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### SYNTHESIS OF SOME NEW THIADIAZOLE, SELENA, TRIAZINE, THIAZOLE AND CYANOPYRIDINE DERIVATIVES WITH ASSAY FOR THEIR ANTITUMOR ACTIVITY

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# **SYNTHESIS OF SOME NEW THIADIAZOLE, SELENA, TRIAZINE, THIAZOLE AND CYANOPYRIDINE DERIVATIVES WITH ASSAY FOR THEIR ANTITUMOR ACTIVITY**

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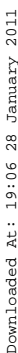
*(Received May 1, 1995; in final form July 22, 1995)*

The synthesis of 2-methyl-3-(4'-acetylphenyl)-quinazol-4-one **II** was accomplished by the condensation of the benzoxazine **I** with 4-aminoacetophenone. The semicarbazone **III** was obtained from **II** by refluxing with an equimolar amount of semicarbazide hydrochloride in ethanol. The latter compound was then subjected to oxidative cyclization either by thionyl chloride or selenium dioxide to give thiadiazole and seleno derivatives **IV** and **V**, respectively. Compound **V** was condensed with different aromatic amines to yield the corresponding Schiff's bases **VI**. The phenylglyoxal derivative **VII** was prepared by oxidation of **II** with selenium dioxide. Condensation of **VII** with thiosemicarbazide in ethanol in the presence of potassium carbonate gave 3-mercapto-1,2,4-triazine derivative **VIII**. Treatment of **II** with bromine in acetic acid gave the bromo derivative **IX** which was reacted with thiourea to give 2-amino-thiazole derivative **X**. Cyanopyridine-2-(1*H*)-thione derivatives **XIVa–h** were obtained via the reaction of arylmethylenecyanothioacetamide **XI** with active methylene carbonyl compound **II**. Assay for anti-tumor activity showed that compound **XIVc** has a significant activity against Ehrlich Ascites Carcinoma tumor cells (in vitro) and displayed a significant percent of the non viable tumor cells to about 40% and 80% at concentration of 10 and 100 ng, respectively.

**Key words:** Thiadiazole, seleno, triazine, thiazole, cyanopyridines, antitumor activity.

## **INTRODUCTION**

Several new compounds bearing a 4(3*H*)-quinazolinone system seem to be active in various biological and pharmacological areas.<sup>1–5</sup> Recently, particular importance has been attributed to compounds containing an aromatic nucleus with a sulfur or thione



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group as anticancer and antimitotic agents.<sup>6-9</sup> On this basis we studied the synthesis of various new thiadiazole, seleno, 1,2,4-triazine, 2-aminothiazole, and cyanopyridine-2(1*H*)-thione derivatives bearing a 4(3*H*)-quinazolinone moiety to evaluate their antitumor activity. The sequence of reactions leading to the formation of the title compounds is depicted in Scheme I.

#### EXPERIMENTAL

Melting points reported are uncorrected. IR spectra (KBr) on a FT-IR 1650 spectrophotometer ( $\nu$  max in  $\text{cm}^{-1}$ ) and  $^1\text{H}$ -NMR spectra in ( $\text{DMSO}-d_6$ ) solution with TMS as internal standard ( $\delta$ , ppm) were recorded on a JEOL FXQ 90 MHz NMR spectrometer. Mass spectra were run using HP MODEL MS 5988.

**2-Methyl-6-iodo-3-(4'-acetylphenyl)quinazol-4-one II:** A mixture of 4-aminoacetophenone (0.01 mol) and  $\text{I}^{10}$  (0.01 mol) was heated at 210 degree centigrade in an oil-bath for 10 minutes. The mixture was cooled and then washed with dilute HCl and water. The solid obtained was recrystallized from acetic acid to give II (Table I).

