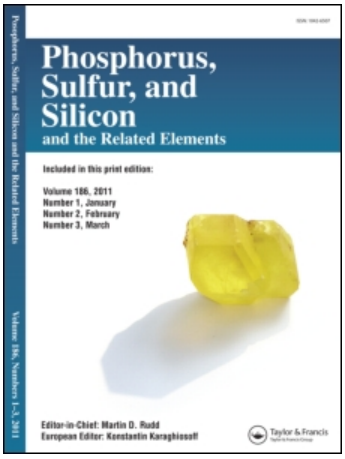

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Ghorab, M. M. , Nassar, O. M. and Hassan, A. Y.(1998) 'Synthesis of Some Sulfur Containing Tetrahydrobenzo[b] Thieno(Pyridines, Quinolines, Oxazines and Pyrimidines) as Possible Radioprotective and Antineoplastic Agents', Phosphorus, Sulfur, and Silicon and the Related Elements, 134: 1, 57 — 76
To link to this Article: DOI: 10.1080/10426509808545452
URL: http://dx.doi.org/10.1080/10426509808545452

Phosphorus, Sulfur and Silicon, 1998, Vol. 134/135, pp. 57-76
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SYNTHESIS OF SOME SULFUR CONTAINING TETRAHYDROBENZO[b] THIENO(PYRIDINES, QUINOLINES, OXAZINES AND PYRIMIDINES) AS POSSIBLE RADIOPROTECTIVE AND ANTINEOPLASTIC AGENTS

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(Received 27 August, 1997; In final form 8 October, 1997)

Synthesis of novel benzothienopyridines, benzothienoquinoline, benzothienoxazines and benzothienopyrimidines utilizing 2-methyl-5,6,7,8-tetrahydro-4H-3,1-benzothienoxazine-4-one are reported. The structure of these compounds were confirmed by microanalyses, IR, ^{1}H-NMR and mass spectrometry. Preliminary biological studies of some compounds showed a promising radioprotection and antineoplastic activities.

Keywords: Thieno(pyridine; quinoline; oxazine); radioprotective and antineoplastic agents

INTRODUCTION

As part of a program designed to investigate the biological activity of tricyclic and tetracyclic heterocyclic systems containing a thiophene ring as the central nucleus,[1–4] recently we have put forward a convenient way to synthesize thieno[2,3-d]pyrimidines[1].

A survey of the literature showed that derivatives of thienopyridine, thienoquinoline, thienoxazine and thienopyrimidine possessed antihypertensive action,[5,6] platelet aggregation inhibition,[7–9] antineoplastic[10] and

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antihistamin activity[11–13]. In addition sulfur compounds are widely used as radioprotective drugs[14–18].

In the light of these facts, and as a continuation of our investigations on sulfur containing tricyclic and tetracyclic systems, we planned to synthesize new derivatives of thienopyridine, thienoquinoline, thienoxazine and thienopyrimidine to evaluate their radioprotection and antineoplastic activities from the point of biochemical and genetical studies.

RESULTS AND DISCUSSION

In a recent series of publications,[19–21] it has been reported that, the reaction of 3,1-benzoxazine-4-ones with active methylene compounds in basic medium gave the corresponding 3-substituted quinoline. In the present investigation, the reaction of 2-methyl-5,6,7,8-tetrahydro-4H-3, 1-benzothienoxazine-4-one (1),[22] with malononitrile using sodium ethoxide as catalyst, gave 2-methyl-3-cyano-5,6,7,8-tetrahydrobenzothienopyridine-4-one (2).

Extending the reaction to include ethyl acetoacetate, diethyl malonate or ethyl cyanoacetate in boiling pyridine yielded one and the same product 2-methyl-3-carboethoxy-5,6,7,8-tetrahydrobenzothienopyridine-4-one (9). IR spectrum of (2) revealed bands at 3500 cm^{-1} (OH), 2920 cm^{-1}(CH aliphatic) and 2200 cm^{-1} (C≡N). IR spectrum of (9) showed bands at 3500 cm^{-1} (OH), 2900 (CH aliphatic) and 1720 cm^{-1}(C=O). ^{1}H-NMR spectrum of (9; in DMSO-d_6) showed signals at 1.2 [3H, t, CH_3 ester], 1.8, 2.5 [8H, 2s, 4CH_2 cyclo], 2.2 [3H, s, CH_3], 4.2 [2H, q, CH_2 ester] and 13 ppm [1H, br, OH].

