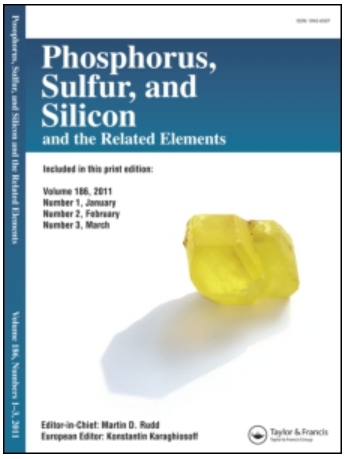

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NOVEL QUINAZOLONE DERIVATIVES AS ANTITUMOR AGENTS

M. M. Ghorab[a]; S. G. Abdel-hamide[b]; S. M. El-sayed[c]
[a] Department of Drug Radiation Research, National Centre for Radiation Research and Technology, (NCRRT), Nasr City, Cairo, Egypt [b] Pharmaceutical Chemistry Department, Faculty of Farmacy, Al-Azhar University, Nasr City, Cairo, Egypt [c] Biology Department, National Centre for Radiation Research and Technology, Cairo, Egypt

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M.M. GHORAB[a*], S.G. ABDEL-HAMIDE[b] and S.M. EL-SAYED[c]

[a]*Department of Drug Radiation Research, National Centre for Radiation Research and Technology, (NCRRT), P.O. Box 29, Nasr City, Cairo, Egypt.*, [b]*Pharmaceutical Chemistry Department, Faculty of Farmacy, Al-Azhar University, Nasr City, Cairo, Egypt and* [c]*Biology Department, National Centre for Radiation Research and Technology, Cairo, Egypt*

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A novel series of quinazolones bearing 2-benzoylmethylthio **3**, 2-benzoylmethylsulfonyl **4**, 1,3,4-oxadiazine **6**, 1,2,4-triazine **7**, ethyl ester **8**, pyrazolidine-3,5-dione **9**, semicarbazide **10**, 1,2,4,5-tetrazine-3-one **11**, pyridazine-3,5-dione **12, 13**, hydrazonoacetic acid **14**, pyridazine-3,6-dione **16**, pyrazole **17**, 1,2,4-triazine-5-one **18**, triazole **19** and thiosemicarbazide **20** have been synthesized. Their structures have been confirmed on the basis of elemental analyses and (IR, ^{1}H-NMR & Mass) spectral data. Preliminary testing for the in vitro antitumor activity of compounds **1, 3, 4,** and **15–20** against Ehrlich Ascites Carcinoma cells was carried out. The most active compounds are those of chloroacetylhydrazine derivative **15,** pyridazine derivative **16**, sulfonyl derivative **4,** and triazine derivative **18,** respectively.

Keywords: 6-Iodo-3-phenyl-4(3H)-quinazolones; antitumor activity

1 INTRODUCTION

Quinazolinones are excellent reservoir of bioactive substances. A number of biological activities are associated with quinazolinones[1–5], especially antitumor activity[6]. The quinazolone function is quite stable and has inspired medicinal chemists to introduce this stable fragment on bioactive moieties to synthesize new potential medicinal agents. In the present study several heterocyclic rings have been incorporated at position-2 of quinazolinone to result 2-substituted quinazolinones likely to have superior antitumor properties.

* Correspondence author

2 MATERIAL AND METHODS

All melting points are uncorrected and were carried out using capillary tube method. Microanalyses were carried out in the Microanalytical Centre, Cairo University. IR spectra were recorded in KBr on a Pye-Unicam SP 1100 infrared spectrophotometer (νmax in cm^{-1}). ^{1}H-NMR spectra were recorded on a Varian GEMINI 200 instrument 200 MHz, using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are expressed as δ ppm Units. Mass spectra recorded on HP MODEL: MS-5988 at 70 eV. Starting materials (la,b) and (5a,b) were prepared by us as described in a previous publication[5].

2.1 Synthesis

Formation of 6-iodo-2-ethylamino-4H-3,1-benzothiazin-4-one (2)

6-Iodo-3-ethyl-2-thioxo-4(3H)quinazolinone (**1a**, 0.01 mol), was refluxed in 75% conc. sulfuric acid at 120–130° on an oil bath for 10hr. It was cooled and diluted with ice cold water. The product obtained was filtered, washed with 5% sodium bicarbonate solution and finally with distilled water. It was dried and crystallized from dioxane to give (**2**; Table I).

