4-dihydro-4-phenyl-7-methyl-8-(4-dimethylaminostyryl)-pyrimido[3,2-b][1,2,4]triazine (**22**)

An equimolar mixture of **2** and ethyl cinnamate was fused for 2 h at 200 °C and cooled. The solid obtained was filtered and crystallized to give **22** (Table 3); IR: 1670 (C=O), 1560 (C=N), 720 (aryl group); M/z (Int. %): 385 (0.06), 131 (0.22), 255 (100), 240 (5.80), 211 (0.44), 168 (6.92), 141 (8.29), 142 (5.18), 128 (3.13), 115 (4.37).

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References

1 Abdel-Rahman, R. M.: Farmaco **46**, 379 (1991)
2 Abdel-Rahman, R. M.: Farmaco **47**, 319 (1992)
3 Abdel-Rahman, R. M.; Seada, M.; Fawzy, M.; El-Baz, I.: Farmaco **48**, 397 (1993)
4 Abdel-Rahman, R. M.; Seada, M.; Fawzy, M.; El-Baz, I.: Pharmazie **49**, 729 (1994)
5 Abdel-Rahman, R. M.; Seada, M.; Fawzy, M.; El-Baz, I.: Pharmazie **49**, 811 (1994)
6 Abdel-halim, A. M.; El-Gendy, Z.; Abdel-Rahman, R. M.: Pharmazie **50**, 726 (1995)
7 Abdel-Rahman, R. M.; El-Gendy, Z.: Indian J. Chem. **28B**, 1072 (1989)
8 Seada, M.; Abdel-Rahman, R. M.; Abdel-Megid, M.: Indian J. Heterocycl. Chem. **3**, 9 (1993)
9 Abdel-Rahman, R. M.; Islam, I. E.: Indian J. Chem. **32B**, 526 (1993)
10 Abdel-Rahman, R. M.; Fawzy, M.; Gabr, Y.; Abdel-Hamide, S. G.; Siad, Abdel-Tawam, M.: Indian J. Heterocycl. Chem. **3**, 281 (1994)
11 Abdel-Hamide, S. G.; Abdel-Tawab, M.; Abdel-Rahman, R. M.: Indian J. Heterocycl. Chem. **3**, 121 (1993)
12 Pesson, M.; Antoine, M.: Bull. Soc. Chim. Fr., 1599 (1970)
13 Weislow, O. S.; Kiser, R.; Fine, D. L.; Bader, J.; Shoemaker, R. M.; Boyed, M. R.: J. Nat. Cancer Inst. **81**, April 19 (1989)
14 Boyed, M. R.: Proc. Am. Assoc. Cancer Res. **30**, 652 (1989)
15 Grever, M. R.; Schepartz, S. A.; Chabner, B. A.: The National Cancer Institute: Cancer Drug Discovery and Development Program; Seminars Oncology, vol. 19 (6) (December) p. 622, 1992
16 Loev, B.; Goodman, M. M.: Tetrahedron Lett, 789 (1968)
17 El-Gendy, Z.: Indian J. Chem., **33B**, 326 (1994)

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