When (2) was heated with arylidenemalononitrile (3a,b) in ethanol with few drops of piperidine the 2-aryl-3-cyano-4-amino-benzothienoquinoline derivatives (6a,b) were obtained. The formation of (6)from reaction of (2) and (3a,b) is assumed to proceed via Michael type addition of the methyl functional group in (2) to the activated double bond yielding acyclic Michael adduct (4a) which then cyclizes into (5a). The latter readily looses HCN to yield the final isolable thermodynamically stable compounds (6a,b).

In contrast to anticipated formation of the ester (7), the reaction of (2) with ethyl arylidenecyanoacetate (3c,d) afforded (6a,b), and are assumed

to proceed via elimination of ethyl formate from the intermediate (5b). Compounds (6a,b) were also synthesized by refluxing of malononitrile or ethyl cyanoacetate with the styryl derivatives (8) in ethanol containing few drops of piperidine. IR spectrum of (6b) exhibited bands at 3500 cm^{-1} (OH), 3350, 3300 cm^{-1} (NH_2) and 2220 cm^{-1} (C≡N). The mass spectrum of (6b) showed a molecular ion peak m/z 405 with a base peak at 60 (100%) (Figure 1). IR spectrum of (8b) revealed bands at 3500 cm^{-1} (OH), 2920 cm^{-1}(CH aliphatic) and 2210 cm^{-1} (C≡N). The ^{1}H-NMR spectrum of (8a in DMSO-d_6) exhibited signals at 1.7, 2.4 [8H, 2s, 4 CH_2 cyclo], 3.4 [3H, s, OCH_3], 7.3–7.8 [4H, m, Ar-H], 8.0 [2H, s, CH=CH] and 11.3 ppm [1H, br, OH].

Compound (2) was condensed with (1 mol) and/or (2 mol) of phenyl isocyanate in dry benzene in the presence of triethylamine, the imino derivative (11) was obtained instead of the expected (10). IR spectrum of (11) showed the absence of (C≡N) and the presence of (NH) at 3280 cm^{-1}, (2C=O) at 1740, 1670 cm^{-1}. The mass spectrum of (11) showed a molecular ion peak m/z 482 with a base peak at 119 (100%) (Figure 2).

Using toluene instead of benzene as solvent alters the outcome of the cyclization reaction. Thus, reaction of (2) with (1 mol) and/or (2 mol) of phenyl isocyanate in toluene using triethylamine as catalyst gave (12). These results indicate that the higher reaction temperature of toluene causes Dimroth,[22] rearrangement of the intermediate (10) to form (12). IR spectrum of (12) showed the absence of (C≡N) and presence of (NH) at 3300 cm^{-1} and (C=O) at 1680 cm^{-1}. The ^{1}H-NMR spectrum of (12 in DMSO-d_6) exhibited signals at 1.9, 2.5 [8H, 2s, 4 CH_2 cyclo], 2.3 [3H, s, CH_3], 7.1–7.7 [5H, m, Ar-H] and 10.2 ppm [1H, s, NH]. Mass spectrum of (12) showed a molecular ion peak m/z 363 with a base peak at 119 (100%) (Figure 3).

Phthalic anhydride, tetrabromophthalic anhydride, succinic anhydride or maleic anhydride condensed with (1) to give derivatives of 1,3-indandione (13a,b); 1,3-cyclopentandione (15) and 4-cyclopentene-1,3-dione (16), respectively. IR spectrum of (13b) showed the presence of (3C=O) at 1750, 1700, 1690 cm^{-1}. Mass spectrum of (13b) showed a molecular ion peak m/z 667 with a base peak at 573 (100%), other significant peaks appeared at 569 (12.6%), 448 (34.0%); 343 (16.0%), 231 (4.2%), 111(11.2%), 76 (4.7%).