TABLE I Physico-Chemical and analytical data of compounds (2–20)

Compd.	*M. P*	*Yield*		*Analysis*		
No.	*°C*	*%*	*Mol.-formula*	*Required /(Found)*		
				C%	*H%*	*N%*
2	>340	76	$C_{10}H_9N_2OSI$	36.14	2.71	8.43
				(36.40)	(2.50)	(8.10)
3	200–202	82	$C_{22}H_{15}N_2O_2SI$	53.01	3.01	5.62
				(52.80)	(2.90)	(5.90)
4	305–307	63	$C_{22}H_{15}N_2O_4SI$	49.81	2.83	5.28
				(49.50)	(2.70)	(5.50)
6	178–80	56	$C_{24}H_{16}N_4O_2SI$	52.26	2.90	10.16
				(52.10)	(2.60)	(10.40)
7	140–42	52	$C_{24}H_{16}N_5OSI$	52.45	2.91	12.75

Compd. No.	*M. P °C*	*Yield %*	*Mol.-formula*	*Analysis*		
				Required /(Found)		
				C%	*H%*	*N%*
				(52.30)	(2.60)	(12.50)
8	130–32	76	$C_{19}H_{17}N_4O_4SI$	43.51	3.24	10.68
				(43.20)	(3.50)	(10.90)
9	302–304	62	$C_{17}H_{11}N_4O_3SI$	42.67	2.30	11.71
				(42.80)	(2.10)	(11.50)
10	268–70	70	$C_{17}H_{15}N_6O_3SI$	40.00	2.94	16.47
				(39.80)	(2.70)	(16.30)
11	230–32	68	$C_{17}H_{13}N_6O_2SI$	41.46	2.64	17.07
				(41.20)	(2..40)	(17.20)
12	185–87	59	$C_{18}H_{13}N_4O_3SI$	43.90	2.64	11.38
				(43.60)	(2.30)	(11.20)
13	178–80	55	$C_{18}H_{11}N_4O_3SI$	44.08	2.24	11.42
				(44.30)	(2.50)	(11.20)
14	>340	51	$C_{18}H_{13}N_4O_4SI$	42.5 1	2.55	11.02
				(42.30)	(2.70)	(11.30)
15	236–38	86	$C_{18}H_{14}N_4O_3SClI$	40.87	2.64	10.59
				(40.60)	(2.90)	(10.80)
16	281–83	61	$C_{18}H_{13}N_4O_3SI$	43.90	2.64	11.38
				(43.60)	(2.50)	(11.10)
17	272–74	75	$C_{22}H_{18}N_5O_4SI$	45.91	3.13	12.17
				(45.60)	(3.40)	(12.50)
18	296–98	68	$C_{18}H_{14}N_5O_2SI$	43.99	2.85	14.25
				(43.60)	(2.50)	(14.50)
19	300–302	61	$C_{17}H_{12}N_5OS_2I$	41.37	2.43	14.19
				(41.60)	(2.20)	(14.40)
20	177–79	79	$C_{17}H_{14}N_5O_2S_2I$	39.92	2.73	13.69
				(39.70)	(2.50)	(13.90)

Formation of 6-iodo-3-phenyl-2-benzoylmethylthio-4(3H) quinazolinone (3)

A mixture of (**1b**, 0.01 mol); phenacyl bromide (0.01 mol) and anhydrous potassium carbonate (2g) in dry acetone (100 ml) was heated under reflux for 24hr. After cooling and dilution with water, the precipitated solid was filtered, washed with water and crystallized from ethanol to give (**3**, Table I).

Formation of 6-iodo-3-phenyl-2-(benzoylmethylsulfonyl)-4(3H) quinazolinone (4)

To a solution of (**3**; 0.01 mol) in glacial acetic acid (30 ml) were added (0.04 mol) of hydrogen peroxide (30%) and the reaction mixture was stirred at room temperature for **7** days and diluted with water. The resultant precipitate was filtered, washed with water and crystallized from ethanol to give (**4**; Table I).

