Heterocyclic Compounds from 4*H*-3,1-Benzoxazin-4-one Derivatives As Anticancer Agent

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Received November 9, 2004

Behaviour of 2-(4-oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)-benzoic acid (**1**) towards nitrogen nucleophiles namely, hydrazine hydrate, in different solvents, ammonium acetate, and *o*-phenylenediamine has been investigated to give aminoquinazolin-4-one, benzotriazepinone, spiro-type compound, and nitrogen bridgehead compounds **3-5**, respectively. Also, reactivity of the aminoquinazolin-4-one **2** towards carbon electrophiles such as ethyl acetoacetate, ethyl phenylacetate, ethyl chloroacetate, and aromatic aldehydes has been discussed. Reaction of Schiff's base **8** with sulfur nucleophiles namely *o*-aminothiophenol and/or thioglycolic acid afforded Michael type adducts. Structural assignments, of products **1-24** have been confirmed by elemental analysis and spectral data (^{1}H- and ^{13}C –NMR and MS fragmentation). The bioassay indicates that some of the target compounds obtained have good selective anticancer activity.

J. Heterocyclic Chem., **42**, 1257 (2005).

Recently it was reported that 2-substituted (4*H*)-3,1-benzoxazin-4-one acts as C1r serine protease inhibitors [1] and the corresponding 4(3*H*)-quinazolin-4-ones acts as non-steroidal anti-inflammatory agents [2], potent anticonvulsant and enzyme initiators [3], and has been shown to posses anti-mitotic, anti-cancer [4], anti-HIV-1 [5] and anti-viral potency [6]. This led us to synthesize new isolated and/or fused heterobicyclic systems starting from compound (**1**) and the corresponding quinazolin-4-one **2** in view of their anticancer activities.

Phthalic anhydride reacts with anthranilic acid in refluxing 1-butanol to give 2-(4-oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)-benzoic acid (**1**). Compound **1** was presented in two conformer **1a** and **1b**. Conformer**1b** seems to be more stable than **1a** due to it exhibits a decrease in steric hindrance and the presence of carboxyl group in the same plane of oxazinone nucleus and its ability to form hydrogen bond with nitrogen atom.

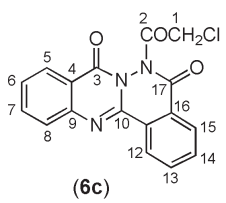
Recently [7], it was reported that 4*H*-3,1-benzoxazin-4-one derivatives bearing alkyl substituents at 2-position undergo hetero ring opening by hydrazine hydrate. In this investigation, the reactivity of **1** towards hydrazine hydrate was studied. Thus, when compound **1** was allowed to react with hydrazine hydrate in boiling ethanol compound **2** was obtained (Scheme 1). On the other hand, when compound **1** was allowed to react with hydrazine hydrate in a high boiling non-polar solvent, *e.g*., xylene, the reaction takes place *via* hetero ring opening followed by cyclization and accompanied by ring expansion leading to triazepinone derivatives **3** (Scheme1).

During the last two decades El-hashash and coworkers, [8-11] studied the reactivity of 2-substituted 4*H*-3,1-benzoxazin-4-one derivatives towards ammonia and/or formamide with the aim of conversion of benzoxazin-4-one derivatives to the more stable quinazolin-4-one derivatives by a facile one step process. The present work deals with the reactivity of the benzoxazin-4-one derivative **1** towards ammonia. Thus when compound **1** was submitted to react with ammonium acetate at 150 °C in an oil bath, hetero ring opening reaction occurs followed by cyclization giving the spiro-type addition compound **4** (Scheme1).

Interaction of the benzoxazin-4-one **1** with *o*-phenylenediamine under drastic conditions yielded the bridgehead nitrogen compound **5** (this may be due to stability of the oxazin-4-one nucleus or partly due to steric hindrance which prevents approach of the nucleophile). Structure **5b** is more thermodynamically stable than **5a** due to conjugation. The reaction possibly takes place *via* hetero ring opening followed by recyclization, (Scheme1)

In this investigation reactivity of **2** towards carbon electrophiles was also investigated. Thus when aminoquinazolin-4-one derivative **2** was allowed to react with ethyl acetoacetate, ethyl phenylacetate and ethyl chloroacetate in refluxing 1-butanol the condensed heterocyclic compounds **6a-c** were obtained, respectively (Scheme 2). The reaction takes place *via* tetrahedral mechanism which needs small energy of activation because such system

Table 1
^{13}C-NMR of Compound (**6c**)



(**6c**)

No.of carbon	δ(ppm)	No.of carbon	δ(ppm)	No.of carbon	δ(ppm)
C-1	32.053	C-7	134.654	C-13	132.213
C-2	175.301	*C-8*	120.036	C-14	128.898
C-3	166.876	C-9	153.202	C-15	128.048
C-4	125.112	C-10	166.022	C-16	131.402
C-5	127.321	C-11	131.765	C-17	166.198
C-6	125.116	C-12	123.243		

receive much of its "energy – payment" from formation of the new bond (N-C) before having to pay its "energy debt" for the breakage of the (C-OEt) bond.