TABLE I  
Physico-chemical and analytical data of compounds II–XIVa–h

Compd. No.	M.P. Degree Centigrade	Yield %	Mol-formula	Analysis		
				Required / Found		
				C%	H%	N%
II	207	62	$\text{C}_{17}\text{H}_{11}\text{IN}_2\text{O}_2$	50.49	3.22	06.93
				50.60	3.10	06.80
III	268	78	$\text{C}_{18}\text{H}_{16}\text{IN}_3\text{O}_2$	46.85	3.47	15.18
				46.80	3.60	15.30
IV	231	52	$\text{C}_{17}\text{H}_{11}\text{IN}_4\text{O S}$	45.84	2.24	12.58
				45.70	2.10	12.70
V	167	57	$\text{C}_{17}\text{H}_9\text{IN}_4\text{O}_2 \text{ Se}$	40.31	1.58	11.07
				40.40	1.70	11.20
VIa	294	61	$\text{C}_{21}\text{H}_{13}\text{IFN}_5\text{OSe}$	46.07	2.00	11.68
				46.00	2.10	11.80
b	246	59	$\text{C}_{21}\text{H}_{13}\text{ICIN}_5\text{OSe}$	44.88	1.95	11.38
				44.80	1.80	11.50
VII	188	63	$\text{C}_{17}\text{H}_{11}\text{IN}_2\text{O}_3$	48.80	2.63	06.70
				48.70	2.70	06.80
VIII	175	58	$\text{C}_{18}\text{H}_{12}\text{IN}_3\text{O S}$	45.66	2.53	14.80
				45.80	2.60	14.90
IX	185	82	$\text{C}_{17}\text{H}_{12}\text{IBrN}_2\text{O}_2$	42.23	2.48	05.80
				42.30	2.60	05.70
X	238	71	$\text{C}_{18}\text{H}_{13}\text{IN}_4\text{OS}$	47.06	2.61	12.20
				47.20	2.50	12.10
XIVa	298	84	$\text{C}_{27}\text{H}_{17}\text{IN}_4\text{OS}$	56.64	2.97	09.80
				56.60	2.80	09.90
b	295	81	$\text{C}_{28}\text{H}_{19}\text{IN}_4\text{OS}$	57.33	3.24	09.55
				57.40	3.30	09.70
c	317	79	$\text{C}_{28}\text{H}_{19}\text{IN}_4\text{O}_2\text{S}$	55.81	3.15	09.30
				55.90	3.20	09.40
d	227	82	$\text{C}_{27}\text{H}_{16}\text{ICl N}_4\text{OS}$	53.46	2.64	09.24
				53.60	2.70	09.30
e	167	64	$\text{C}_{27}\text{H}_{15}\text{ICl}_2 \text{ N}_4\text{OS}$	50.54	2.34	08.73
				50.70	2.40	08.80
f	301	85	$\text{C}_{27}\text{H}_{16}\text{IBrN}_4\text{OS}$	49.76	2.45	08.60
				49.90	2.60	08.50
g	192	59	$\text{C}_{26}\text{H}_{16}\text{IN}_5\text{OS}$	54.45	2.79	12.21
				54.60	2.90	12.30
h	188	62	$\text{C}_{25}\text{H}_{16}\text{IN}_4\text{O S}_2$	51.81	2.76	09.67
				51.70	2.60	09.80

**2-Methyl-6-iodo-3-[4'-(1'-semicarbazonoethyl)phenyl]quinazol-4-one III:** To a solution of **II** (0.01 mol) in ethanol (50 ml) was added a solution of semicarbazide hydrochloride (0.01 mol) and sodium acetate (0.02 mol) in water (20 ml). The reaction mixture was refluxed for one hour, evaporated to one half of its volume, and then poured into ice-water. The precipitated solid was filtered, washed with water, dried and recrystallized from dioxan to give **III** (Table I).

**2-Methyl-6-iodo-3-[4'-(1',2',3'-thiadiazol-4-yl)phenyl]quinazol-4-one IV:** Thionyl chloride (20 ml) was gradually added to the semicarbazone **III** (0.01 mol), and the mixture was gently warmed and then left for 24 hr at room temperature. An ice-cold saturated  $\text{NaHCO}_3$  solution was then added, and the product obtained was recrystallized from ethanol to give **IV** (Table I).

**2-Formyl-6-iodo-3-[4'-(1',2',3'-selenadiazol-4-yl)phenyl]quinazol-4-one V:** The semicarbazone **III** (0.01 mol) was dissolved in boiling glacial acetic acid (50 ml). To this boiling solution was added portionwise, with stirring, powdered selenium dioxide (0.012 mol). After complete addition, boiling and stirring were continued for 1 hr. The reaction mixture was then filtered into ice water, and the solid obtained was recrystallized from ethanol to give **V** (Table I).

**2-Arylazomethine-6-iodo-3-[4'-(1',2',3'-selenadiazole-4-yl)phenyl]quinazol-4-one VIa,b:** To a solution of **V** (0.01 mol) in absolute ethanol (20 ml) was added the appropriate primary aromatic amine (0.01 mol). The reaction mixture was refluxed for 2 hr, concentrated, cooled, and filtered. The Schiff's bases so obtained were recrystallized from ethanol to give **VIa,b** (Table I).