Formation of 2-[6-iodo-3-phenyl-4(3H)quinazolinone-2-yl) thiomethyl]- 1,3,4-oxadiazine-6-phenyl (6)

A mixture of (**5b**; 0.01 mol) and phenacyl bromide (0.01 mol) in ethanol (50 ml) was refluxed for 2hr, followed by the addition of triethylamine (0.5 ml) with continuous reflux for an extra 2hr. The reaction mixture was concentrated, cooled and filtered. The solid separated out was crystallized from dioxane to give (**6**; Table I).

Formation of 3-[6-iodo-3-phenyl-4(3H)quinazolinone-2-yl) thiomethyl]- 1,2,4-triazine-6-phenyl (7)

A mixture of (**5b**; 0.02 mol) and phenacyl bromide (0.01 mol) in ethanol (50 ml) containing a few drops of dimethylformamide was heated under reflux for 12hr. The solid that separated after cooling was filtered and crystallized from DMF-H_2O to give (**7**; Table I).

Formation of ethyl ester derivative (8)

A mixture of (**5b**; 0.01 mol) and ethyl chloroformate (0.01 mol) in dimethylformamide (10 ml) was heated under reflux for 15 min, cooled and acidified with dilute HCl. The solid obtained was filtered and crystallized from ethanol to give (**8**; Table I).

Formation of 4-[6-iodo-3-phenyl-4(3H)quinazolinone-2-yl) thio]- pyrazolidine-3,5-dione (9)

To a solution of sodium ethoxide [prepared by disolving 0.23g sodium in (20 ml) absolute ethanol] was added **8** and the reaction mixture was refluxed for 3hr. The solid, obtained upon dilution and acidification of the reaction mixture, was filtered and crystallized from dioxane to give (**9**; Table I).

Formation of semicarbazide derivative (10)

A mixture of (**8**; 0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (50 ml) was heated under reflux for 5hr. The solid obtained after cooling was filtered and crystallized from DMF-H_2O to give (**10**; Table 1).

Formation of 6-[6-iodo-3-phenyl-4(3H)quinazolinone-2-yl) thiomethyl]- 1,2,4,5-tetrazine-3-one (11)

Compound **10** was heated at 250° in an oil-bath for 15 min. The solid obtained was triturated with ethanol and crystallized from dioxane to give (**11**; Table I).

Formation of 4-[6-iodo-3-phenyl-4(3H)quinazolinone-2-yl) thio]pyridazine- 6-dihydro-3,5-dione (12)4-[6-iodo-3-phenyl-4(3H) quinazolinone2-yl)thio]pyridazine-3,5-dione (13); hydrazonoacetic acid (14) and 4-[6-iodo-3-phenyl-4(3H)quinazolinone-2-yl)thio] pyridazine-3,6-dione (16).

An equimolecular mixture of **5b** and monochloroacetic acid, dichloroacetic acid, chloroacetaldehyde diethyl acetal or chloroacetyl chloride in aq. NaOH solution (10%, 100 ml) was heated under reflux for 3hr, cooled, diluted with water, and the resultant solid obtained filtered and crystallized from DMF-H_2O to give (**12**, **13**, **14** or **16**), (Table I).

Compound **13** was obtained also via refluxing **14** in sodium ethoxide for 2hr (m.p and mixed m.p).

Formation of chloroacetylhydrazine derivative (15)

A solution of (**5b**; 0.01 mol) in DMF (10 ml) was added chloroacetyl chloride (0.01 mol) with stirring at room temperature for lhr, cooled and poured into ice-water.The solid obtained was crystallized from acetic acid to give (**15**, Table I).

Formation of 2-[6-iodo-3-phenyl–4(3H)quinazolinone–2-yl) thioacetyl]- pyrazole-3-amino-4-carbethoxy (17)

A mixture of (**5b**; 0.01 mol) and ethyl-2-cyano-3-ethoxyacrylate (0.01 mol) in methanol (50 ml) and glacial acetic acid (6 drops) was refluxed for 6hr and methanol was then removed. The solid thus obtained was filtered off, washed with water and crystallized from methanol to give (**17**, Table I).

Formation of 3-[6-iodo-3-phenyl-4(3H)quinazolinone-2-yl) thiomethyl]- 1,2,4-triazine-6-dihydro-5-one (18)

An equimolecular mixture of **5b** and chloroacetamide in dimethylformamide (20 ml) was heated under reflux for 12hr. The solid that separated after cooling and dilution was filtered and crystallized from dioxane to give (**18**, Table I).