Condensation of phenylacetic acid with (13a) by fusion yielded 2-(1 -benzylidene-3-oxo-2-indanyl)-5,6,7,8-tetrahydro-4H-3,1-benzothienox-

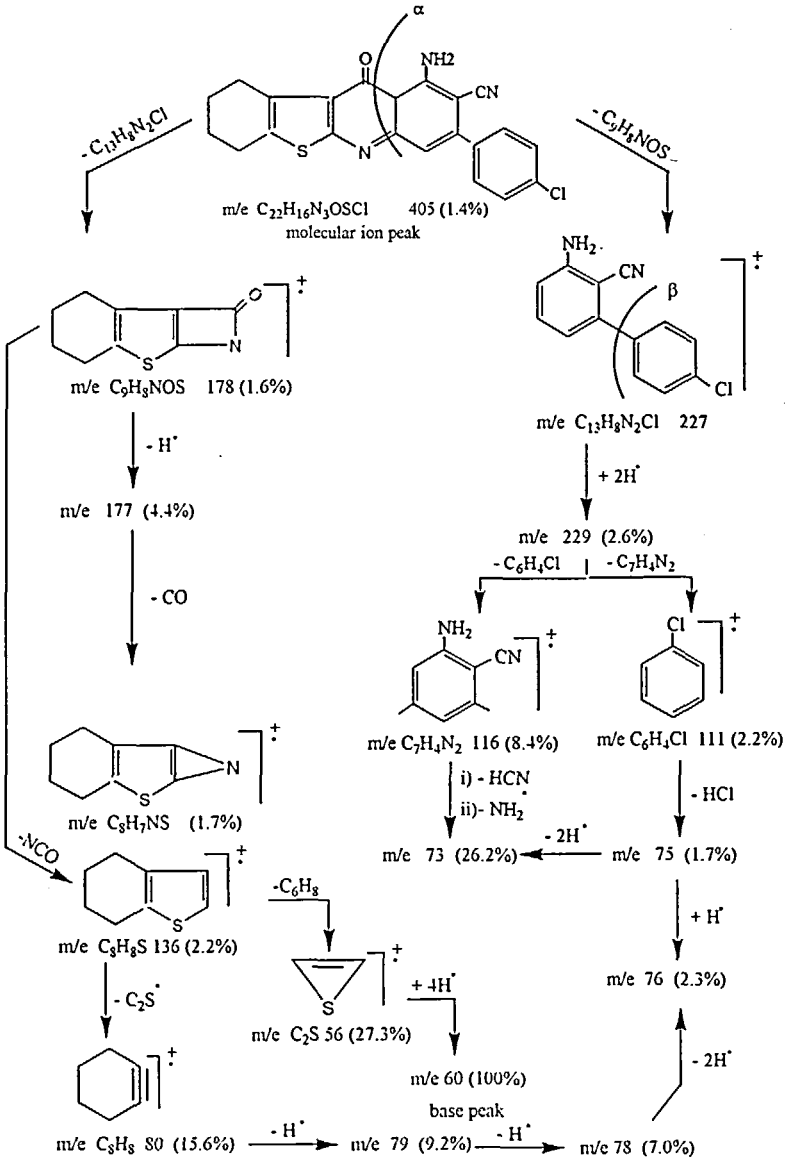


FIGURE 1 Mass fragmentation pattern of compound (6b)

