

This article was downloaded by:

On: 28 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713618290>

Synthesis of Heterobicyclic Nitrogen Systems Bearing a 1,2,4-Triazine Moiety as Anticancer Drugs: Part IV

Z. El-Gendy^a; J. M. Morsy^a; H. A. Allimony^a; W. R. Abdel-Monem^a; R. M. Abdel-Rahman^a

^a Ain Shams University, Cairo, Egypt

To cite this Article El-Gendy, Z. , Morsy, J. M. , Allimony, H. A. , Abdel-Monem, W. R. and Abdel-Rahman, R. M.(2003) 'Synthesis of Heterobicyclic Nitrogen Systems Bearing a 1,2,4-Triazine Moiety as Anticancer Drugs: Part IV', *Phosphorus, Sulfur, and Silicon and the Related Elements*, 178: 9, 2055 — 2071

To link to this Article: DOI: 10.1080/10426500390228738

URL: <http://dx.doi.org/10.1080/10426500390228738>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

SYNTHESIS OF HETEROBICYCLIC NITROGEN SYSTEMS BEARING A 1,2,4-TRIAZINE MOIETY AS ANTICANCER DRUGS: PART IV

Z. El-Gendy, J. M. Morsy, H. A. Allimony, W. R. Abdel-Monem,
and R. M. Abdel-Rahman
Ain Shams University, Roxy, Cairo, Egypt

(Received February 18, 2002; accepted February 18, 2003)

Some new isolated and fused heterobicyclic nitrogen systems such as thiazolidinone, imidazolone, pyrimidinone, quinazolone, as-triazolone, as-triazinones, tetrazino-as-triazines, and the related compounds 3,4-diaminotriazine and sulfa derivatives 2–27 have been synthesized via treatment of 4-amino-6-styryl-3-thioxo-1,2,4-triazin-5(2,4H)ones (1) with cyclic and acyclic oxygen and nitrogen compounds. The structures of the products have been established from their elemental and spectral analyses. Some new compounds exhibited significant anticancer activities, where compounds 11j > 2a > 6 and 11i > 14 > 11k showed a moderate activity toward leukemia, ovarian cancer, and non-small cell lung cancer.

Keywords: 1,2,4-Triazines; biological activity; condensed heterocycles

Among 1,2,4-triazine derivatives; Sencor [4-amino-3-methylthio-6-*tert*-butyl-1,2,4-triazin-5(4H)one] is being used as a commercial herbicide for the control of weeds in potato crops.¹ Some heterocyclic systems such as thiazolidinone, imidazolone, and quinazolinone derivatives exhibited remarkable pharmacological activity.^{2,3}

Also, some 3-thioxo-1,2,4-triazin-5-one derivatives are used as anti-cancer and anti-HIV drugs.^{4–6} During the search for new chemotherapeutic agents, some new heterobicyclic nitrogen systems derived from 4-amino-3-thioxo-1,2,4-triazin-5-ones (1) have been synthesized, in view of potential anticancer activities (Schemes 1–5).

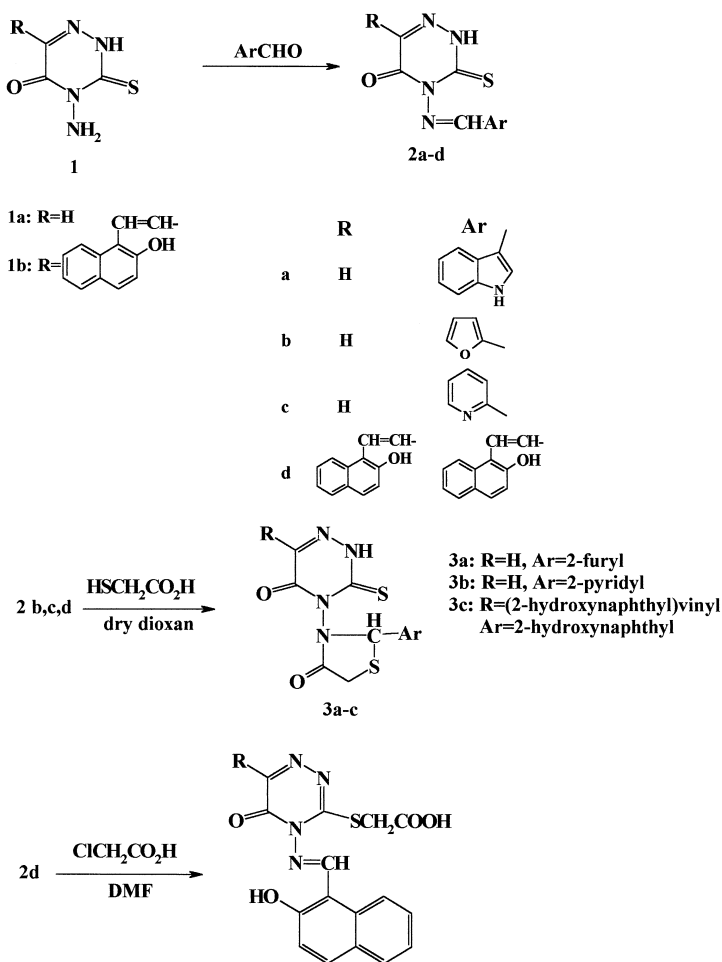
The authors are very grateful to Prof. Dr. Johan P. Bader, Chief Antiviral Evaluations Branch and Prof. Dr. V. L. Narayanan, Chief Drug Synthesis, Chemistry Branch National Cancer Institute, Bethesda, Maryland, USA for evaluation of the *in vitro* antitumor tests as development program. Thanks also are due to the members of the NCI staff.

Address correspondence to R. M. Abdel-Rahman, Ain Shams University, Department of Chemistry, Faculty of Education, Roxy, Cairo, Egypt.