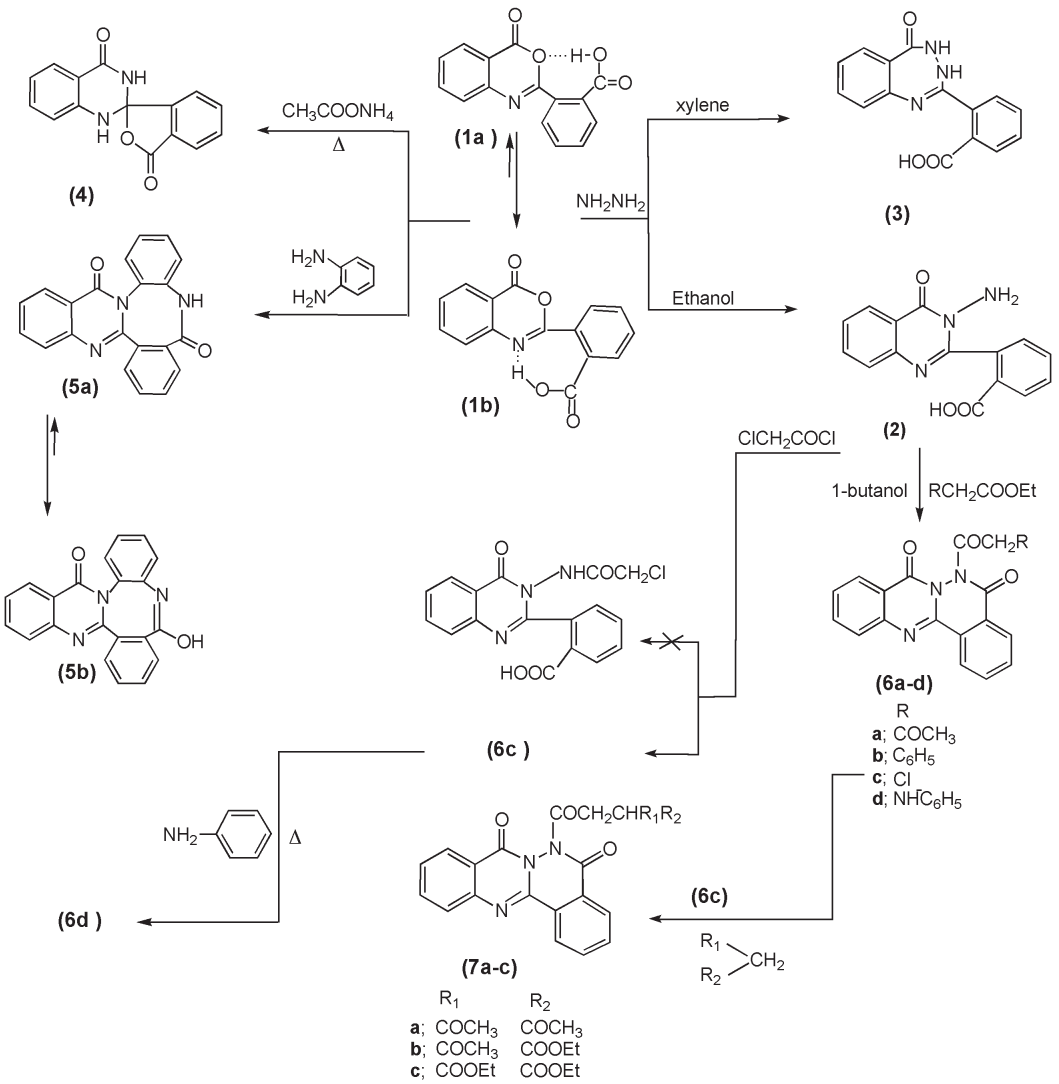
On the other hand, treatment of compound **6c** with aniline in an oil bath at 150 °C gave the nitrogen bridgehead compound **6d** (Scheme 1). Treatment of compound **2** with chloroacetylchloride gives compound **6c** which is identified *via* mp and mixed mp determination.

Recently[12], it was reported that 2-chloroacetyl 4(3*H*)quinazolin-4-one is easily replaced by nucleophiles. This prompted us to investigate the reactivity of **6c** towards carbon nucleophiles. Thus when compound **6c** was allowed to react with active methylene compounds namely, acetylacetone, ethyl acetoacetate and diethyl malonate, in presence of sodium ethoxide yielded C-alkylated derivatives **7a-c** respectively (Scheme 1).

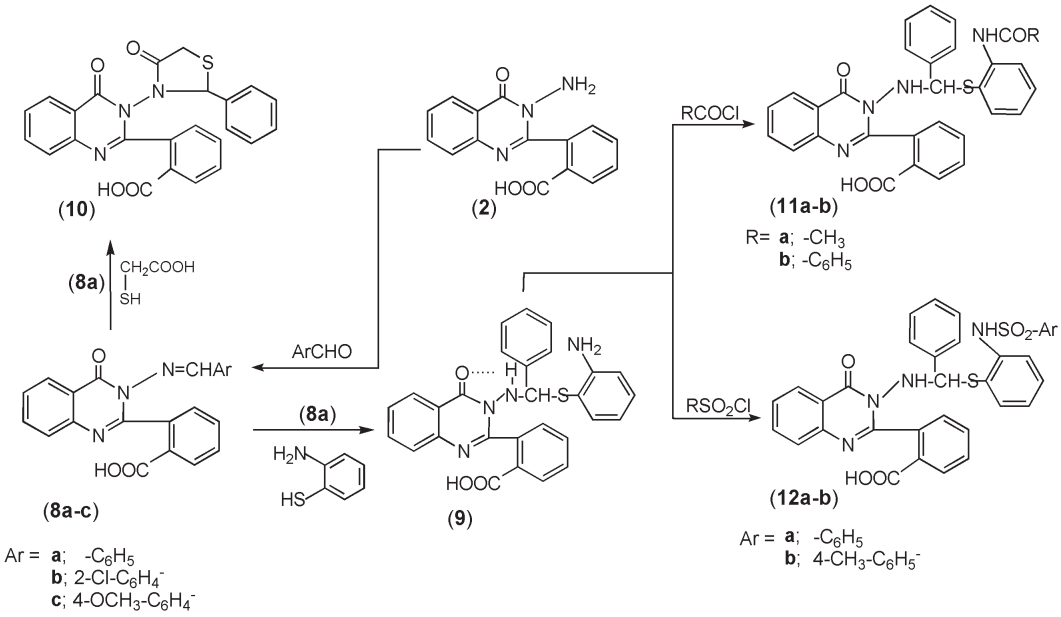
Moreover, as a part of our program on the chemical reactivity of the 3-aminoquinazolinone **2** towards electrophiles, we report here the reaction of **2** with aromatic aldehydes namely, benzaldehyde, *o*-chlorobenzaldehyde and *p*-methoxybenzaldehyde affording the Schiff's bases **8a–c** respectively (Scheme 2). When compound **8a** was allowed to react with thioglycolic acid in ethanol **10** was obtained (Scheme 2).

The Michael type adduct **9** was obtained by allowing compound **8a** to react with *o*-aminothiophenol. Compound **9** has been reacted with acetyl chloride and benzoyl chloride to give N-acetyl or benzoyl derivatives **11a** and **11b** respectively. Acetylation and/or benzoylation of the secondary NH does not take place due to formation of an intramolecular hydrogen bond. Also compound **9** has been reacted with benzene sulphonylchloride and *p*-toulene sulphonyl chloride to give N-sulphonyl derivatives **12a** and **12b**, respectively (Scheme 2).

Scheme 1



Scheme 2



On the other hand, treatment of compound **6c** with thiosemicarbazide [13] in methanol gave **13**, which was reacted with different aromatic aldehydes namely, benzaldehyde, 4-methylbenzaldehyde and 3,4.5-trimethoxy benzaldehyde in absolute ethanol and a few drops of glacial acetic acid, which resulted in the formation of compounds **14a-c**. Compounds **14a-c** on cyclo condensation with thioglycolic acid in the presence of a pinch of anhydrous zinc chloride furnished compounds **15a-c** (Scheme 3).

Treatment of compounds **7a-c** with hydrazine hydrate in boiling ethanol gave pyrazole derivatives **16-18** respectively. However **7a-c** reacts with urea and/or thiourea in the presence of sodium ethoxide as a catalyst to afford pyrimidine and thiopyrimidine derivatives **19a-b**, **20a-b** as well as barbituric acid and thiobarbituric acid derivatives **21a-b** respectively. On the other hand, treatment of compounds **7a-c** with hydroxyl amine hydrochloride in pyridine gave isoxazole derivatives **22-24** respectively (Scheme 4).