**Formation of Glyoxal Derivative VII:** A mixture of **II** (0.01 mol) was dissolved in dioxan (30 ml). To this boiling solution was added portionwise, with stirring, powdered selenium dioxide (0.012 mol). After complete addition, boiling and stirring were continued for 2 hr. The reaction mixture was then filtered into ice water, and the solid obtained was recrystallized from ethanol to give **VII** (Table I).

**2-Methyl-6-iodo-3-[4'-(3'-mercapto-1',2',4'-triazine)phenyl]quinazol-4-ones VIII:** A mixture of **VII** (0.01 mol), thiosemicarbazide (0.01 mol), and anhydrous  $\text{K}_2\text{CO}_3$  in ethanol (50 ml) was refluxed for 16 hr. The reaction mixture was filtered while hot, and the solid obtained was recrystallized from ethanol to give **VIII** (Table I).

**Formation of the Bromo Derivative IX:** To a solution of **II** (0.01 mol) in glacial acetic acid (50 ml) was added dropwise at 60–70 degree centigrade bromine (0.02 mol). The solution was further stirred for 2 hr, then cooled in an ice bath. The precipitated product was filtered off, washed with light petroleum 40–60 degree centigrade and stirred with ammonium hydroxide for 15 minutes. The solid obtained was recrystallized from ethanol to give **IX** (Table I).

**Formation of 2-Aminothiazole Derivative X:** A mixture of **IX** (0.01 mol) and thiourea (0.01 mol) in ethanol (50 ml) in presence of sodium hydroxide (0.1g) was refluxed for 5 hr. The solid obtained after concentration and cooling was recrystallized from ethanol to give **X** (Table I).

**Formation of Cyanopyridinethione Derivatives XIVa–h or XVa–h:** A mixture of **II** (0.01 mol), arylmethylenecyanothioacetamides **XI<sup>11</sup>** (0.01 mol) in ethanol (50 ml) containing ammonium acetate (1 g) was refluxed for 5 hr. The reaction mixture was cooled, filtered, washed with water, dried, and recrystallized from ethanol to give **XIVa–h** or **XVa–h** (Table I).

## RESULTS AND DISCUSSION

The aim of this work was the synthesis of some new compounds containing a sulfur atom to evaluate their antitumor activity.

Thus, 4-aminoacetophenone was treated with 2-methyl-6-iodo-3,1-benzoxazine-4-one **I<sup>10</sup>** to produce the corresponding 2-methyl-6-iodo-3-(4'-acetylphenyl)quinazol-4-one **II**. The condensation was achieved by heating the reaction to just over their melting points for a few minutes with the elimination of water. IR analysis of **II** revealed bands at  $1710, 1680\text{ cm}^{-1}$  ( $2\text{C}=\text{O}$ ).  $^1\text{H-NMR}$  analysis of **II** (in  $\text{DMSO}-d_6$ ) showed signals at  $\delta$  2.2 [s, 3H,  $\text{CH}_3$ ]; 2.9 [s, 3H,  $\text{COCH}_3$ ], 7.5–8.8 [m, 7H, Ar—H].