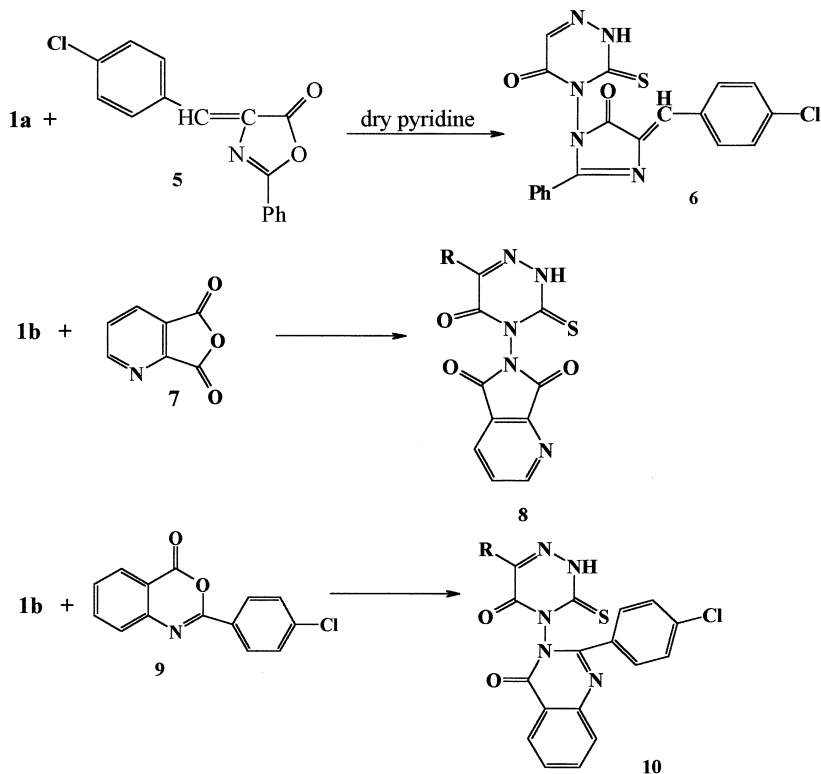
INVESTIGATIONS AND RESULTS

Chemistry

Condensation of the 4-amino-6-styryl-3-thioxo-1,2,4-triazin-5-ones **1** with aromatic aldehydes⁷ in the presence of absolute ethanol concentrated sulfuric acid produced the hydrazone **2**, which upon cyclo-addition with mercaptoacetic acid in dry dioxan, yielded the 3-thiazolidinyl-1,2,4-triazine derivative **3**. Treatment of **2d** with monochloroacetic acid in DMF gave the carboxymethyl derivative **4** by electrophilic attack on sulfur atom (Scheme 1).



SCHEME 1



SCHEME 2

On the other hand, condensation of compound **1a** with heterocyclic carbonyl compounds such as oxazolinone **5**, pyridine-2,3-dicarboxylic anhydride **7**, and 3,1-benzoxazin-4-one **9** in dry pyridine furnished 1,2,4-triazine derivatives connected with imidazolinone (**6**) pyridine-2,3-dicarboximide (**8**) and quinazolinone (**10**) moieties (Scheme 2).

The structures of **8** and **10** were deduced from elemental and spectroscopic analyses. The mass spectrum showed the correct molecular ion peak of **8** at m/z 443 and, in addition, the base peak at m/z = 169 attributable to the 2-hydroxynaphthylethenyl moiety. The absorptions at 3543 (OH), 3060 (NH), 1764, 1660 (2C=O), 1594 (C=N), 1175 (C=S), 756 (phenyl CH), and 681 cm^{-1} (C–Cl) in the IR spectrum; the display of a molecular ion peak at m/z (Int., M) = 551 (6.05; $\text{C}_{29}\text{H}_{18}\text{N}_5\text{ClSO}_2$) and the base peak at 57 (100, CHN_2O^+), in addition to the ions at 111 (96.13, $^+\text{C}_6\text{H}_4\text{Cl}$), 169 (4.97, 2-hydroxynaphthylethylene ion) and 102 (20.34; $^+\text{C}_6\text{H}_4\text{CN}$) supported the structure **10** (Figure 1).

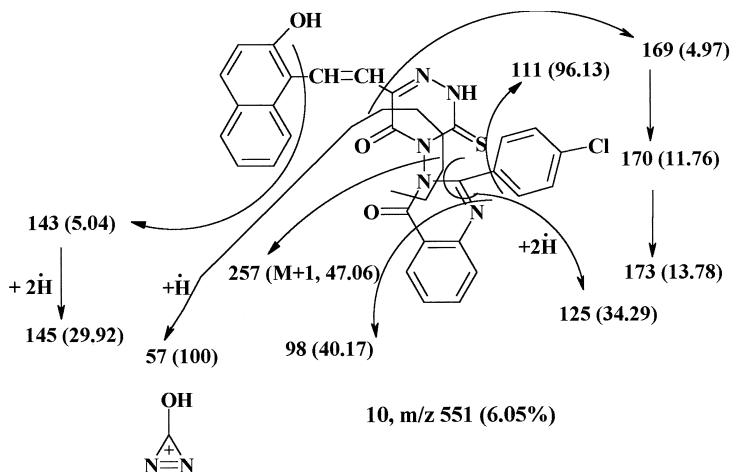


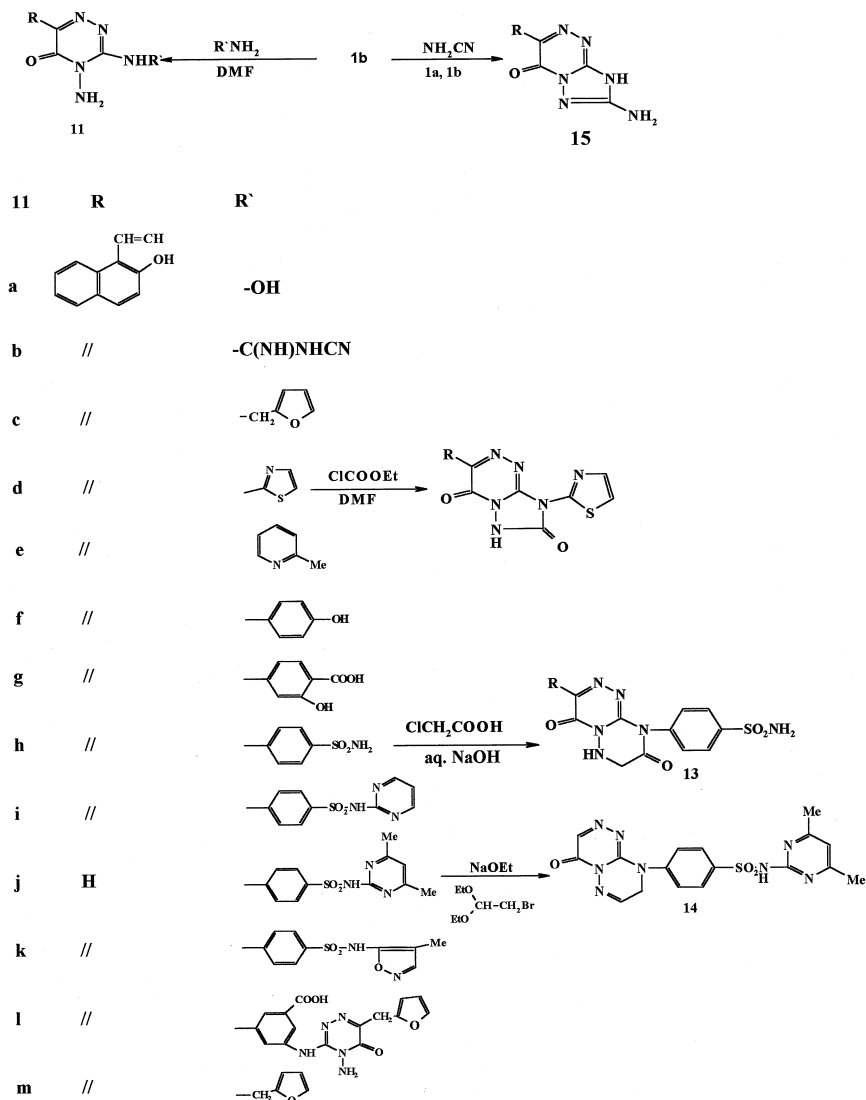
FIGURE 1 Mass fragmentation of compound **10**.