Formation of 3-[6-iodo-3-phenyl-4(3H)quinazolinone-2-yl)thiomethyl] 1,2,4- triazole-1H-5-mercapto (19)

Equimolecular amounts of the appropriate hydrazide **5b** and thiourea (0.01 mol) were fused together at 195° in an oil bath for 0.5hr. On cooling the solid mass was dissolved in 8% NaOH and filtered. The filterate was neutralized with dilute HCl. to pH 7 and the precipitated solid was filtered, washed with water and crystallized from ethanol to give (**19**, Table I).

Formation of thiosemicarbazide derivative (20)

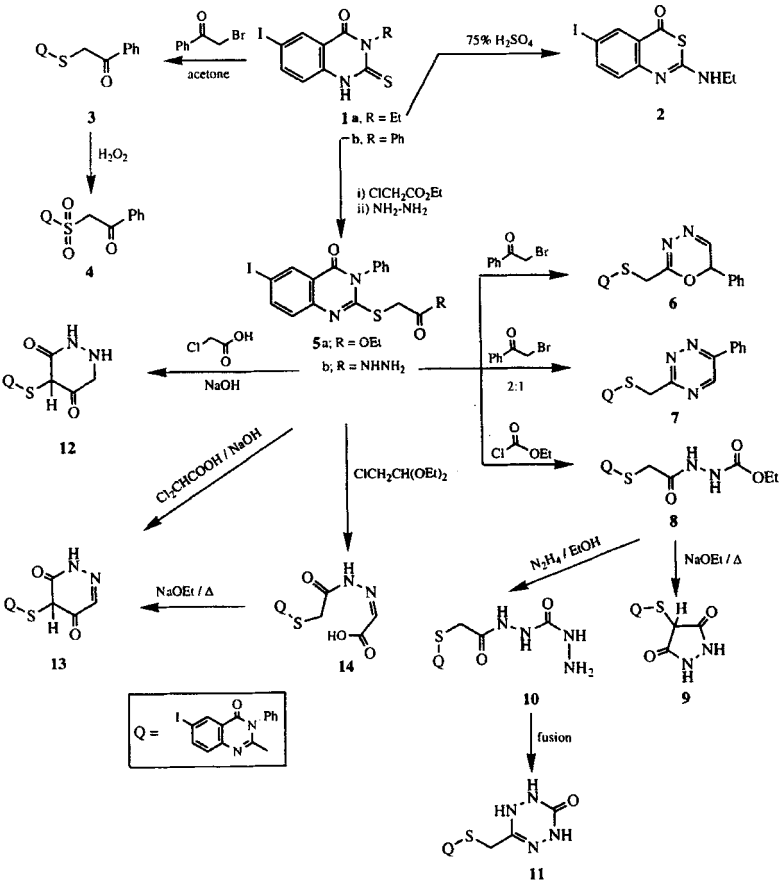
A mixture of hydrazide (**5b**; 0.01 mol), ammonium thiocyanate (0.03 mol), conc. HCl (4 ml) was refluxed in ethanol (100 ml) for 18hr. Compound **20** thus formed was dried and crystallized from dioxane (Table I).

3 RESULTS AND DISCUSSION

To realize the synthesis of the target antitumor compounds. The following schemes were adopted.

Treatment of 6-iodo-3-ethyl-2-thioxo-4(3H)quinazolinone **1a**[5] with 75% conc. H_2SO_4[7] gave the corresponding benzothiazine derivative **2** (Scheme 1). IR spectrum of **2** exhibited bands at 3230 cm^{-1}(NH), 2900 (CH aliphatic), 1690 cm^{-1} (C=O), 1630 (C=N). ^{1}H-NMR spectrum of (**2**

in DMSO-d_6) showed signals at 1.1 [t, 3H, CH_3], 3.9 [q, 2H, CH_2], 7.1–7.8 [m, 3H, Ar-H], 11.7 [s, 1H, NH, cancelled with D_2O],