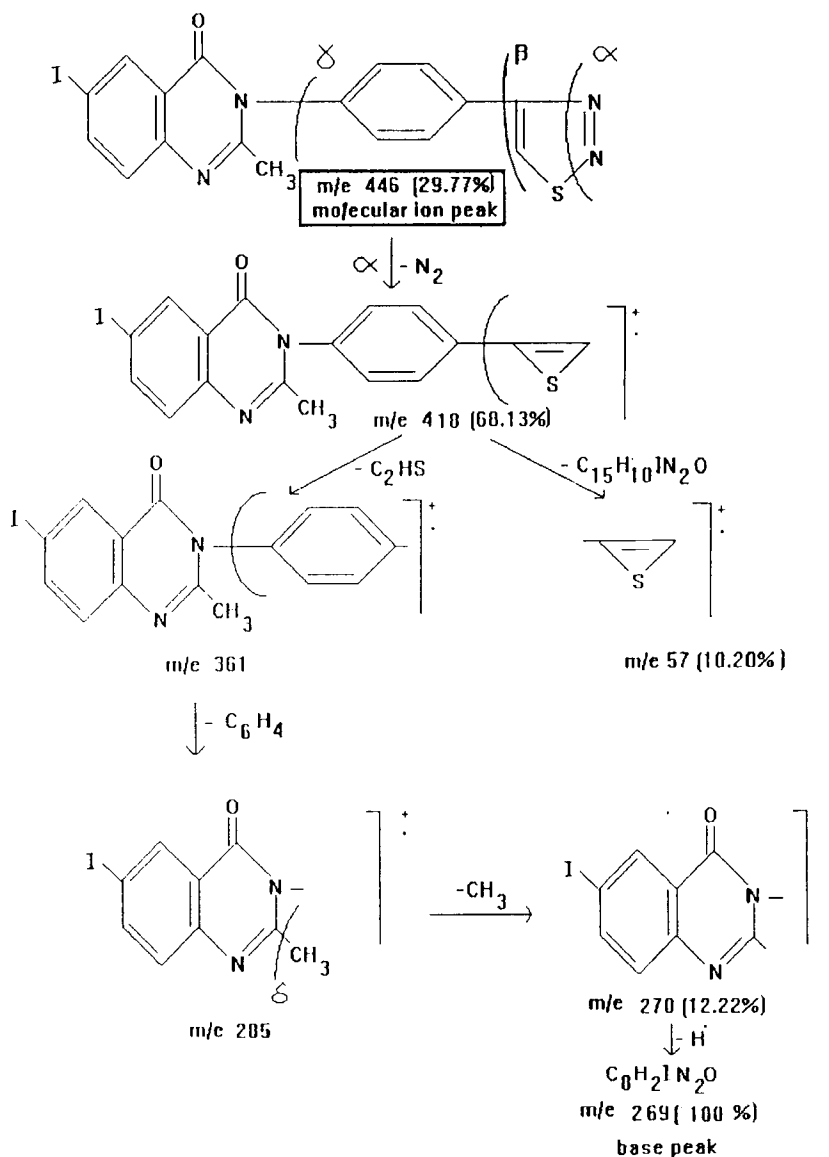


FIGURE 1 Mass fragmentation pattern of compound (IV).

Compound **II** was condensed with semicarbazide hydrochloride in aqueous ethanol solution and gave the semicarbazone **III**. IR analysis of **III** showed bands at 3400, 3350  $\text{cm}^{-1}$  ( $\text{NH}_2$ ,  $\text{NH}$ ) and 1700, 1690  $\text{cm}^{-1}$  ( $2\text{C}=\text{O}$ ).

The semicarbazone **III** was allowed to react with thionyl chloride to give 2-methyl-6-iodo-3-[4'-(1',2',3'-thiadiazole-4-yl)phenyl]-quinazol-4-one **IV**. The IR analysis of **IV** showed the absence of  $\text{NH}_2$  and the presence of a characteristic absorption due to  $\text{C}-\text{S}$  of a thiadiazole at 700–760  $\text{cm}^{-1}$ . The mass spectrum of **IV** showed a