3,4-Diamino-1,2,4-triazin-5-ones are used as starting materials for the preparation of fused heterobicyclic systems as herbicides.^{8,9} Thus, nucleophilic displacement reactions of compound **1** with primary amino compounds yielded 3,4-diamino-1,2,4-triazin-5-ones (**11a–g**), which upon heterocyclization, afforded fused heterobicyclic systems. Refluxing compound **1** with 3,5-diaminobenzoic acid in DMF yielded 3,5-disubstituted aminobenzoic acid **11 l**.

The 1,2,4-triazolidino [5,1-c]-1,2,4-triazine-4,7-dione (**12**) was obtained from the heterocyclization reaction of **11d** with ethyl chloroformate in DMF (Scheme 3).

Various types of sulfa drugs containing heterocyclic rings have been prepared and their biological activities have been studied. Thus, several new sulfa compounds (**11h–k**) bearing 1,2,4-triazine and/or 1,2,4-triazinotriazine moieties have been synthesized by reaction of compound **1** with sulfa drugs such as sulfanilamide, sulfadiazine, sulfadimidine, and sulfoxazole in the presence of DMF. Heterocyclization reactions of compounds **11h** and **11j** on refluxing with monochloroacetic acid and/or 1,1-diethoxy-2-bromoethane in basic medium led to the direct formation of the 1,2,4-triazino[4,3-b]-1,2,4-triazine (**13**) and the 1,2,4-triazino [4,3-b]-1,2,4-triazin-4-one (**14**) respectively (Scheme 3).

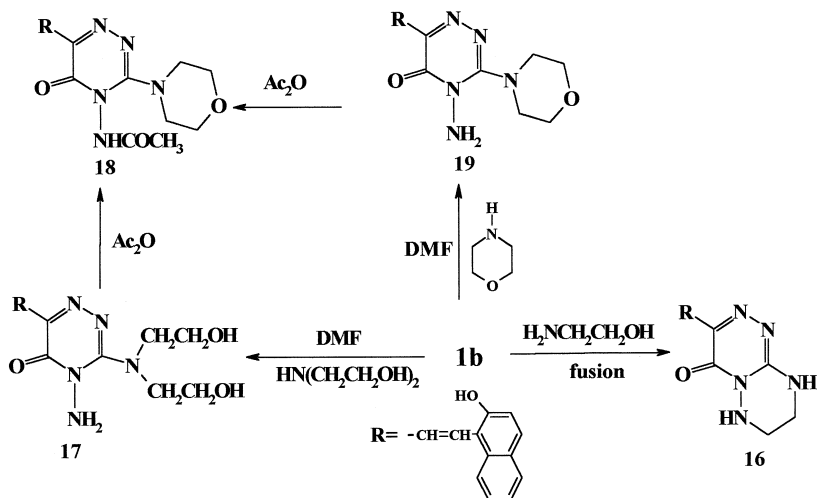
The structures of **11** and **14** were assigned on the basis of IR, ¹HNMR, and mass spectral data. The absorptions at 3546 (OH), 3445 (NH₂), 3182, 3052 (NH, NH), 1683 (C=O), 1319, 1178 cm⁻¹ (SO₂) in the IR spectrum, the display of signals at δ 1.8 (Me₂), 3.8 (NHSO₂), 4.4 (NH₂), 7.1–7.5 (4H, aromatic), 7.6–7.7 (CH=CH), 8.3 (C₅–H of pyrimidine),



SCHEME 3

9.7 ppm (OH) protons in the ^1H NMR spectrum are in agreement with the proposed structure of **11g**.

On the other hand, the ^1H NMR spectrum of **14** revealed a signal at δ 3.8 (CH_2), in addition to the spectrum of **11**. The mass fragmentation of **14** followed several pathways involving the fission of one or more bonds of the 1,2,4-triazinotriazine ring and showed the molecular ion



SCHEME 4

at m/z (Int., M) = 582 (0.01, $C_{19}H_{19}N_5O_3S$), the base peak at 527 (100, M-HCON₂), and 145 (29.92, $C_6H_4N_2O$), 128 ($C_3H_2N_3S$).