SCHEME 1

Reaction of **1b**[5] with phenacyl bromide in acetone in presence of anhydrous potassium carbonate yielded 6-iodo-3-phenyl-2-benzoylmethylthio-4(3H)quinazolinone **3**. IR spectrum of **3** showed bands at 1710, 1680 cm^{-1} (2C=O). ^{1}H-NMR spectrum of (**3** in DMSO-d_6) reveald signals at 4.7 [s, 2H, SCH_2], 6.9–8.3 [m, 13H, Ar-H]. Oxidation of **3** was carried out using 30% H_2O_2 in presence of acetic acid at room temperature for 7 days

to give the sulfonyl derivative **4**. IR spectrum of **4** showed bands at 1690, 1670 cm^{-1} (2C=O), 1370, 1145 (SO_2). ^{1}H-NMR spectrum of (**4** in DMSO-d_6) exhibited signals at 5.9 [s, 2H, CH_2], 7.0–8.1 [m, 13H, Ar-H].

Cyclocondensation of the hydrazide derivative **5b** with phenacyl bromide in ethanolic solution containing triethylamine[8] afforded 1,3,4-oxadiazine derivative **6**, while on refluxing in DMF (2:1)[9] in the presence of ethanol for long time gave 1,2,4-triazine derivative **7**. IR spectrum of **7** showed bands at 3100–3090 cm^{-1} (CH aromatic), 2950–2890 cm^{-1} (CH aliphatic), 1630–1610 (C=N), 1600, 1580 (C – C). Mass spectrum of **6** reveald the molecular ion peak m/z 551 (M^+, 0.4%), with a base peak at 69 (100%), other significant peaks at 437 (1.14%), 370 (8.41%), 341 (4.64%), 263 (25.34%), 253 (95.40%), 219 (25.15%), 185 (10.58%), 152 (12.90%), 127 (69.91%), 99 (18.40%), 73 (70.50%). Mass spectrum of **7** showed a molecular ion peak m/z 549 (M^+, 0.18%), with a base peak at 421 (100%), other significant peaks appeared at 521 (38.70%), 516 (4.79%), 437 (9.23%), 379 (62.35%), 347 (17.40%), 295 (29.79%), 245 (21.87%), 216 (29.96%), 192 (14.24%), 126 (14.70%), 102 (25.76%) and 77 (45.67%).

Treatment of **5b** with ethyl chloroformate in the presence of dimethylformamide gave the ethyl ester derivative **8,** which underwent cyclization on heating with sodium ethoxide to give pyrazolidine-3,5-dione derivative **9.** IR spectrum of **8** showed bands at 3370, 3260 cm^{-1} (-(-NH-NH), 2920 cm^{-1} (CH aliphatic), 1750 cm^{-1} (C=O) ethyl carboxylate, 1710 cm^{-1} (C=O) – CH_2CONH, 1690 cm^{-1}(quinazoline, C=O), 1620 cm^{-1}(C=N), 1050 cm^{-1} (ether-CO-OC_2H_5) and 1000 cm^{-1} (phenyl group). The ^{1}H-NMR spectrum of (**8** in DMSO-d_6) exhibited signals at 1.2 [t, 3H, CH_3], 4.0 [q, 2H, CH_2], 4.6 [s, 2H, SCH_2], 7.3–8.3 [m, 8H, Ar-H], 9.2, 10.0 [2s, 2H, 2NH, cancelled with D_2O]. Mass spectrum of **9** showed a molecular ion peak m/z 476 (M-2, 0.20%), with a base peak at 364 (100%), other significant peaks at 320 (3.36%), 272 (17.87%), 245 (41.43%), 217 (7.33%), 126 (0.83%), 119 (4.46%), 90 (6.80%), 63 (7.0%).

Reaction of **8** with hydrazine hydrate afforded the semicarbazide derivative **10** which underwent cyclization by losing one mole of water to give 1,2,4,5-tetrazine-3-one derivative **11.** IR spectrum of **10** showed bands at 3400, 3360, 3220 cm^{-1} 1 (NH, NH_2), 2920 cm^{-1} (CH aliphatic), 1720, 1690, 1660 cm^{-1}(3C=O), 1610 cm^{-1} (C=N). The ^{1}H-NMR spectrum of (**10** in DMSO-d_6) showed signals at 4.4 [s, 2H, SCH_2], 5.7 [s, 2H, NH_2, cancelled with D_2O], 7.0–8.2 [m, 8H, Ar-H], 8.3, 9.3, 9.4 (3s, 3H, 3NH, cancelled with D_2O]. Mass spectrum of **11** showed a molecular ion peak

m/z 492 (M^+, 2.32%), with a base peak at 254 (100%), other significant peaks at 493 (M+1; 0.72%), 494 (M+2, 0.44%), 388 (6.89%), 363 (67.89%), 313 (17.14%), 207 (8.42%), 127 (55.23%), 55 (14.87%).