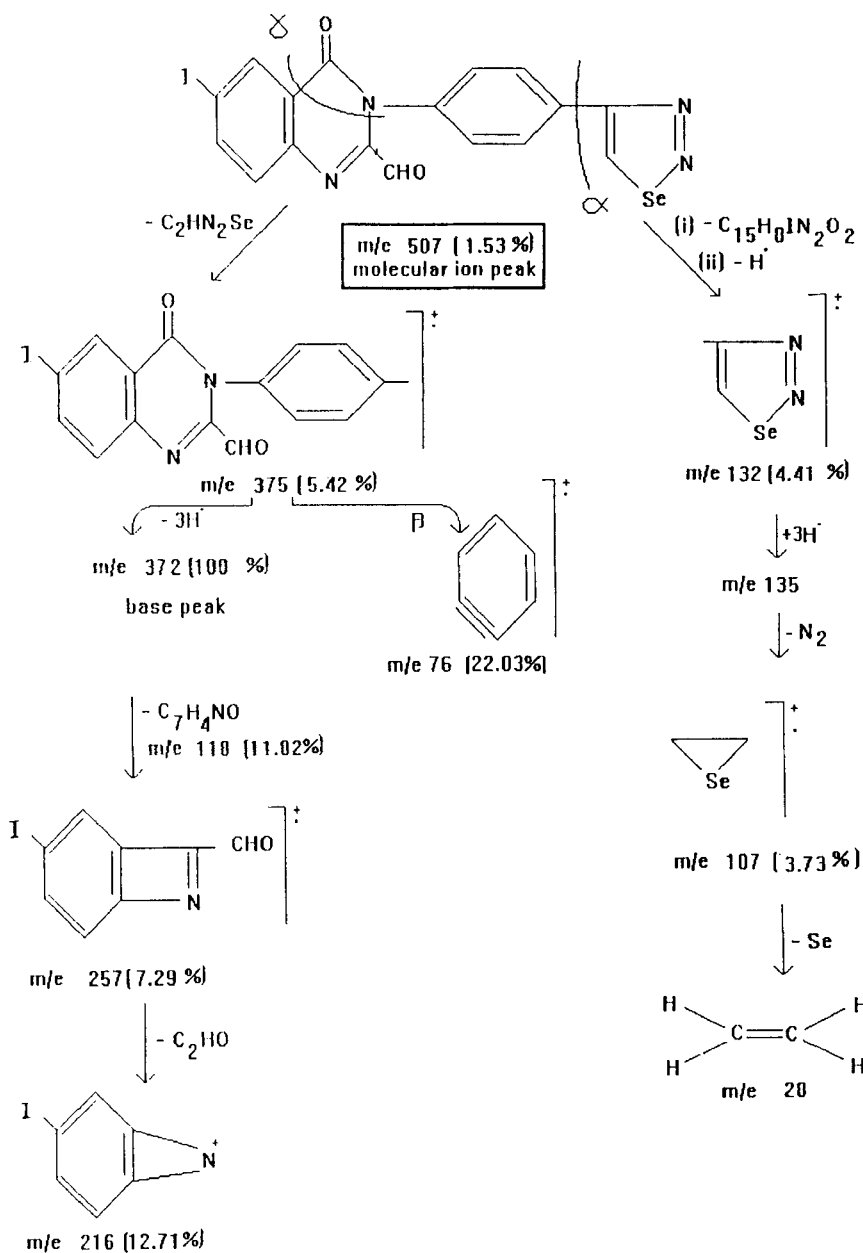


FIGURE 2 Mass fragmentation pattern of compound (V).

molecular ion peak at  $m/z$  446 (29.77%) with a base peak at 269 (100%) (Figure 1).

Again the semicarbazone **III** was oxidized by selenium dioxide in glacial acetic acid to give **V**. The IR analysis of **V** showed absorption bands at  $830\text{ cm}^{-1}$  due to

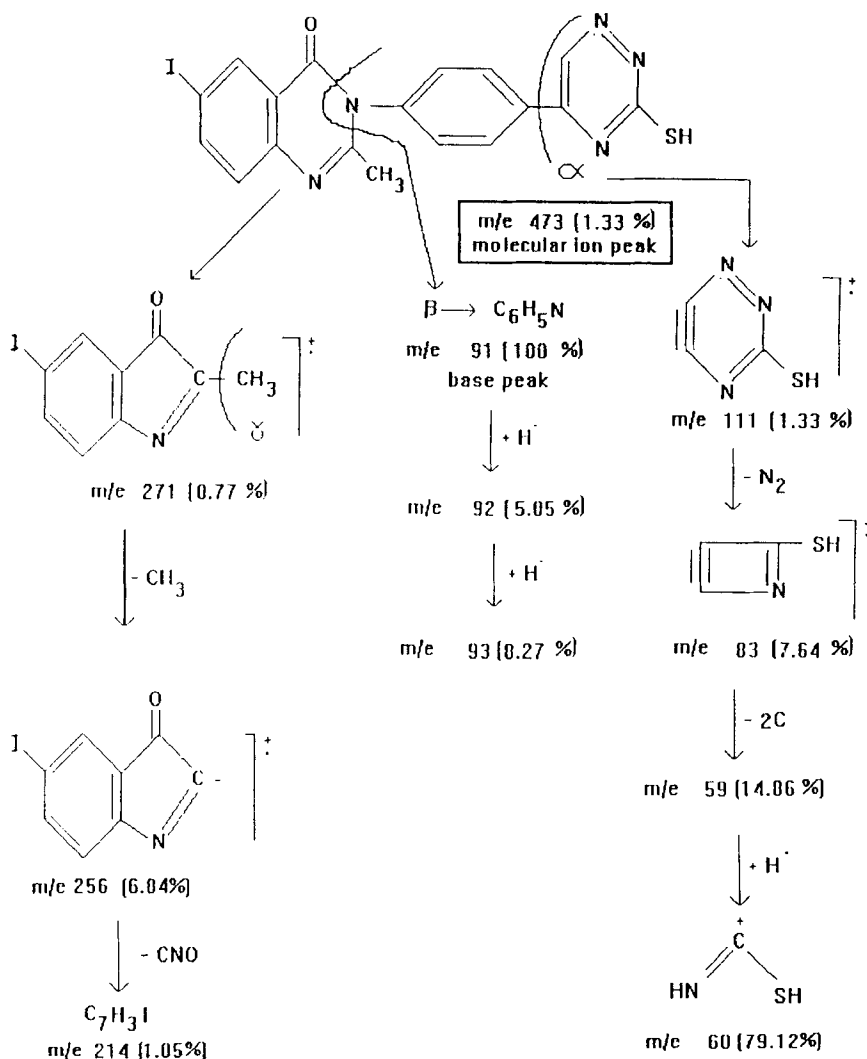


FIGURE 3 Mass fragmentation pattern of compound (VIII).