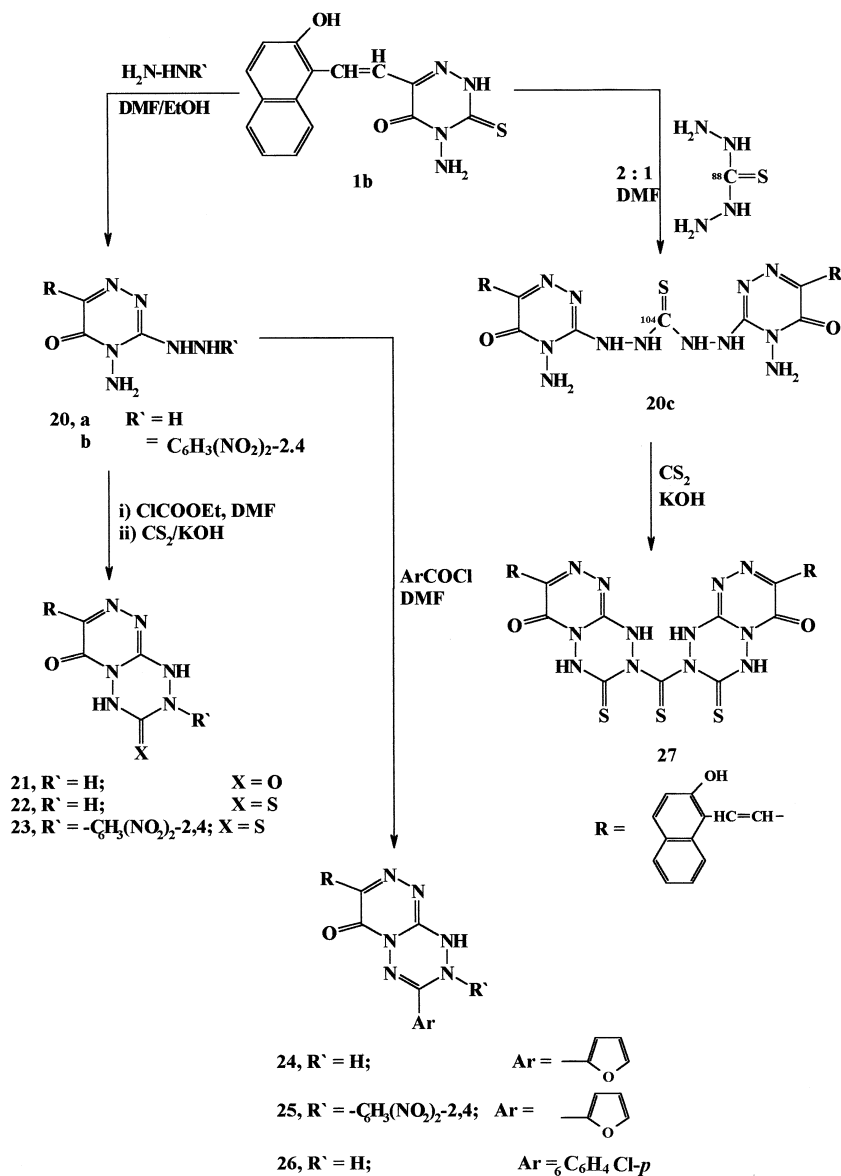
Similarly, fusion of compound **1** with bifunctional nitrogen compounds such as cyanamide and ethanolamine afforded the 1,2,4-triazolino[5,1-c]-1,2,4-triazin-4-one **15**, and the 1,2,4-triazino[4,3-b]-1,2,4-triazin-4-one **16** respectively (Scheme 4).

On the other hand, treatment of compound **1** with diethanolamine in DMF yielded 4-amino-3-[bis(2-hydroxyethyl)amino]-1,2,4-triazin-5-one **17**, which, upon heterocyclization with acetic anhydride, led to the formation of 4-acetamido-3-morpholino-1,2,4-triazin-5-one **18**. The structure of compound **18** was elucidated from the independent reaction of compound **1** with morpholine in DMF to give **19** followed by acylation (Scheme 4).

Nucleophilic displacement at the thiocarbonyl carbon atom of **1** using bis-amino reagents such as hydrazine hydrate, 2,4-dinitrophenylhydrazine and thiocarbonylhydrazide in isopropyl alcohol afforded the 1,2-disubstituted hydrazines **20a-c** (Scheme 5).

Some 1,2,4-triazino-1,2,4,5-tetrazine derivatives also were obtained by heterocyclization reactions of compound **20**. Thus, acylation of compound **20a** with ethyl chloroformate in DMF afforded the 1,2,4-triazino[4,3-e]-1,2,4,5-tetrazin-3,6-dione **21** while refluxing **20a,b** with carbon disulfide in ethanolic potassium hydroxide yielded the isomeric thiones **22** and **23** respectively (Scheme 5).

The structures of **20a** and **21** were confirmed on the basis of spectral data. The IR spectrum of **20a** showed characteristic



SCHEME 5

absorptions at ν 3566 (OH), 3416 (NH_2), 3291 (NH_2NH), 3052 (NH), 1742 cm^{-1} ($\text{C}=\text{O}$), while that of **21** showed the absorptions at ν 3524 (OH), 3551 (OH), 3034 (NH, NH), 1679 cm^{-1} ($\text{C}=\text{O}$) with disappearance of the NH_2 group. The ^1H NMR spectrum of **21** displayed signals at

δ 7.0–7.5 (Ar–CH), 7.8–7.9 (CH=CH), 8.3, 8.4 (NH), 9.8 and 12.5 ppm (OH).

Aroylation of compound **20a,b** using furoyl chloride and 4-chlorobenzoylchloride in DMF resulted in the formation of the 1,2,4-triazino[3,4-c]-1,2,4,5-tetraazin-6-ones **24–26** (Scheme 5). The structure of **20b** and **25** was elucidated from elemental and spectroscopic data. The IR spectrum of **20b** showed the presence of absorption bands at ν 3267 (NH₂), 3089 (NH, NH), 1744 (C=O), 1612 (def. NH₂), 1511, 1329 cm⁻¹ (asy. and sy. NO₂). ¹H NMR of **20b** revealed the signals at 6.7–7.5 (furan and Ar–CH), 7.6–8.0 (*cis* CH=CH), 8.0–8.7 (Ar–CH of 2,4-dinitrophenyl), 9.4, 9.7 (NH, NH) and at 12.5 ppm (OH) while that of **25** at 6.7–7.6 (furan and Ar–CH), 7.7–8.0 (*cis* CH=CH), 8.2–8.4 (Ar–CH of 2,4-dinitrophenyl), 9.3–9.7 (OH), and 12.5 ppm (NH).

An inspection of the mass spectra of compounds **20a** and **25** reveals that the fragmentation process common to all compounds involves: i) splitting of both side chains styryl and/or 2,4-dinitrophenyl moieties, and ii) fission of the 1,2,4-triazinone nucleus, base peaks of **20a** at *m/z* 112 (100, C₃H₄N₄O) and at 170 (100, C₁₂H₁₀O) for **25** iii) formation of ions involving some kind of rearrangement (Figure 2).