Compound **5b** also reacted with halo compounds such as monochloroacetic acid and dichloroacetic acid in the presence of aq NaOH to afforded pyridazine-3,5-dione **12** and **13**, respectively, while refluxing of **5b**with chloroacetaldehyde diethyl acetate in the presence of aq NaOH yielded the hydrazonoacetic acid derivative **14,** which underwent cyclization with sodium ethoxide to give **13.** IR spectrum of **12** showed bands at 3410, 3380 cm^{-1} (NH-NH-), 1690 cm^{-1}(quinazolinone C=O), 1680, 1660 cm^{-1} (2C=O ofpyridazine dione), 1620 cm^{-1} (C=N). IR spectrum of **13** showed bands at 3300 cm^{-1} (NH), 1700 cm^{-1} (quinazolinone C=O), 1680, 1660 cm^{-1} (2C=O of pyridazine dione), 1610 cm^{-1} (C=N). Mass spectrum of **12** showed a molecular ion peak m/z 492 (M^+, 0.1%), with a base peak at 263 (100%), other significant peaks at 388 (0.1%), 368 (0.2%), 341 (0.8%), 245 (92.29), 216 (27.40%), 127 (21.26%), 108 (19.58%), 90 (47.88%), 63 (52.34%). Mass spectrum of **13** showed a molecular ion peak m/z 490 (M^+, 0.1%), with a base peak at 263 (100%), other significant peaks at 362 (0.1%),289 (0.28%), 245 (91.71%), 216 (27.05%), 127(21.27%), 75 (5.03%). ^{1}H-NMR spectrum of (**14** in DMSO-d_6) exhibited signals at 4.0 [s, 2H, SCH_2], 6.6 [s, 1H, N=CH], 7.2–7.8 [m, 8H, Ar-H], 8.4 [s, 1H, NH, cancelled with D_2O], 13.0 [br, 1H, OH], gave acidity test with bicarbonate solution.

Treatment of **5b** with chloroacetyl chloride in dimethylformamide at room temperature gave chloroacetylhydrazino derivative **15** (Scheme 2), while on refluxing in DMF gave the pyridazine-3,6-dione derivative **16.** IR spectrum of **15** showed bands at 3190 cm^{-1} (NH), 2920 cm^{-1}(CH aliphatic), 1700, 1680, 1660 cm^{-1} (3C=O). Mass spectrum of **16** showed a molecular ion peak m/z 492 (M^+, 0.13%), 493 (M+1, 0.55%), with a base peak at 364 (100%), other significant peaks at 465 (3.54%), 388 (13.82%), 380 (40.78%), 320 (7.18%), 272 (15.99%), 253 (20.19%), 245 (51.16%), 217 (20.72%), 127 (33.64%), 119 (36.30%), 91 (73.78%), 77 (73.87%).

The pyrazole derivative **17** was obtained via reaction of **5b** with ethyl-2-cyano-3-ethoxyacrylate. The IR spectrum of **17** exhibited bands at 3280, 3260 cm^{-1} (NH_2), 1740, 1710, 1690 cm^{-1} (3C=O), 1615 (C=N), 1650, 1550 and 1450 cm^{-1} (aromatic ring). The ^{1}H-NMR spectrum of (**17** in DMSO-d_6) reveald signals at 1.9 [t, 3H, CH_3], 3.9 [q, 2H, CH_2], 2.5 [s,

2H, NH_2. Cancelled with D_2O], 4.2 [s, 2H, SCH_2], 7.4–7.9 [m, 8H, Ar-H], 8.2 [s, 1H, N=CH].

Interaction of **5b** with chloroacetamide in presence of dimethylformamid[10] for long time gave 1,2,4-triazine-5-one derivative **18.** Mass spectrum of **18** showed a molecular ion peak m/z 491 (M^+, 0.93%), 492 (M+1, 1.47%), 493 (M+2, 0.84%), 494 (M+3, 0.22%), with a base peak at 379 (100%), other significant peaks at 474 (1.46%), 402 (10.30%), 364 (13.58%), 245 (20.89%), 217 (10.77%), 127 (18.26%), 90 (22.95%), 63 (43.48%).