C—Se—N and at  $1590\text{ cm}^{-1}$  ( $C=N$ ). The mass spectrum exhibited a molecular ion peak  $m/z$  507 (1.53%) with a base peak at 372 (100%) (Figure 2).

Interaction of **V** with primary aromatic amines in ethanol gave the corresponding azomethines **VI**. The IR analysis showed the presence of a strong absorption band around  $1620\text{ cm}^{-1}$  characteristic for ( $C=N$ ) of azomethine group.

Phenylglyoxal derivative **VII** was prepared by the oxidation of **II** with selenium dioxide in dioxan. The IR analysis showed bands at  $1690$  and  $1650\text{ cm}^{-1}$  ( $2C=O$ ). The  $^1\text{H-NMR}$  analysis of **VII** (in  $\text{DMSO-}d_6$ ) exhibited signals at  $\delta$  2.2 [s, 3H,  $\text{CH}_3$ ], 6.0 [s, 1H, CHO], and 7.8–9.0 [m, 7H, Ar—H].

Further condensation of phenylglyoxal derivative **VII** with thiosemicarbazide resulted in the formation of the corresponding thiosemicarbazone derivative which was



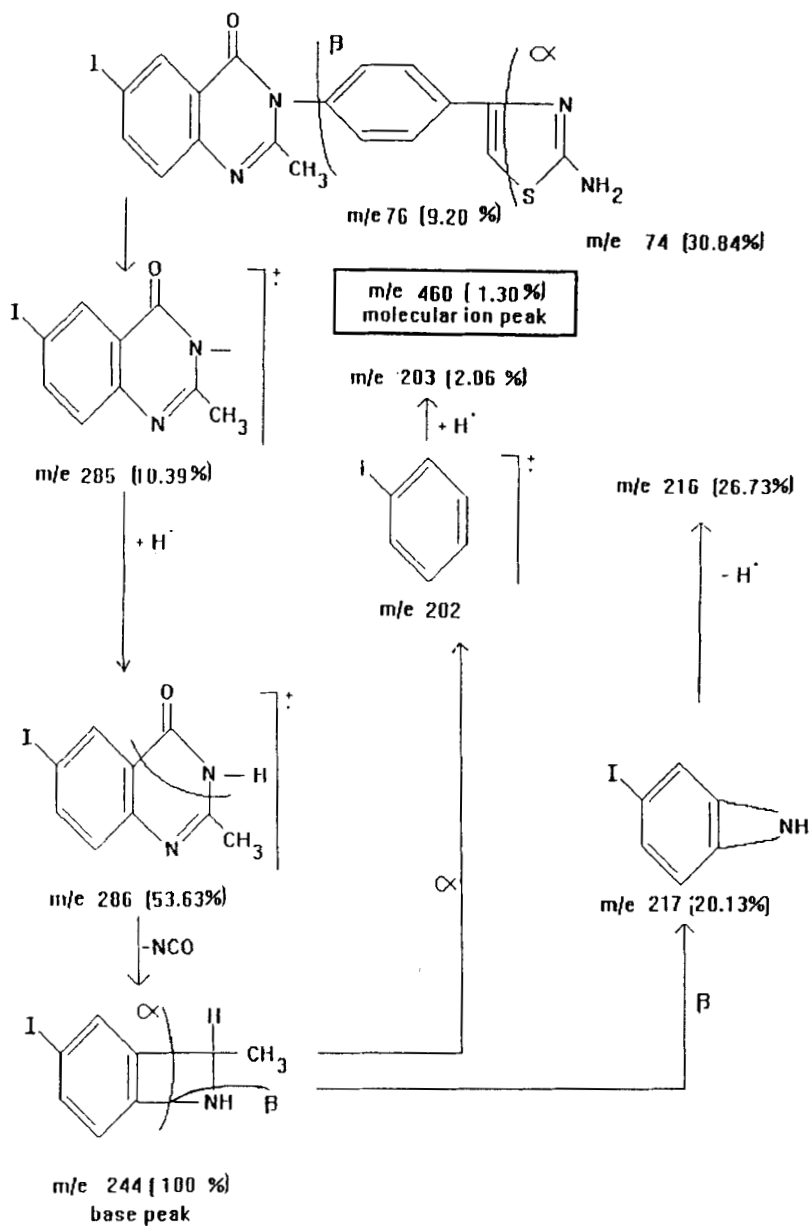


FIGURE 4 Mass fragmentation pattern of compound (X).

cyclized *in situ* to yield 3-mercapto-1,2,4-triazine derivative **VIII**. The IR analysis of **VIII** showed bands at  $3270\text{ cm}^{-1}$  (N—H stretching),  $1650\text{ cm}^{-1}$  (C=O), and  $1285\text{ cm}^{-1}$  C=S. The mass spectrum of **VIII** exhibited a molecular ion peak  $m/z$  473 (1.33%) with a base peak at 91 (100%) (Figure 3).