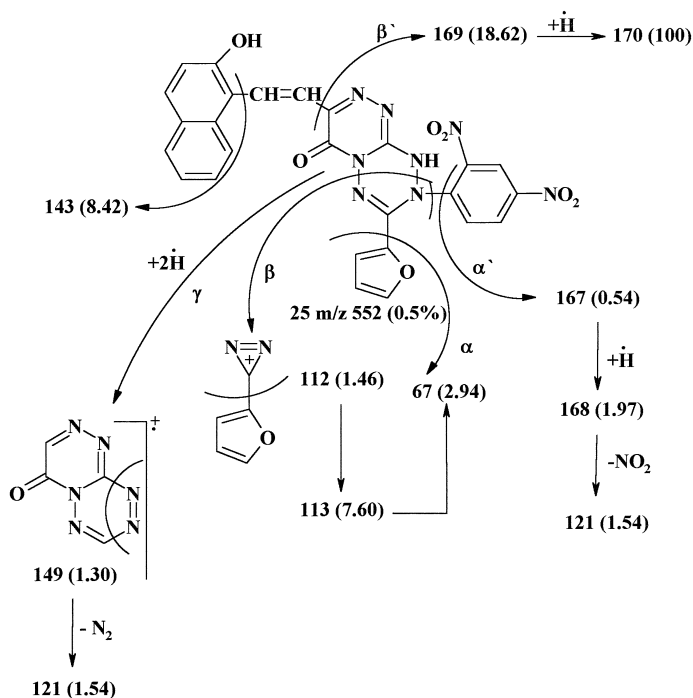


FIGURE 2 Mass fragmentation of compound **25**.

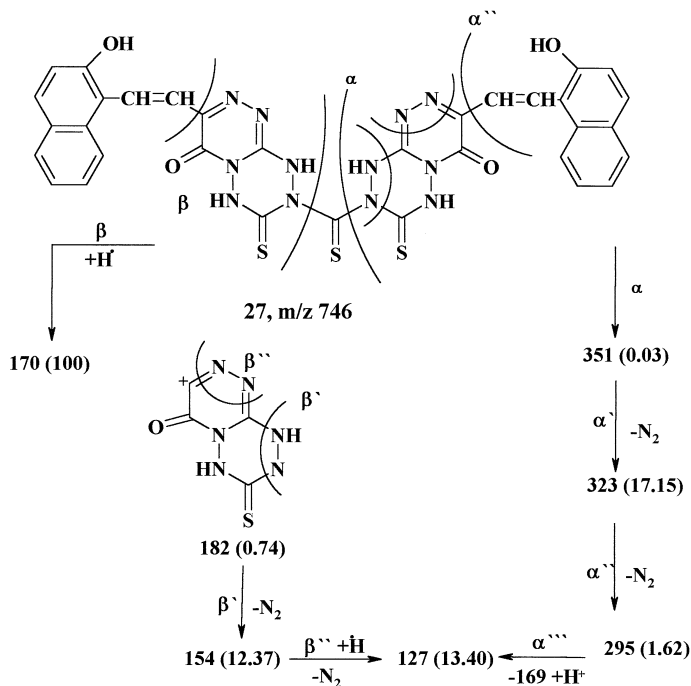


FIGURE 3 Mass fragmentation of compound **27**.

Finally, refluxing compound **20c** with carbon disulfide in ethanolic potassium hydroxide led to the direct formation of the tris-thioxotriazine compound **27** (Scheme 5). The structure of **27** was derived from elemental and spectroscopic data. The UV absorption spectrum showed λ_{\max} at 410, 325, and 270 nm. The IR spectrum of **27** showed ν at 3542 (OH), 3679, 3619 (NH, NH), 1744, 1708 (2C=O), 1177 (C=S), and 787, 749 cm^{-1} . The high resolution mass spectrum of compound **27** (Figure 3) shows that the molecular ion constitutes the base peak at m/z 170 (100%) and suffers cleavage of C–C and C–N with hydrogen transfer giving rise to differ heterobicyclic ions.

Pharmacology

In Vitro Antitumor Testing

Most of the newly synthesized compounds have been evaluated in vitro for antitumor activity according to the described method^{10,11} in different concentrations: a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth. The primary and fine results

obtained for the tested compounds are outlined in Tables II and III were carried out in the National Cancer Institute, Bethesda, Maryland, USA.

DISCUSSION

In continuation of our program directed to the development of an effective drug for the treatment of cancer,^{12–14} various heterocycles containing sulfur and a 1,2,4-triazine moiety have been synthesized and the results of the antitumor screening of the synthesized compounds are recorded in Tables I and II.

Quantitative Relation Between Structure and Activity at the Primary Anticancer Activity

Most of the tested compounds showed a moderate in vitro model primary anticancer activity especially towards Lung cancer (NCI-H460), Breast cancer (MCF7) and central nervous system cancer SF268 in the following order **11j** > **2a** > **6** and **11i** > **14** > **11k**. Only compound **11j** highly reduced the growth of any one of the cell lines towards all tested cancers, which seems to be due to the conjugation between the sulfadimidine and the 4-amino-5-oxo-1,2,4-triazin-3-yl substituent (Table I).

TABLE I The in vitro Model Primary Anticancer Data of Some New Compounds^a

Compd. no.	Concentration	Growth percentages ^b			Activity ^c
		(Lung) NCI-H460	(Breast) MCF7	(CNS) SF 268	
2a	11.00E-04 Molar	30	28	72	active
3d	11.00E-04 Molar	–52	–3	–23	active
6	11.00E-04 Molar	46	–28	26	active
11a	11.00E-04 Molar	126	84	109	inactive
11b	11.00E-04 Molar	120	88	120	inactive
11i	11.00E-04 Molar	–47	–60	–11	active
11j	11.00E-04 Molar	0	1	4	active
11k	11.00E-04 Molar	–5	–100	–76	active
11l	11.00E-04 Molar	–26	–13	3	active
11m	11.00E-04 Molar	100	40	98	inactive
11n	11.00E-04 Molar	–25	–18	–5	active

^aResults for each test agent are reported as the percent of growth of the treated cells when compound to the untreated control cells.

^bActive compounds reduce the growth of any one of the cell lines to 32%.

^cNegative numbers indicate cell kill.

Quantitative Relation Between Structure and Activity at the In Vitro Anticancer Activity

In view of the in vitro anticancer activity, we showed that most of the tested compounds exhibited a moderate anticancer activity in the order **11h** > **2a** > **3c** > **6** > **11k** > **1b** especially toward leukemia (Table IIa).