Scheme 3

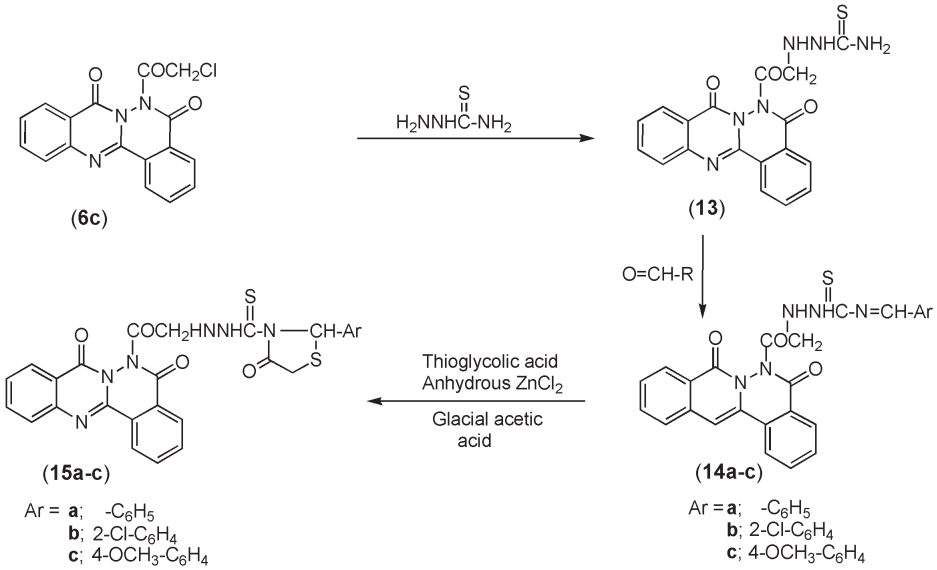
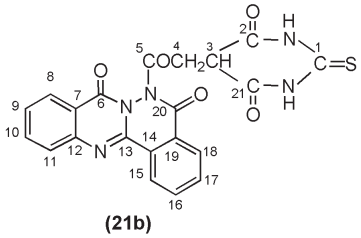


Table 2

^{13}C-NMRof Compound (**21b**)



(21b)

No.of	δ(ppm) carbon	No.of	δ(ppm) carbon	No.of	δ(ppm) carbon
C-1	191.035	C-8	127.297	C-15	123.387
C-2	184.027	C-9	125.230	C-16	132.112
C-3	53.126	C-10	134.706	C-17	128.835
C-4	32.067	C-11	120.039	C-18	128.064
C-5	175.112	C-12	153.136	C-19	131.448
C-6	166.997	C-13	166.024	C-20	166.236
C-7	125.230	C-14	131.837	C-21	184.013

Table 3

In *vitro* antitumor activity data of some selected new compounds.

Compds.	cell line	**IC**$_{50}$
DOX	brain tumor cell line (U251)	0.7 µg/ml
DOX	liver carcinoma cell line (Hepg 2)	0.8 µg/ml
3	brain tumor cell line (U251)	9.32 µg/ml
	liver carcinoma cell line (Hepg 2)	8.97 µg/ml
6c	brain tumor cell line (U251)	9.32 µg/ml
	liver carcinoma cell line (Hepg 2)	9.88 µg/ml
6d	brain tumor cell line (U251)	5.16 ug/ml
	liver carcinoma cell line (Hepg 2)	8.67 µg/ml
11b	brain tumor cell line (U251)	5.96 µg/ml
	liver carcinoma cell line (Hepg 2)	9.02 µg/ml
12b	brain tumor cell line (U251)	2.36 µg/ml
	liver carcinoma cell line (Hepg 2)	4.03 µg/ml
15b	brain tumor cell line (U251)	5.65 µg/ml
	liver carcinoma cell line (Hepg 2)	9.43 µg/ml
18	brain tumor cell line (U251)	5.39 µg/ml
	liver carcinoma cell line (Hepg 2)	9.24 µg/ml
21b	brain tumor cell line (U251)	3.65- µg/ml
	liver carcinoma cell line (Hepg 2)	3.43-µg/ml

IC$_{50}$: Dose of the drug that reduces survival to 50%.