Reaction of **5b** with thiourea and/or ammonium thiocyanate afforded the triazole or thiosemicarbazide derivatives **19** and **20,** respectively. IR spectrum of **20** showed bands at 3400, 3370, 3280 cm^{-1}(NH, NH_2), 2930 cm^{-1}(CH aliphatic), 1700, 1680 cm^{-1} (2C=O) 1610 cm^{-1} (C=N), 1340 cm^{-1} (C=S). Mass spectrum of **19** showed a molecular ion peak m/z 493 (M^+, 0.2%), with a base peak at 379 (100%), other significant peaks at 421 (0.12%), 381 (13.96%), 363 (18.61%), 304 (0.22%), 271 (5.06%), 245 (33.06%), 216 (13.90%), 166 (4.11%), 127 (18.11%), 112 (8.22%), 90 (35.08%), 77 (45.66%), 63 (54.84%).

3.1 In-vitro antitumor activity

Reagents

1. RPMI 1640 medium (Sigma).
2. Ehrlich Ascites Carcinoma cells (EAC), suspension ($2.5.10^5$/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 **1, 3, 4, 15, 16, 17, 18, 19** and **20**.

Procedure

1. Ehrlich Ascites Carcinoma cells were obtained by needle aspiration of ascitic fluid from the preinoculated mice under aseptic conditions[11].
2. The cells were tested for viability and contamination by staining certain cell-volume of this fluid by an equal volum of working solution of trypan blue dye[12], [13].

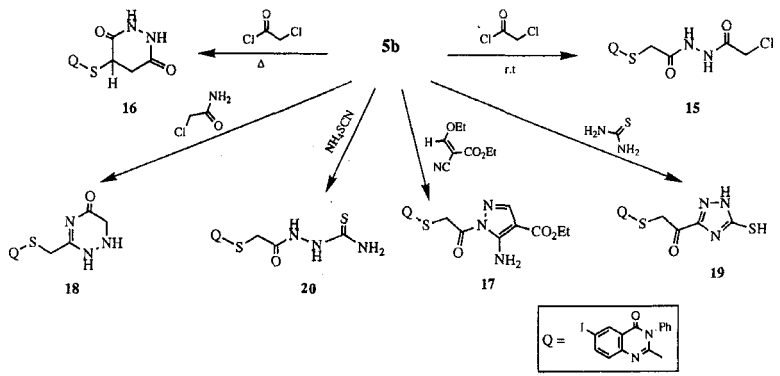
3. The ascitic fluid was diluted to 1:10 with saline to contain $2.5.10^6$ cells on a hemocytometer.
4. In a set of sterile test tubes 0.1 ml of tumor cells suspension, 0.8 ml RPMI 1640 media and 0.1 ml of each tested compound (corresponding to 25 μg, 50 μg and 100 μg) were mixed. The test tubes were incubated at 37 degree centigrade for 2hr. Trypan blue[13] exclusion test was carried out to calculate the percentage of non-viable cells. The results are presented in (Table II).

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

TABLE II In-vitro antitumor activity against Ehrlich Ascites Carcinoma cells

Compd. No.	*% Viability*			
	Conc. μg/ml			
	100	*50*	*25*	*0*
1	64	67	73	100
3	51	60	70	100
4	36	44	67	100
15	0	10	40	100
16	20	30	70	100
17	44	53	84	100
18	38	52	63	100
19	60	80	100	100
20	75	90	100	100

From the above results (Table II), it is clear that the presence of chloroacetylhydrazine moiety (which is a very good alkylating moiety to DNA) bearing quinazolone ring with sulfur atom compound **15,** and a pyridazine moiety bearing quinazolone ring with sulfur atom compound **16** led to an increase in the in-vitro antitumor activity, which displayed a significant percent of the non-viable cells to about 100% and 80% respectively at a concentration of 100 μg. In addition benzoylmethylsulfonyl derivative **4** and triazine derivative **18** showed a moderate activity against Ehrlich Ascites carcinoma tumor cells.



SCHEME 2

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