Quantitative relation between sulfur element percentage and allular sensitivity Δ of each tested compound were recorded (Table IIb). By, increasing of sulfur percentage record increasing of Δ values in the following order **2a** > **3a** > **1b** > **14** > **11j**, and increasing of sulfur percentage afforded decreasing the Δ values in the order **20c** > **11h** > **6** > **11k** (Table IIb).

In view of these facts we report that:

- i) Hydrazone **2** is more active than compound **1**, due to the extension of electronic conjugation between the heterocyclic moiety and the unsaturated N=CH group.

TABLE IIa In vitro Antitumor Activity Data of Some New Compounds

Compd.	GI ₅₀ ^a	Selectivity	
		Different allular sensitivity (Δ ^b)	Different subpanel sensitivity
1c	-4.41	1.44 2.15	leukemia, non-small cell lung cancer, ovarian cancer, breast cancer
2a	-4.54	2.07 2.25	leukemia, ovarian cancer
3c	-4.69	2.06 3.65	leukemia, non-small cell lung cancer, colon cancer, ovarian cancer
6	-4.92	1.19 1.59	leukemia, breast cancer
11h	-4.80	2.08 2.57	leukemia, ovarian cancer
11i	-4.65	0.27 0.82	leukemia
11j	-4.92	0.76 1.21	leukemia
11k	-4.45	1.52 2.11	leukemia, colon cancer
14	-4.49	0.41 0.96	colon, renal, breast cancers
20c	-4.50	2.80 2.95	leukemia

^aGI₅₀ concentration giving 50% inhibition.

^bThe reported data represent the logarithmic 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 IIb The Sulfur Percentage and Δ Values for Some Tested Compounds

Compd.	Sulfur %	Δ	Compd.	Sulfur %	Δ
2a	11.80	2.07	11i	6.06	0.27
3a	11.80	2.06	11k	8.24	1.52
1b	10.25	1.44	6	7.81	1.19
14	7.72	0.41	11h	7.11	2.08
11j	5.75	0.76	20c	4.83	2.80

- ii) The presence of a thiazolidinone moiety in compound **3** caused a higher activity than an imidazolone moiety in the compound **6**.
- iii) The allular sensitivity increased by replacement of SH group in compound **1** by sulfa groups in compounds **11h-k**.
- iv) Also, the results reveal that the compounds **2a**, **3d**, and **11h** ($\Delta > 2$) are more active than the compounds **1c**, **6**, and **11k** ($\Delta < 2$), which is mainly due to the presence of indole, thiazolidinone, and sulfanilamide moieties.

In conclusion, the anticancer activities were improved when compounds that contain a 1,2,4-triazine moiety were connected with other heterocyclic rings, such as thiazolidinone and imidazolone or a sulfa moiety.

EXPERIMENTAL

M.p. are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 293 FT spectrophotometer (ν_{\max} in cm^{-1}). UV absorption spectra in DMF were recorded on a Perkin-Elmer, Lambda 4B controller accessory interface UV-VIS spectrophotometer (λ_{\max} in nm). ^1H NMR spectra were recorded on an EM NMR spectrometer 200 MHz PMR using DMSO as a solvent and TMS as internal reference (Chemical shifts in ppm) and MS were recorded on a Gas Chromatographic GCMSqp 1000ex Shimadzu instrument at 70 eV. Compounds **1a,b** were prepared following a reported procedure.¹⁵ The physical data of the synthesized compounds are given in Table III.

4-Arylidene-6-styryl-3-thioxo-1,2,4-triazin-5(2H)-ones (**2a-d**)

A mixture of **1a** or **1b** (0.01 mmol) and indol-3-carboxaldehyde, furan-2-carboxaldehyde, pyridin-2-carboxaldehyde, or 2-hydroxynaphthaldehyde (0.01 mmol) in EtOH (20 ml) and conc. H_2SO_4 (2 drops)

TABLE III Physical Data of the New Heterobicyclic Nitrogen Systems

Compd. no. ^a	Crystallized from	m.p. (°C)	Mol. formula	M. Wt.	Sulfur analysis	
					Found/calcd.%	
2a	MeOH	230	C ₁₂ H ₉ N ₅ OS	271	11.1	11.80
2b	MeOH	165	C ₈ H ₆ N ₄ O ₂ S	222	14.3	14.41
2c	MeOH	225	C ₉ H ₇ N ₅ OS	233	13.3	13.73
2d	MeOH	200	C ₂₆ H ₂₀ N ₄ O ₃ S	468	5.9	6.83
3a	MeCO ₂ Et	200	C ₁₀ H ₈ N ₄ O ₃ S ₂	296	21.1	21.62
3b	MeCO ₂ Et	285	C ₁₁ H ₉ N ₅ O ₂ S ₂	307	20.9	20.84
3c	MeCO ₂ Et	250	C ₂₈ H ₂₀ N ₄ O ₄ S ₂	540	11.2	11.85
4	MeOH	260	C ₂₈ H ₂₀ N ₄ O ₅ S	524	5.9	6.10
6	MeOH	115	C ₁₉ H ₁₂ N ₅ O ₂ SCl	409.5	7.3	7.80
8	MeOH	170	C ₂₂ H ₁₃ N ₅ O ₄ S	443	7.1	7.22
10	MeOH	140	C ₂₉ H ₁₈ N ₅ O ₃ SCl	551.5	5.6	5.79
11a	MeOH	190	C ₁₅ H ₁₃ N ₅ O ₃	311	—	—
11b	MeOH	270	C ₁₅ H ₁₅ N ₇ O ₂	325	—	—
11c	Dil DMF	320	C ₂₀ H ₁₇ N ₅ O ₃	375	—	—
11d	MeOH	180	C ₁₈ H ₁₄ N ₆ O ₂ S	378	8.0	8.46
11e	MeOH	135	C ₂₁ H ₁₈ N ₆ O ₂	386	—	—
11f	Dil DMF	265	C ₂₁ H ₁₇ N ₅ O ₃	387	—	—
11g	Dil DMF	295	C ₂₂ H ₁₇ N ₅ O ₅	431	—	—
11h	MeOH	195	C ₂₁ H ₁₈ N ₆ O ₄ S	450	6.4	7.11
11i	MeOH	215	C ₂₅ H ₂₀ N ₈ O ₄ S	528	5.7	6.06
11j	MeOH	235	C ₂₇ H ₂₄ N ₈ O ₄ S	556	5.6	5.75
11k	MeOH	185	C ₁₅ H ₁₆ N ₈ O ₃ S	388	7.4	8.24
11l	MeOH	220	C ₂₅ H ₂₁ N ₇ O ₅ S	531	5.7	6.02
11m	MeOH	170	C ₂₃ H ₂₀ N ₁₀ O ₆	532	—	—
12	MeOH	230	C ₁₉ H ₁₂ N ₆ O ₃ S	404	7.4	7.92
13	MeOH	285	C ₂₃ H ₁₈ N ₆ O ₅ S	490	5.9	6.53
14	EtOH	240	C ₁₇ H ₁₈ N ₈ O ₃ S	412	7.1	7.76
15a	MeOH	180	C ₄ H ₄ N ₆ O	152	—	—
15b	MeOH	295	C ₁₆ H ₁₂ N ₆ O ₂	320	—	—
16	MeOH	280	C ₁₇ H ₁₅ N ₅ O ₂	312	—	—
17	MeOH	140	C ₁₉ H ₂₁ N ₅ O ₄	383	—	—
18	MeOH	198	C ₂₁ H ₂₁ N ₅ O ₄	407	—	—
19	MeOH	280	C ₁₉ H ₁₉ N ₅ O ₃	365	—	—
20a	MeOH	170	C ₁₅ H ₁₄ N ₆ O ₂	310	—	—
20b	MeOH	205	C ₂₁ H ₁₆ N ₈ O ₆	476	—	—
20c	MeOH	195	C ₃₁ H ₂₆ N ₁₂ O ₄ S	662	4.2	4.83
21	MeOH	350	C ₁₆ H ₁₂ N ₆ O ₃	336	—	—
22	MeOH	140	C ₁₆ H ₁₂ N ₆ O ₂ S	352	8.2	9.09
23	MeOH	160	C ₂₂ H ₁₄ N ₈ O ₆ S	518	6.1	6.17
24	MeOH	150	C ₂₀ H ₁₄ N ₆ O ₃	386	—	—
25	MeOH	240	C ₂₆ H ₁₆ N ₈ O ₇	552	—	—
26	MeOH	210	C ₂₂ H ₁₅ N ₆ O ₂ Cl	431	—	—
27	DMF	310	C ₃₃ H ₂₂ N ₁₂ O ₄ S ₃	746	12.3	12.86