Treatment of **II** with bromine in acetic acid gave the bromo derivative **IX**. The

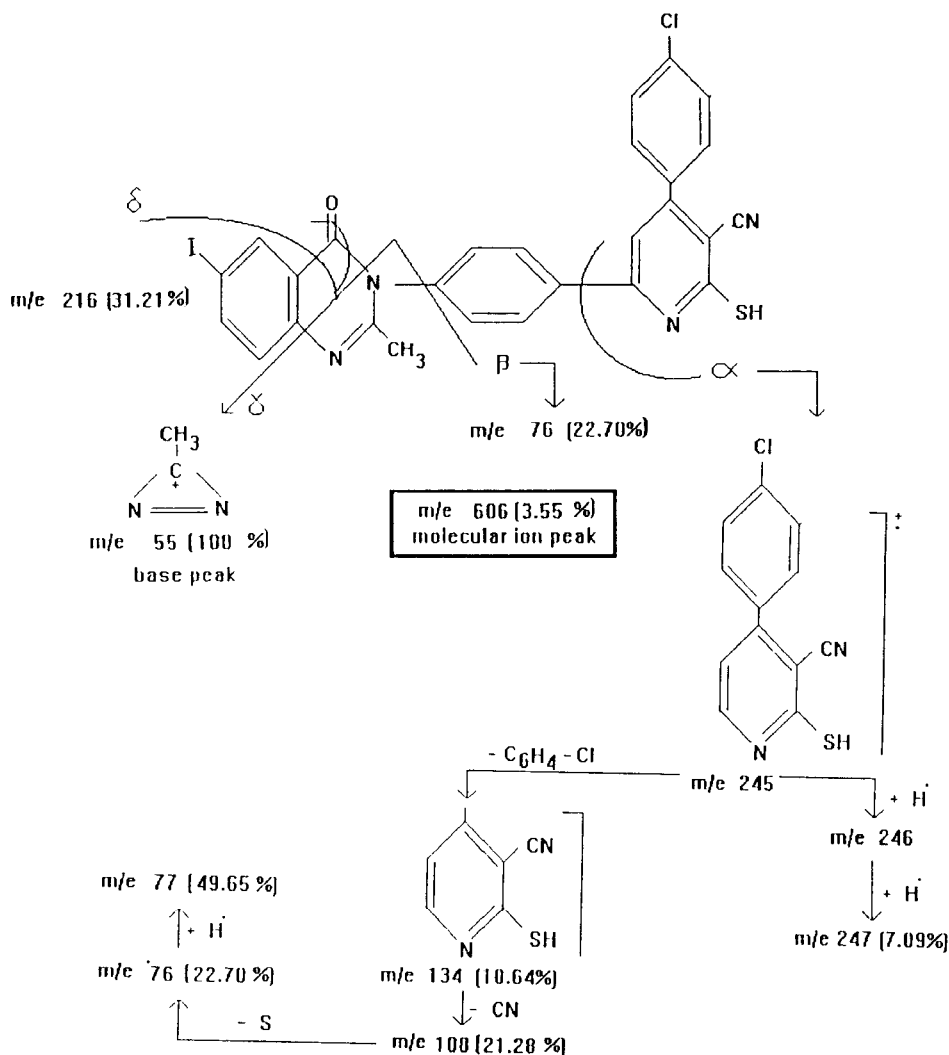


FIGURE 5 Mass fragmentation pattern of compound (XIVd).

$^1H$ -NMR analysis of IX (in  $DMSO-d_6$ ) showed signals at  $\delta$  2.2 [s, 3H,  $CH_3$ ], 3.7 [s, 2H,  $CH_2-Br$ ], and 7.5–8.9 [m, 7H, Ar—H].

Treatment of the bromo derivative IX with thiourea in the presence of sodium hydroxide yielded the corresponding 2-aminothiazole derivative X. The IR analysis of X showed bands at  $3320\text{ cm}^{-1}$  ( $NH_2$ ) and  $1680\text{ cm}^{-1}$  ( $C=O$ ). The mass spectrum of X exhibited a molecular ion peak  $m/z$  460 (1.30%) with a base peak at 244 (100%) (Figure 4).