Scheme 4

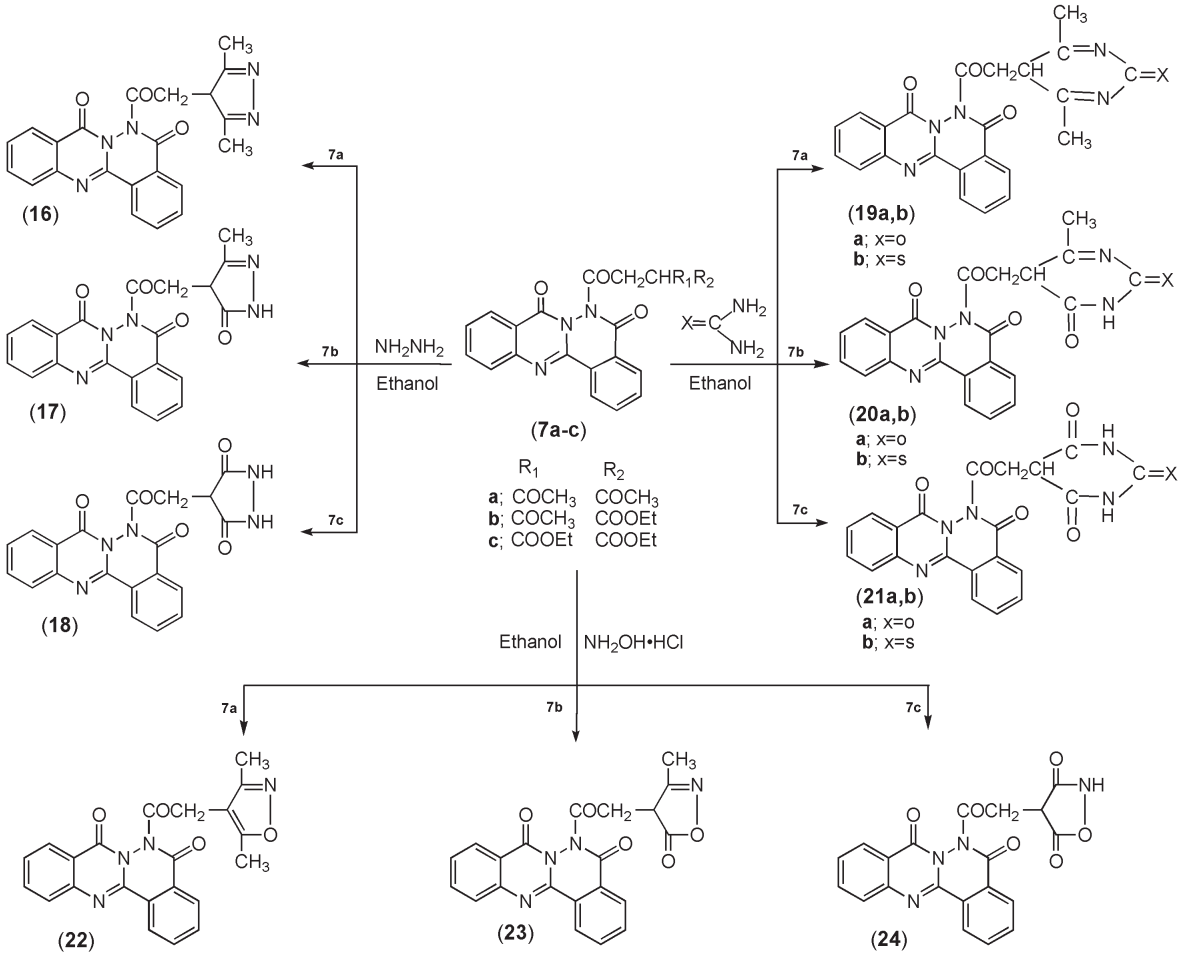


Table 4
Characterization Data of Various Compounds Prepared

Compd.	Solvent	MP °C (Yield)	MolecularFormula(MolecularWeight)	Analysis % Calculated (Found)				
				C	H	Cl	N	S
1	A	155-6	$C_{15}H_9NO_4$	67.42	3.39		5.24	
		(55)	(267.24)	67.61	3.46		5.19	
2	E	176-7	$C_{15}H_{11}N_3O_3$	64.05	3.94		14.94	
		(63)	(281.27)	64.29	4.00		15.09	
3	M	188-190	$C_{15}H_{11}N_3O_3$	64.05	3.94		14.94	
		(75)	(281.27)	64.32	4.01		14.79	
4	P	162-3	$C_{15}H_{10}N_2O_3$	67.67	3.79		10.52	
		55	(266.25)	67.94	3.85		10.63	
5	B	180-1	$C_{21}H_{13}N_3O_2$	74.33	3.86		12.38	
		(52)	(339.35)	74.52	3.92		12.51	
6a	B	186-8	$C_{19}H_{13}N_3O_4$	65.70	3.77		12.10	
		(62)	(347.32)	65.96	3.84		12.01	
6b	A	296-8	$C_{23}H_{15}N_3O_3$	72.43	3.96		11.02	
		44	(381.38)	72.62	3.89		11.13	
6c	E	183-5	$C_{17}H_{10}ClN_3O_3$	60.10	2.97	10.44	12.37	
		(50)	(339.73)	59.88	2,91	10.32	12.25	
6d	E	200-2	$C_{23}H_{16}N_4O_3$	69.69	4.07		14.13	
		(55)	(396.40)	69.45	3.99		13.98	
7a	E	214-5	$C_{22}H_{17}N_3O_5$	65.50	4.25		10.42	
		(48)	(403.39)	65.33	4.17		10.31	
7b	B	227-9	$C_{23}H_{19}N_3O_6$	63.74	4.42		9.70	
		(73)	(433.41)	63.98	4.35		9.59	
7c	E	217-9	$C_{24}H_{21}N_3O_7$	62.20	4.57		9.07	
		(55)	(463.44)	62.04	4.49		9.16	
8a	E	293-5	$C_{22}H_{15}N_3O_3$	71.54	4.09		11.38	
		(56)	(369.37)	71.33	4.02		11.26	
8b	M	216-8	$C_{22}H_{14}ClN_3O_3$	65.43	3.49	8.78	10.41	
		(76)	(403.82)	65.19	3.41	8.69	10.30	
8c	M	212-2	$C_{23}H_{17}N_3O_4$	69.17	4.29		10.52	
		(59)	(399.41)	69.39	4.21		10.64	
9	A	219-221	$C_{28}H_{22}N_4O_3S$	68.00	4.48		11.33	6.48
		(54)	(494.57)	67.77	4.41		11.23	6.55
10	E	264-5	$C_{24}H_{17}N_3O_4S$	65.00	3,86		9.48	7.23
		(49)	(443.48)	64.79	3.79		9.39	7.16
11a	P	250-2	$C_{30}H_{24}N_4O_4S$	67.15	4.51		10.44	5.98
		(66)	(536.60)	66.92	4.45		10.35	6.04
11b	E	281-2	$C_{35}H_{26}N_4O_4S$	70.22	4.38		9.36	5.36
		(73)	(598.67)	69.98	4.32		9.25	5.29
12a	P	289-91 (73)	$C_{34}H_{26}N_4O_5S_2$	64.34	4.13		8.83	10.10
			(634.73)	64.57	4.07		8.74	9.99
12b	P	291-3	$C_{35}H_{28}N_4O_5S_2$	64.80	4.35		8.64	9.89
		(37)	(648.75)	65.03	4.28		8.70	10.01
13	P	204-6	$C_{18}H_{14}N_6O_3S$	54.81	3.58		21.31	8.13
		(45)	(396.41)	55.05	3.65		21.19	8.04
14a	B	227-9	$C_{25}H_{18}N_6O_3S$	62.23	3.76		17.42	6.65
		(36)	(482.52)	61.97	3.69		17.27	6.73
14b	B	228-6	$C_{26}H_{20}N_6O_3S$	62.89	4.06		16.93	6.46
		(73)	(496.54)	63.14	3.99		17.09	6.53
14c	B	277-9	$C_{28}H_{24}N_6O_6S$	58.73	4.22		14.68	5.60
		(55)	(572.59)	58.97	4.17		14.80	5.67
15a	E	272-4	$C_{27}H_{20}N_6O_4S_2$	58.26	3.62		15.10	11.52
		(59)	(556.62)	58.53	3.55		14.97	11.63
15b	M	275-7	$C_{28}H_{22}N_6O_4S_2$	58.93	3.89		14.73	11.24
		(48)	(570.64)	59.18	3.96		14.62	11.36
15c	E	289-91 (64)	$C_{30}H_{26}N_6O_7S_2$	55.72	4.05		13.00	9.92
			(646.70)	55.98	3.97		12.89	10.04
16	A	201-3	$C_{22}H_{17}N_5O_3$	66.16	4.29		17.53	
		(70)	(399.40)	66.40	4.20		17.38	
17	E	199-200	$C_{21}H_{15}N_5O_4$	62.84	3.77		17.45	
		(59)	(401.38)	62.59	3.69		17.30	
18	E	206-8	$C_{20}H_{13}N_5O_5$	59.56	3.25		17.36	
		(82)	(403.35)	59.78	3.18		17.50	