^aYield = 40–70%.^bElemental analysis (C,H,N) are within ±0.5% of the theoretical values.^cChlorine elemental analysis: 6 = Found: 8.2, Calcd.: 8.65%; 10 = Found: 6.2, Calcd.: 6.43%; 26 = Found: 7.3, Calcd.: 8.23%.

was refluxed for 4 h. The reaction mixture was cooled and poured onto ice. The solid obtained was filtered off and recrystallized to give **2a-d** (Table III).

2-Aryl-3-(5-oxo-6-substituted-3-thioxo(2H-1,2,4-triazin-4-yl))-1,3-thiazolidin-4-ones (3a-c)

A mixture of **2** (0.01 mmol) and thioglycolic acid (10 ml) in dry dioxane (20 ml) was refluxed for 12 h, the reaction mixture was concentrated and neutralized with K₂CO₃ solution. The solid obtained was filtered off and recrystallized to give **3a-c** (Table III).

Carboxymethyl Derivative 4

A mixture of **2d** (0.01 mmol) and monochloroacetic acid (0.01 mmol) in DMF (20 ml) was refluxed for 4 h, cooled, and poured onto ice. The solid obtained was filtered and crystallized to give **4** (Table III).

Imidazolinone 6

A mixture of **1a** (0.01 mmol) and oxazolidin-4-one **5** (0.01 mmol) in dry pyridine (10 ml) was refluxed for 4 h, cooled, and poured onto ice-HCl. The solid obtained was filtered and crystallized to give **6** (Table III).

Pyridine-2,3-dicarboximide Derivative 8

A mixture of **1b** (0.01 mmol) and pyridine-2,3-dicarboxylic anhydride **7** (0.01 mmol) in glacial acetic acid (20 ml) was heated under reflux for 4 h, cooled, and poured onto ice. The solid obtained was filtered off and crystallized to give **8** (Table III).

Quinazolinone 10

A mixture of **1b** (0.01 mmol) and quinazolin-4-one **9** (0.01 mmol) in dry pyridine (15 ml) was heated under reflux for 8 h, cooled, and poured onto ice and HCl. The solid obtained was filtered off and crystallized to give **10** (Table III).

3,4-Diamino-1,2,4-triazin-5-ones 11a-k & 3,5-Disubstituted Amino Benzoic Acid 11l

A mixture of **1a** and/or **1b** (0.01 mmol) and primary amines, such as, hydroxylamine hydrochloride, cyanoguanidine, furylamine, 2-amino-thiazole, 2-amino-6-methylpyridine, 4-aminophenol, 4-aminosalicylic

acid, sulfanilamide, sulfapyrimidine, sulfadimidine, sulfaisoxazole, and 3,5-diaminobenzoic acid (0.01 mmol) in DMF (20 ml) was refluxed for 12 h, cooled, and poured onto ice. The solid obtained was filtered off and recrystallized to give **11a-m** (Table III).

1,2,4-Triazolidino[5,1-c][1,2,4]triazin-4,7-dione 12

A mixture of **11d** (0.01 mmol) and ethyl chloroformate (0.01 mmol) in DMF (20 ml) was refluxed for 8 h, cooled, and poured onto ice. The solid obtained was filtered off and crystallized to give **12** (Table III).

1,2,4-Triazino[4,3-b][1,2,4]triazine 13

A mixture of **11h** (0.01 mmol) and monochloroacetic acid (0.01 mmol) in aq. NaOH (10%) was refluxed for 4 h, cooled, and poured onto ice and HCl. The solid obtained was filtered off and crystallized to give **13** (Table III).

1,2,4-Triazino[4,3-b][1,2,4]triazin-4-one 14

A mixture of **11j** (0.01 mmol) and bromoacetaldehyde diethyl acetal (0.01 mmol) in sodium ethoxide (0.02 mmol Na, 20 ml abs. EtOH) was refluxed for 4 h, cooled, and poured onto ice and HCl. The solid obtained was filtered off and crystallized to give **14** (Table III).