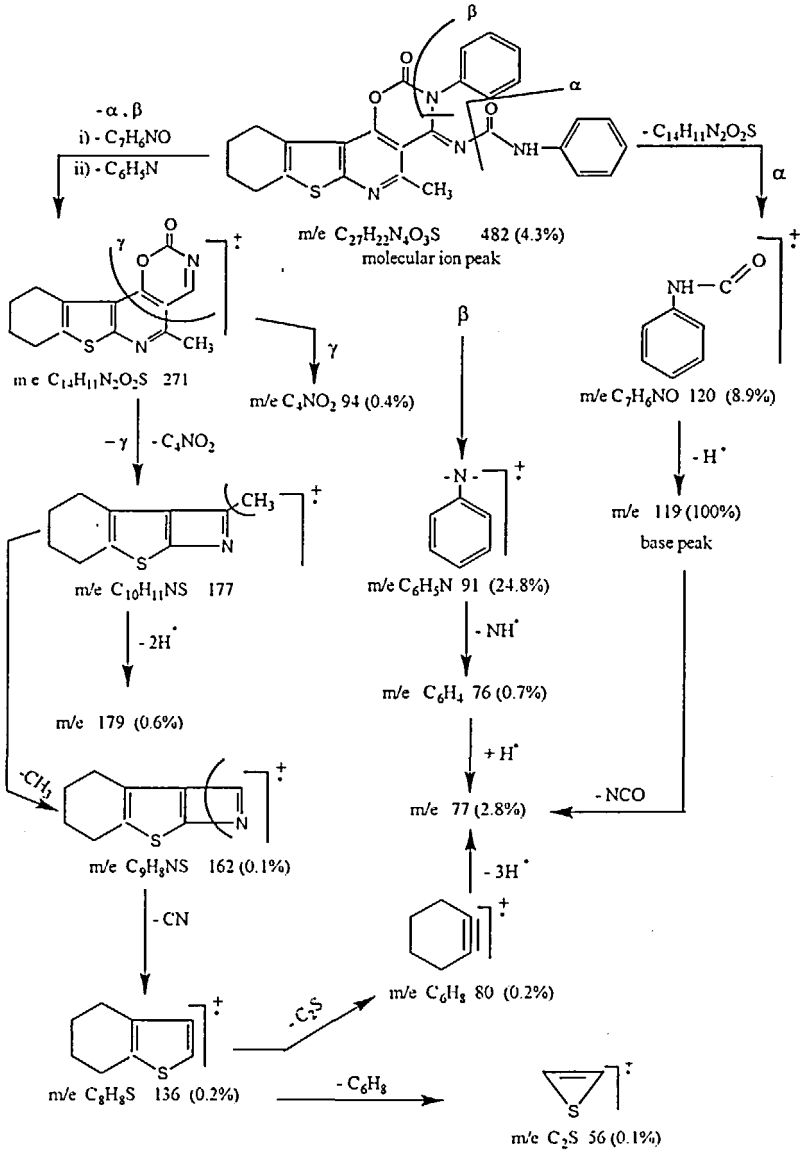


FIGURE 2 Mass fragmentation pattern of compound (11)

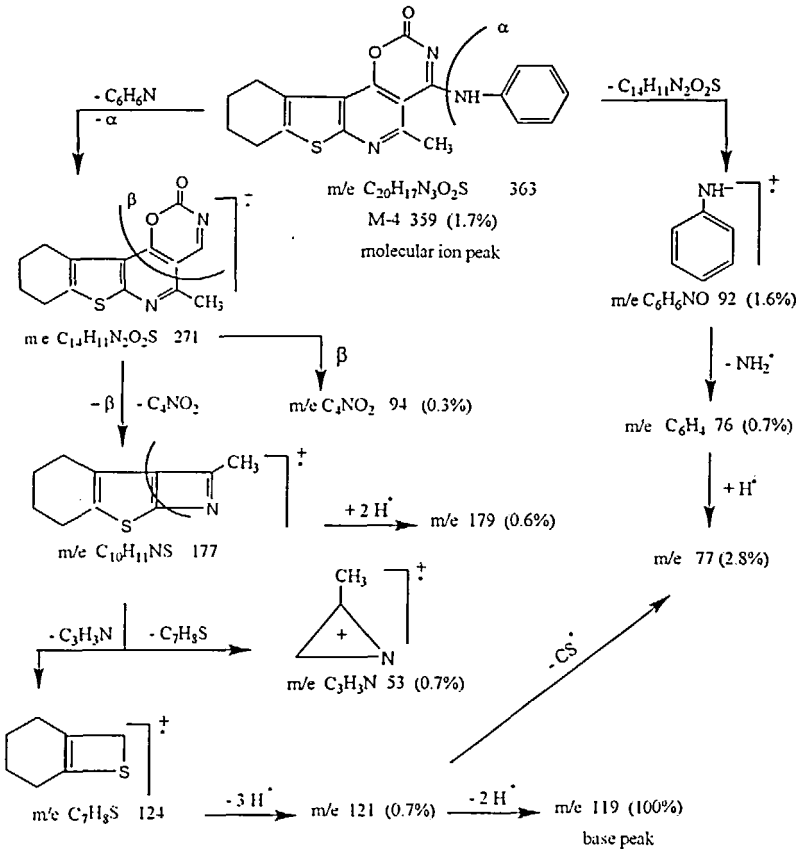


FIGURE 3 Mass fragmentation pattern of compound (12)

azine-4-one (14). IR spectrum of (14) showed bands at 1690, 1660 cm^{-1}(2C=O). The ^{1}H-NMR spectrum of (14; in DMSO-d_6) showed signals at 1.9, 2.4 [8H, 2s, 4 CH_2 cyclo], 6.0 [2H, s, 2CH], 7.4–7.8 [9H, m, Ar-H].