The cyanopyridine-2(1*H*)-thione derivative XIVa–h or XVa–h were obtained via the reaction of arylmethylenecyanothioacetamide XI<sup>11</sup> with active methylene carbonyl compound II. Thus, it was found that XI reacted with II in refluxing ethanol containing ammonium acetate to give cyanopyridine-2-(1*H*)-thiones. This reaction

was proceeded via a Michael-type addition of the methyl function in **II** to the activated double bond in **XI** to yield **XII** which then lost H<sub>2</sub>O. The product oxidized to give cyanopyridine-2-(1*H*)-thione derivatives **XIVa–h** or **XVa–h**. The IR analysis of **XIVc** showed bands at 3200 cm<sup>-1</sup> (NH), 3080 cm<sup>-1</sup> (CH aromatic), 2900 cm<sup>-1</sup> (CH aliphatic), 2200 cm<sup>-1</sup> (C≡N), 1690 cm<sup>-1</sup> (C=O) and 1620 cm<sup>-1</sup> (C=N). The IR analysis of **XIVd** exhibited bands at 3340 cm<sup>-1</sup> (NH) and 2200 cm<sup>-1</sup> (C≡N). The <sup>1</sup>H-NMR analysis of **XIVc** (in DMSO-*d*<sub>6</sub>) exhibited signals at δ 2.4 [s, 3H, CH<sub>3</sub>], 3.5 [s, 3H, OCH<sub>3</sub>], 7.3–8.9 [m, 11H, Ar—H], 8.7 [s, 1H, CH-pyridine ring], and 12.9 [bs, 1H, NH, exchangeable-D<sub>2</sub>O]. The mass spectrum of **XIVd** showed a molecular ion peak *m/z* 606 (3.55%) with a base peak at 55 (100%) (Figure 5).

### *Antitumor Activity: (In Vitro Study)*

#### *Reagents*

1. RPMI 1640 medium (Sigma)
2. Ehrlich Ascites Carcinoma cells (EAC), suspension (2.5 · 10<sup>5</sup>/ml)
3. Trypan blue dye

A stock solution was prepared by dissolving one gram of the dye in (100 ml) distilled water. The working solution was then prepared by diluting (1 ml) of the stock solution with (9 ml) of distilled water. The stain was used then for staining the dead EAC cells.

4. The compounds tested were **XIVa**, **XIVb**, **XIVc**, and **XIVd**.

#### *Procedure*

1. EAC cells were obtained by needle aspiration of ascitic fluid from the pre-inoculated mice under aseptic conditions.<sup>12</sup>

2. The cells were tested for viability and contamination by staining certain cell-volume of this fluid by an equal volume of the working solution of trypan blue dye.<sup>13,14</sup>

3. The ascitic fluid was diluted to 1:10 with saline to contain 2.5 · 10<sup>6</sup> cells on a hemocytometer.

4. In a set of sterile test tubes 0.1 ml of tumor cells suspension, 0.8 ml RPMI 1640 media and 0.1 ml of each tested compound (corresponding to 0.1, 1.0, 10, 10<sup>2</sup>, 10<sup>3</sup>, 10<sup>4</sup>, 10<sup>5</sup> and 10<sup>6</sup> ng) were mixed. The test tubes were incubated at 37 degree centigrade for 2 hr. Trypan blue<sup>13,14</sup> exclusion test was carried out to calculate the percentage of non viable cells. Compounds producing more than 70% non viable cells are considered active.<sup>15</sup>

$$\% \text{ of non-viable cells} = \frac{\text{No. of non-viable}}{\text{Total No. of cells}} \times 100$$

The results of antitumor activity for the synthesized compounds indicated that compounds **XIVc** and **XIVd** showed a significant activity toward Ehrlich Ascites Carcinoma tumor cells (in vitro). The active compounds having a methoxy group **XIVc** and chloro group **XIVd** were found to have more powerful activity than the other compounds (Table II).

TABLE II  
In vitro study of antitumor activity of compounds XIVa–d

Compound No. Concentration (ng)	% Viability			
	XIVa	XIVb	XIVc	XIVd
0.1	100	100	90	100
1.0	100	100	90	100
10	100	100	60	100
10 <sup>2</sup>	100	80	20	100
10 <sup>3</sup>	100	80	0	80
10 <sup>4</sup>	100	50	0	50
10 <sup>5</sup>	90	50	0	50
10 <sup>6</sup>	70	50	0	30

"0" All cells are non viable

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