Table 4 (continued)

Compd.	Solvent	MP °C (Yield)	MolecularFormula(MolecularWeight)	Analysis % Calculated (Found) C	H	Cl	N	S
19a	A	206-4	$C_{23}H_{17}N_5O_4$	64.63	4.01		16.39	
		(63)	(427.41)	64.86	3.94		16.55	
19b	A	215-3	$C_{23}H_{17}N_5O_3S$	62.29	3.86		15.79	7.23
		(76)	(443.48)	62.50	3.79		15.64	7. 16
20a	A	204-6	$C_{22}H_{15}N_5O_5$	61.54	3.52		16.31	
		(71)	(429.39)	61.31	3.45		16.18	
20b	M	207-9	$C_{22}H_{15}N_5O_4S$	59.32	3.39		15.72	7.20
		(75)	(445.45)	59.10	3.46		15.58	7.13
21a	M	215-7	$C_{21}H_{13}N_5O_6$	58.47	3.04		16.24	
		(72)	(431.36)	58.69	3.12		16.09	
21b	E	222-4	$C_{21}H_{13}N_5O_5S$	56.37	2.93		15.65	7.17
		(74)	(447.42)	56.58	3.01		15.49	7.23
22	A	207-9	$C_{22}H_{16}N_4O_4$	65.99	4.03		13.99	
		(34)	(400.39)	66,23	4.11		14.14	
23	A	211-4	$C_{21}H_{14}N_4O_5$	62.69	3.51		13.92	
		(46)	(402.36)	62.91	3.44		14.07	
24	E	217-8	$C_{20}H_{12}N_4O_6$	59.41	2.99		13.86	
		(53)	(404.33)	59.63	3.07		14.00	

B = benzene, E = Ethanol, A = Acetic acid , M = Methanol, P = Petroleum ether 60-80 °C.

Some of the new compounds have been evaluated for in *vitro* antitumor activity according to the described method of Skehan and coworkers, [14] against brain tumor cell line (**U251**) and liver carcinoma cell line (**Hepg 2**) at drug concentration between (1.00-10.00 µg/ml) using sulforhodamine **B** (**SRB**) protein assay [14]. The IC_{50} percent control of infected and uninfected response values were calculated for the various active compounds are reported in Table **3**. Compounds having IC_{50} < 5 µg/ml. are considered potentially active and exposed to further *in vivo* studies. The results obtained in Table 3 showed that: 1-The compounds **12b** and **21b** possessed significant effect on both cell lines [brain tumor (**U251**) and liver carcinoma (**Hepg 2**)], which might be due to the presence of N-Phenyl-benzenesulfonamide and thiobarbituric acid moieties. 2-The compounds **6d**, **11b**, **15b** and **18** were moderately active against brain tumor cell line (**U251**) and possess lethal activity against liver carcinoma (**Hepg 2**). 3-The compounds **3** and **6c** possess lethal activity against both cell lines.

EXPERIMENTAL

The reported mp's are uncorrected. Elemental analysis were carried out in the Micro analytical center, Cairo university and Anticancer activity "Doxirubsin was used as positive stander" in the National center Institute, Cancer Biology Department, Pharmacology Unit, Cairo University, Egypt. IR spectra (KBr) were recorded on BRUKER VECTOR 22 FT spectrophotometer (ν_{max} in cm^{-1}), ^{1}H-NMR spectra were recorded on a Varian Gemini 200 MHz (Germany) using DMSO as a solvent and TMS as an internal reference δ (chemical shifts in ppm) and mass spectra were recorded on a gas chromatographic GC/MS-HEWLETT PACKARD 5988A GC/MS instrument at 70 eV. Compound **1** was prepared following an reported procedure [7]. The physical data of the synthesized compounds are given in Table 4

2-(4-Oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)-benzoic Acid (**1**).

To a solution of anthranilic acid (0.01 mol) in dry butanol (50 ml) was added phthalic anhydride (0.01 mol), and the reaction mixture was heated under a reflux for 20 hrs. The product that separated on cooling was recrystallized from benzene to give **1** (Table 4). IR (KBr, ν_{max} in cm^{-1}): 1701, 1681(C=O), 3475 (OH, H-bridge); ^{1}H NMR δ_H (DMSO-d_6): 7.45-8.12 (m, 8H, Ar-H), 11.48 (s. 1H, OH) ppm; ^{13}C NMR δ_C (DMSO-d_6): 118.57, 120.98, 128.64, 128.82, 129.41, 130.96, 132.09, 132.45, 132.82, 133.84, 135.87, 156.47, 158.56, 162.07, 172.64.

2-(3-Amino-4-oxo-3,4-dihydroquinazolin-2yl)-benzoic Acid (**2**).

A solution of **1** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (40 ml) was heated under reflux for 3 hrs. The product that separated on cooling was recrystallized from a suitable solvent to give **2** (Table 4). IR (KBr, ν_{max} in cm^{-1}): 3482 (OH, H-bridge) 3274, 3183 (NH_2), 1705,1650(C=O). ^{1}H-NMR δ_H (DMSO-d_6): 2.56 (s, 2H, NH_2), 7.45-8.12 (m, 8H, Ar-*H*), 11.55 (s,1H, O*H*) ppm.; MS: m/z: (Int %): 281.05(0.04), 266.95 (0.08), 252.95 (0.10), 223(0.52), 179(20.15), 137 (54.53), *119(100)*, 91.95(42.61), 64.95 (26.49).

2-(5-Oxo-4,5-dihydro-3*H*-benzo[*e*][1,2,4]triazepin-2-yl)-benzoic Acid (**3**).

A solution of compound (**1**) (0.01 mol) and hydrazine hydrate (0.015 mole, 0.75 ml) in xylene (50 ml) was heated under reflux for 3 hrs. The product that separated on cooling was recrystallized from a suitable solvent to give **3** (Table 4); IR (KBr, ν_{max} in cm^{-1}): 3487 (OH-H-bridge), 3186, 3165 (NH), 1701, 1665(C=O), 1610(C=N); ^{1}H-NMR δ_H (DMSO-d_6): 2.51 (s, H, N*H*), 7.47-8.10 (m, 8H, Ar-*H*),8.38 (s, 1H, N*H*-C=O), 11.47(s, H, O*H*) ppm; MS: m/z: (Int %): 281.70(0.03), 262.95(0.04), 222.00(0.14), 221(0.50), 164.00(1.18), 163.00

(12.61), 162.00 (99.73), 132.95 (4.65), 131.95(21.10), 118.05 (1.42), 105.05 (23.43), *103.95(100)*, 91.05(4.57), 676.95(30.14), 75.95 (37.74), 74.95 (11.87), 73.95(14.48), 72.95(3.81), 63.95(2.44), 62.95(4.27), 52.95(4.98), 51.95(6.71), 50.95(29.78).