1,2,4-Triazino[5,1-c][1,2,4]triazin-one 15

A mixture of **1a** and/or **1b** (0.01 mmol) and cyanamide (0.01 mmol) in DMF (20 ml) was refluxed for 12 h, cooled, and poured onto ice. The solid obtained was filtered off and crystallized to give **15a,b** (Table III).

Perhydro 1,2,4-Triazino[4,3-b][1,2,4]triazin-4-one 16

A mixture of **1b** (0.01 mmol) and ethanolamine (0.01 mmol) was refluxed for 8 h, cooled, and poured onto ice-MeOH. The solid obtained was filtered off and crystallized to give **16** (Table III).

4-Amino-3-[bis(2-hydroxyethyl)amino][1,2,4]triazin-5-one 17

A mixture of **1b** (0.01 mmol) and diethanolamine (0.01 mmol) in DMF (20 ml) was refluxed for 4 h, cooled, and poured onto ice. The solid obtained was filtered off and crystallized to give **17** (Table III).

4-Acetamido-3-morpholino-1,2,4-triazin-5-one 18

A mixture of **17** (0.01 mmol) and Ac₂O (0.01 mmol) in dry pyridine (10 ml) was refluxed for 6 h, cooled, and poured onto ice. The solid obtained was filtered off and crystallized to give **18** (Table III).

4-Amino-3-morpholino-1,2,4-triazin-5-one 19

A mixture of **1b** (0.01 mmol) and morpholine (0.01 mmol) in DMF (10 ml) was refluxed for 8 h, cooled, and poured onto ice. The solid obtained was filtered off and crystallized to give **19** (Table III).

Formation of 18 From 19

A mixture of **19** (0.01 mmol) and Ac₂O (0.01 mmol) was refluxed for 4 h, cooled, and poured onto ice. The solid obtained was filtered off and crystallized to give **18** (Table III).

1,2-Disubstituted Hydrazines 20a–c

A mixture of **1b** (0.01 mmol) and hydrazine hydrate (0.04 mmol) in EtOH (30 ml) and/or 2,4-dinitrophenyl hydrazine (0.01 mmol) in DMF (20 ml) and/or thiocarbohydrazide (0.005 mmol) in DMF (20 ml) was refluxed for 4 h, cooled, and poured onto ice. The solid obtained was filtered off and crystallized to give **20** (Table III).

1,2,4-Triazino[4,3-b][1,2,4,5]tetrazin-3,6-dione 21

A mixture of **20a** (0.01 mmol) and ethyl chloroformate (0.02 mmol) in DMF (20 ml) was refluxed for 8 h, cooled, and poured onto ice. The solid obtained was filtered off and crystallized to give **21** (Table III).

2,7-Disubstituted-3-thioxo-1H,4H-1,2,4-triazino[4,3-e]-1,2,4,5-tetra-azaperhydroin-6-ones (22 and 23)

A mixture of **20a** and **20b** (0.01 mmol) and carbon disulfide (0.02 mmol) in EtOH (20 ml) and KOH (10%), was refluxed for 4 h, cooled, and poured onto ice-HCl. The solid obtained was filtered off and crystallized to give **22** and **23** (Table III). UV absorptions of **22** were observed at λ_{\max} 430, 410, 380, 325, and 268 nm while that of **23** at 439, 412, 389, 330, and 270 nm.

1,2,4-Triazino[3,4-c][1,2,4,5]tetrazin-6-one **24–26**

A mixture of **20a** and/or **20b** (0.01 mmol) and furyl benzoyl chloride or 4-chlorobenzoyl chloride (0.01 mmol) in DMF (20 ml) was refluxed for 6 h, cooled, and poured onto ice. The solid obtained was filtered off and crystallized to give **24**, **25** and **26** respectively (Table III).

Tris-thioxotriazine **27**

A mixture of **20c** (0.01 mmol) and carbondisulfide (0.04 mmol) in EtOH (20 ml) and KOH (10%), was refluxed for 4 h, cooled, and poured onto ice-HCl. The solid obtained was filtered off and crystallized to give **27** (Table III).

REFERENCES

- [1] L. Eue and H. Tietz, *Pflanzenschutz-Nachr.*, **23**, 208 (1970); *Chem. Abstr.*, **77**, 330196a (1972).
- [2] R. M. Abdel-Rahman, J. M. Morsy, F. Hanafy, and H. A. Amine, *Pharmazie*, **54**, 347 (1999).
- [3] R. M. Abdel-Rahman, J. M. Morsy, S. El-Edfawy, and H. A. Amine, *Pharmazie*, **54**, 667 (1999).
- [4] R. M. Abdel-Rahman, M. Seada, M. Fawzy, and I. El-Baz, *Pharmazie*, **49**, 729 (1994).
- [5] R. M. Abdel-Rahman, M. Seada, M. Fawzy, and I. El-Baz, *Pharmazie*, **49**, 811 (1994).
- [6] A. M. Abdel-Halim, Z. El-Gendy, and R. M. Abdel-Rahman, *Pharmazie*, **50**, 726 (1995).
- [7] B. S. Holla, R. Gonsalves, and M. K. Shivananda, *Boll. Chim. Farmaceutico*, **137**, 93 (1998).
- [8] J. P. Laverigne, P. Viallefont, and J. Daunis, *J. Heterocycl. Chem.*, **12**, 1095 (1975).
- [9] E. Kranz, H. J. Santel, and R. R. Schmidt, (Bayer A.-G.) Eur. Pat. Appl. Ep., **374**, 622 (1990); *Chem. Abstr.*, **113**, 773, 212022 k (1990).
- [10] M. R. Boyed, *Proc. Am. Assoc. Cancer Res.*, **30**, 653 (1989).
- [11] M. R. Grever, S. A. Schepartz, and B. A. Chabner, The National Cancer Institute; Cancer Drug Discovery and Development Program; Seminars Oncology, **19**(6) December (1992), p. 622.
- [12] R. M. Abdel-Rahman, M. Seada, M. M. Fawzy, and I. El-Baz, *Farmaco*, **48**, 397 (1993).
- [13] R. M. Abdel-Rahman, *Farmaco*, **46**, 379 (1991).
- [14] R. M. Abdel-Rahman, *Farmaco*, **47**, 319 (1992).
- [15] Z. El-Gendy, J. Morsy, H. A. Allimony, W. R. Abdel-Monem, and R. M. Abdel-Rahman, *Pharmazie*, **56**(5), 376 (2001).