Formation of the Spiro Compound (**4**).

A mixture of compound **1** (1 g) and ammonium acetate (4 g) was heated in an oil bath at 150 °C for 3 hrs., then cooled and poured onto water. The product that separated was recrystallized from a suitable solvent to give **4** (Table 4); IR (KBr, ν_{max} in cm^{-1}): 3243, 3197 (NH), 1775, 1731 and 1666 (C=O); ^{1}H-NMR δ_H (DMSO-d_6): 4.09 (s, H, N*H*-Ar) ,6.71-7.97(m, 8H, Ar-*H*), 8.24 (s, H, *NH*-C=O), ppm.

Formation of Compound (**5**).

A mixture of compound **1** (0.01mol) and *o*-phenylenediamine (0.01 mol) was fused in oil bath at 170 °C for 3 hrs. then poured into water. The solid that separated on cooling was recrystallized from a suitable solvent to give **5** (Table 4); IR(KBr, ν_{max} in cm^{-1}): 3361 (NH), 1683,1645(C=O); ^{1}H-NMR δ_H (DMSO-d_6): 6.66-7.97 (m, 12H, Ar*H*), 8.18(brs, H, N*H*-C=O) ppm.

6-(3-Oxobutanoyl)-phalazino[1,2-*b*]quinazoline-5,8-dione (**6a**), 6-Phenylacetylphalazino[1,2-*b*]quinazoline-5,8-dione (**6b**) and 6-(2-Chloro-acetyl)-phalazino[1,2-*b*]quinazoline-5,8-dione (**6c**).

A solution of compound **2** (0.01 mol) with ethyl esters namely, ethyl acetoacetate, ethyl phenylacetate and ethyl chloroacetate (0.01 mol) in 1-butanol (40 ml) was heated under reflux 3 hrs. The products that separated after cooling were crystallized from the proper solvents to give **6a-c** (Table 4). IR (KBr, ν_{max} in cm^{-1}): (**6b**) 3013 (CH-aromatic), 2914 (CH-aliphatic), 1683, 1675 and 1660 (C=O); ^{1}H NMR:(**6b**) 3.42 (s,2H,-COCH_2Ph), 7.09-7.90 (m,13H,Ar*H*) ppm. ^{1}H-NMR δ_H (DMSO-d_6):(**6c**)**,** 4.27 (s,2H,COCH_2 Cl),7.46-8.00 (m, 8H,Ar-*H*) ppm.; MS: m/z: (Int %): (**6b**) 385.45(21.92), 384.70 (15.07), 343.95(17.81), 292.40(15.07), 241.40(23.29), 204.30(20.55), 161.95(45.21), 127.40(19.18), 76.90 (39.73), *53(100)*.51.90(49.32), 51.00(73.97).

6-(2-Phenylaminoacetyl)-phalazino[1,2-*b*]quinazoline-5,8-dione (**6d**).

A mixture of compound **6c** (0.01 mol) and aniline (0.01 mol) was heated in an oil bath at 150 °C for 3 hrs. The reaction mixture after cooling was treated with ice/conc. HCl. The solid that separated was collected by filtration and recrystallized from the proper solvent to give **6d** (Table 4). IR (KBr, ν_{max} in cm^{-1}): (**6d**); 3183(N*H*); 1684 and 1662(C=O); ^{1}H-NMR δ_H (DMSO-d_6): (**6d**) 3.81(s, 2H,-CO CH_2NH Ph), 4.22 (s, H, N*H*-Ar), 6.48-7.99 (m, 13H, Ar-*H*)ppm.

6-(3-Acetyl-4-oxo-pentanoyl)-phalazino[1,2-*b*]quinazoline-5,8-dione (**7a**), 2-Oxo-[(5,8-dioxophalazino[1,2-*b*]quinazoline-6-yl)-ethyl]-butyric Acid Ethyl Ester (**7b**) and 2-Oxo-[(5,8-dioxophalazino[1,2-*b*]quinazoline-6-yl)-ethyl]-Malonic Acid Diethyl Ester (**7c**).

A mixture of **6c** (0.01 mol) and active methylene compounds namely, acetyl acetone, ethyl acetoacetate and diethyl malonate (0.01 mol) was treated with ethanol (30 ml) containing sodium metal (0.75 gm) and heated under reflux for 3 hrs. Excess of solvent was removed under reduced pressure and the reaction mixture was treated with ice/HCl solution. The solids that separated were recrystallized from the proper solvent to give compounds **7a-c** (Table 4). IR (KBr, ν_{max} in cm^{-1}): (**7a**) 1705, 1708, 1697, 1673 and 1661 (C=O); ^{1}H-NMR δ_H (DMSO-d_6): (**7b**) 1.36 (t, 3H, CH_2CH_3), 1.99 (s, 3H, $COCH_3$), 2.72 (d, 2H, $COCH_2CH$), 3.53 (t, H, CH_2CHCO_2), 4.14 (q, 2H, $COOCH_2CH_3$), 7.61-8.00 (m, 8H, Ar-*H*) ppm.

2-[3-(Benzylideneamino)-4-oxo-3,4-dihydro-quinazolin-2-yl]-benzoic Acid (**8a**), 2-[3-(2-Chloro-benzylidene)-amino}-4-oxo-3,4-dihydro-quinazolin-2-yl) benzoic Acid (**8b**) and 2-{3-[4-Methoxy-benzylidene)-amino]-4-oxo-3,4-dihydro-quinazolin-2-yl}benzoic Acid (**8c**).

A solution of compound **2** (0.01 mol) and aromatic aldehydes, namely, benzaldehyde, *o*-chlorobenzaldehyde and *p*-methoxybenzaldehyde (0.01 mol) in ethanol (30 ml) was heated under reflux for 3 hrs. The products that separated on cooling were recrystallized from suitable solvents to give **8a-c** (Table 4). IR (KBr, ν_{max} in cm^{-1}): (**8b**) 3482 (OH, H-bridge), 1700, 1672 (C=O), 1618 (C=N).; ^{1}H-NMR δ_H (DMSO-d_6): (**8c**) 3.70 (s, 3H,OCH_3), 7.04-8.18 (m, 13H, Ar-*H* and -N=C*H*-), 11.48 (s, H, O*H*) ppm; MS: m/z: (Int %): (**8a**) 368.05(0.51), 366.45(0.56), 336.95(0.51), 310.15(0.56), 267.40(0.46), 223.05(2.41), 162(52.87), 104(95.65), 77(75.49), *76(100)*, 75.09(47.09), 74.00(77.15) (**8c**) 399.41(00.00), 344.20(2.37), 256.20 (2.37), 224.05 (10.21), *161.95(100)*, 162.95(11.07), 132(20.10), 121(10.64), 104(77), 77(18.05), 76(18.01), 73(12.73).

Formation of Michael Type Adducts.

2-(3-{[2-Amino-phenylsulfanyl)-phenyl-methyl]-amino}-4-oxo-3,4-dihydro-quinazolin-2-yl)-benzoic Acid (**9**).

A solution of compound **8** (0.005 mol) and 2-aminothiophenol (0.005 mol) in benzene (30 ml) containing 3 drops of piperidine was left aside for 4 days at room temperature. The product was collected by filtration and recrystallized from the suitable solvent to give the Michael adduct (**9**) (Table 4). IR(KBr, ν_{max} in cm^{-1}): 3444(OH,H-bridge), 3351, 3274 (NH_2), 3182(NH), 1701, 1648 (C=O).; ^{1}H-NMR δ_H (DMSO-d_6): 2.51 (brs,1H, N*H*)) 4.23(s,2H,NH_2-Ph),4.95(s, H, N-C*H*-Ph), 6.48-8.18 (m, 17H,Ar-*H*). 11.53 (s, H,O*H*) ppm.; MS: m/z: (Int %): 494.57(0.00), 427.20 (9.32),394.20 (9.50), 320.05(40.43), 255.05(30.10), *211.05(100)*, 161.05 (45.81) ,103 (33.57).

2-[4-Oxo-3,4-oxo-2-phenyl-thiazolidin-3-yl)-3,4-dihydro-quinazolin-2-yl}benzoic acid (**10**).

A solution of compound **8a** (0.01 mol) and thioglycolic acid (0.01 mol) and piperidine 3 drops in ethanol (30 ml) was heated under reflux for 3 hrs. The product separated on cooling was recrystallized from a suitable solvent to give compound **10** (Table 4); IR (KBr, ν_{max} in cm^{-1}): 3475 (OH, H-bridge), 1743, 1693 and 1681(C=O); ^{1}H-NMR δ_H (DMSO-d_6): 3.28 (s, 2H, $COCH_2$-of thiazolidinone ring), 5.5 (s, H, C*H*-of thiazolidinone ring), 7.09-8.18 (m, 13H, Ar-*H*), 11.50 (s, H, O*H*) ppm; MS: m/z: (Int %): 443.49(0.00), 365.20(0.20), 313.30(0.22), 236.20(0.27), *161.85(100)*, 138(15.81), 104(3.00), 76(26), 51(14).

2-(3-{[2-Acetylamino-phenylsulfanyl)-phenylmethyl]amino-4-oxo-3,4-dihydro-quinazolin-2-yl}benzoic Acid (**11a**) and 2-(3-{[2-Benzoylamino-phenylsulfanyl)-phenylmethyl]amino-4-oxo-3,4-dihydro-quinazolin-2-yl}benzoic Acid (**11b**).

A solution of compound **9** (0.005 mol) and acetyl chloride and/or benzoyl chloride (10 ml) was heated under reflux for 1 hr. The products separated after removing excess of acid chloride were recrys-

tallized from suitable solvents to give **11a,b** (Table 4); IR (KBr, ν_{max} in cm^{-1}): (**11b**) 3430 (OH, H-bridge), 3172, 3121 (NH), 1701, 1673, and 1661 (C=O); ^{1}H-NMR δ_H (DMSO-d_6): (**11a**) 2.03 (s, 3H, COCH_3), 2.52 (s, 1H, N*H*), 4.84 (s, 1H, S-C*H*-Ph), 7.04-8.12 (m, 17H, Ar-*H*), 8.12 (brs, 1H, N*H*-COCH$_3$), 11.55 (s, H, O*H*) ppm; MS: m/z: (Int %): (**11b**) 599(65), 505(60), 446(70), 399.70(55), 283(75), 229(70), *122.15(100),* 105.15(95), 74.15(60), 54.90(70).

2-(3-{[2-Benzenesulfonylamino-phenylsulfanyl)-phenyl-methyl]-amino}-4-oxo-3,4-dihydro-quinazolin-2-yl}benzoic Acid (**12a**) and 2-[4-Oxo-3-({phenyl-[2-(toluene-4-sulfonylamino)-phenylsulfanyl]-methyl}-amino)-3,4-dihydro-quinazolin-2-yl}benzoic Acid (**12b**).

A solution of compound **9** (0.01 mol) and benzene sulphonyl chloride and/or *p*-toluene sulphonyl chloride (10 ml) was heated under reflux for 1 hr. The products that separated after removing excess of acid chloride were recrystallized from suitable solvents to give **12a,b** (Table 4); IR (KBr, ν_{max} in cm^{-1}): (**12b**) 3429 (OH, H-bridge), 3172, 3113 (NH), 1705 and 1663 (C=O), 1156(S=O); ^{1}H-NMR δ_H (DMSO-d_6): (**12a**) 2.51 (brs, 1H, N*H*-Ph), 4.22 (s, 1H, N*H*-SO$_2$), 4.84 (s, 1H, N-C*H*-Ph), 632-8.12 (m, 22H, Ar-*H*), 11.47 (s, H, O*H*) ppm.

6-Acetylthiosemicarbazidophalazino[1,2-*b*]quinazoline-5,8-dione (**13**).

A mixture of thiosemicarbazide (0.01 mol) and (0.01 mol) of compound **6c** in methanol was refluxed on a steam bath for 6 hrs. The excess solvent was distilled off and the reaction mixture was poured into ice cold water, the solid collected by filtration and recrystallized from an appropriate solvent to give compound (**13**) (Table 4). IR (KBr, ν_{max} in cm^{-1}): 3342, 3274 (NH_2), 3183, 3114 (NH), 1675, 1668, 1660 (C=O), 1190 (C=S); ^{1}H-NMR δ_H (DMSO-d_6): 2.51-2.59 (complex m, 4H, N*HNH* CSNH_2) 3.62 (s, 2H, COCH_2), 7.41-7.86 (m, 8H, Ar-*H*) ppm.

6-Acetylthiosemicarbazido(substitudedarylidene)-phalazino[1,2-*b*]-quinazoline-5,8-dione (**14a-c**).

A mixture of compound **13** (0.01 mol) in absolute ethanol (30 ml), a few drops of glacial acetic acid and aromatic aldehydes (0.01 mol) namely, benzaldehyde, 4-methylbenzaldehyde and 3,4.5-trimethoxybenzaldehyde was refluxed on a steam bath for 6-8 hrs. The excess solvent was distilled off and the residue was poured onto ice. The separated solids were collected by filtration and recrystallized from appropriate solvents to give compounds **14a-c**, (Table 4); IR (KBr, ν_{max} in cm^{-1}): (**14a**) 3282, 3179 (NH), 1693, 1676 and 1658 (C=O), 1601 (C=N), 1180 (C=S); ^{1}H-NMR δ_H (DMSO-d_6): (**14a**) 2.53, 2.57 (bs, 2H, 2N*H*), 3.66 (s, 2H, CO CH_2), 7.32- 8.12 (m, 14H, Ar-*H* and -N=C*H*-Ph) ppm.

4-Oxo-2-phenyl-thiazolidine-3-carbathioic Acid *N*'-Phalazino-[1,2-*b*]quinazoline-5,8-dione-6-yl)-2-oxo-ethyl]-hydrazide (**15a**), 4-Oxo-2-*p*-tolyl-thiazolidine-3-carbathioic Acid *N*'-Phalazino[1,2-*b*]quinazoline-5,8-dione-6-yl)-2-oxo-ethyl]-hydrazide (**15b**) and 4-Oxo-2-(3,4,5-trimethoxy-phenyl)-thiazolidine-3-carbathioic Acid *N*'-Phalazino[1,2-*b*]quinazoline-5,8-dione-6-yl)-2-oxo-ethyl]-hydrazide (**15c**).

To a stirred solution of compound **14a-c** (0.01 mol) in dry DMF, containing a pinch of anhydrous $ZnCl_2$ and thioglycolic acid (0.02 mol), was heated under reflux for 8 hrs. then the excess solvent was distilled off and the residual reaction mixture was cooled and poured into cold water. The separated solid was collected by filtration and recrystallised from appropriate solvents to afford compounds **15a-b**, (Table 4); IR (KBr, ν_{max} in cm^{-1}): (**15b**) 3263, 3095 (NH), 2835 (CH_2) 1766, 1675, 1667 and 1653 (C=O), 1586 (C=N), 1176 (C=S), 1142(C-S); ^{1}H-NMR δ_H (DMSO-d_6) (**15a**): 2.53, 2.61 (brs, 2H, 2N*H*), 3.25 (s, 2H, CH_2 of thiazolidinone ring), 3.65 (s, 2H, COCH_2), 5.86 (s, H,C*H*-of thiazolidinone ring), 7.04-7.99 (complex m, 13H, Ar-*H*) ppm.

6-[2-(3,5-Dimethyl-4*H*-pyrazol-4-yl)-acetyl]-phalazino[1,2-*b*]-quinazoline-5,8-dione (**16**), 6-[2-(3-Methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)-acetyl]- phalazino[1,2-*b*]quinazoline-5,8-dione (**17**) and 6-[2-(3,5-Dioxo-pyrazolidin-4-yl)-acetyl]-phalazino[1,2-*b*]quinazoline-5,8-dione (**18**).

A solution of compounds **7a-c** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (40 ml) was heated under reflux for 3 hrs. The product that separated on cooling was recrystallized from a suitable solvent to give compounds **16-18** (Table 4); IR (KBr, ν_{max} in cm^{-1}): (**16**) 1693, 1667 and 1656 (C=O), 1604 (C=N); ^{1}H-NMR δ_H (DMSO-d_6): (**16**) 1.85 (t, 1H, C*H*), 2.03, 2.04, (s, 6H, 2CH_3), 2.52 (d, 2H, COCH_2), 7.44-8.01 (m, 8H, Ar-*H*) ppm.

6-[2-(4,6-Dimethyl-2-oxo-2,5-dihydro-pyrimidin-5-yl)-acetyl]-phalazino[1,2-*b*]quinazoline-5,8-dione (**19a**), 6-[2-(4,6-Dimethyl-2-thioxo-2,5-dihydro-pyrimidin-5-yl)-acetyl]-phalazino[1,2-*b*]quinazoline-5,8-dione (**19b**), 6-[2-(4-Methyl-1-2,6-dioxo-1,2,5,6-tetrahydro-pyrimidin-5-yl)-acetyl]-phalazino[1,2-*b*]quinazoline-5,8-dione (**20a**), 6-[2-(4-Methyl-6-oxo-2-thioxo-1,2,5,6-tetrahydro-pyrimidin-5-yl)-acetyl]-phalazino[1,2-*b*]quinazoline-5,8-dione (**20b**), 5-[2-(5,7-Dioxo-5,7-dihydrophalazino[1,2-*b*]quinazoline-6-yl)-2-oxo-ethyl]-pyrimidine-2,4,6-trione (**21a**) and 6-[2-(4,6-Dioxo-2-thioxo-hexahydro-pyrimidin-5-yl)-acetyl]-phalazino[1,2-*b*]quinazoline-5,8-dione (**21b**).

A solution of compound **7a-c** (0.01 mol) and urea and/or thiourea (0.01 mol) in ethanol (40 ml) was treated with sodium ethoxide (0.015 mol) and heated under reflux for 3 hrs. The reaction mixture after concentration and cooling was treated with ice/HCl solution. The solid product obtained was recrystallized from a suitable solvent to give barbituric and thiobarbituric acid derivatives **19a-b, 20a-b and 21a-b** respectively, (Table 4); IR(KBr, ν_{max} in cm^{-1}): (**19a**) 1679, 1675, 1660 and 1645 (C=O); (**20b**) 3242 (NH), 1690, 1675, 1667 and 1647 (C=O), 1160 (C=S), 1595 (C=N); ^{1}H-NMR δ_H (DMSO-d_6): (**19a**) 1.20 (s, 6H, 2CH_3), 1.81 (t, 1H, C*H*-C*H*), 2.51 (d, 2H, COCH_2), 7.37-8.01 (m, 8H, Ar-*H*) ppm; ^{1}H-NMR: (**21a**) 2.73 (d, 2H, COCH_2), 3.68 (t, H, C*H*-CH$_2$), 7.36-8.05 (m, 8H, Ar-*H*), 10.06 and 10.09(s, 2H, 2N*H*) ppm.

6-[2-(3,5-Dimethyl-isoxazol-4-yl)-acetyl]-phalazino[1,2-*b*]-quinazoline-5,8-dione (**22**), 6-[2-(3-Methyl-5-oxo-4,5-dihydro-isoxazol-4-yl)-acetyl]- phalazino[1,2-*b*]quinazoline-5,8-dione (**23**) and 6-[2-(3,5-Dioxo-isoxazolidin-4-yl)-acetyl]-phalazino[1,2-*b*]quinazoline-5,8-dione (**24**).

A solution of compound **7a-c** (0.01 mol) and hydroxyl amine hydrochloride (0.015 mol) in pyridine (30 ml) was refluxed for 3 hrs. The reaction mixture was cooled, then poured into crushed ice/HCl solution. The solid that separated was collected by filtration and recrystallized from the proper solvent to give **22-24**, (Table 4); ^{1}H-NMR δ_H (DMSO-d_6) (**22**) 2.51(s, 6H, 2CH_3), 3.49 (s, 2H, COCH_2), 7.43-8.01 (m, 8H, Ar-*H*) ppm.

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