Interaction of (1) with o-phenylenediamine; anthranilamide and/or thiosemicarbazide in glacial acetic acid and in presence of fused sodium acetate yielded benzimidazole derivative (17); quinazolinone derivative (19) and triazole derivative (22), respectively. However, formation of the quinazolinone (19) was mediated, most likely, by 2-methyl-3-(o-carbamoylphenyl)-5, 6, 7, 8-tetrahydrobenzothieno[2,3-d]pyrimidine-4-one

intermediate (18) which could undergo cyclodehydration to afford (19). IR spectrum of (17) showed the absence of (C=O) and presence of (C=N) at 1630, 1610 cm^{-1}. IR spectrum of (19) exhibited bands at 1700 cm^{-1} (C=O) and 1640, 1620 (C=N). The ^{1}H-NMR spectrum of (19 in DMSO-d_6) showed signals at 1.7, 2.4 [8H, 2s, 4 CH_2 cyclo] ; 2.1 [3H, s, CH_3], 7.0–7.6 [4H, m, Ar-H]. The mass spectrum of (22) showed a molecular ion peak m/z 276 with a base peak at 115 (100%) (Figure 4).

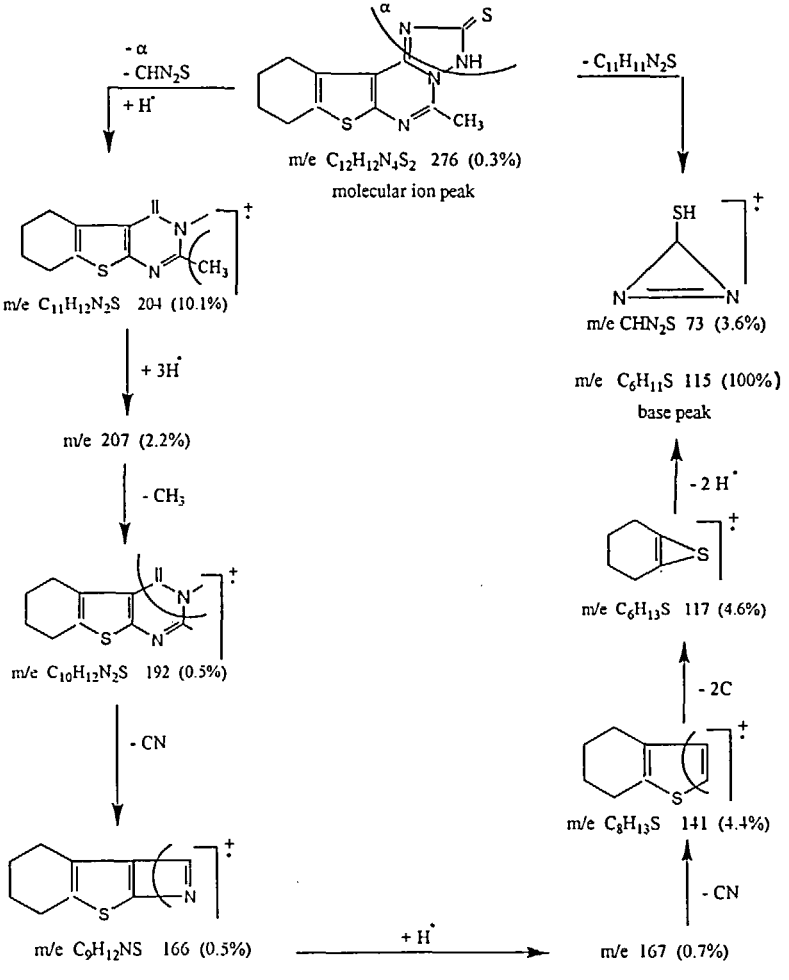


FIGURE 4 Mass fragmentation pattern of compound (22)

Reaction of (1) with anthranilic acid gave the thienopyrimidine derivative (20). IR spectrum of (20) revealed a broad band at 3500 cm^{-1}(OH), 2900 cm^{-1} (CH aliphatic), 1720, 1690 cm^{-1} (2C=O) and 1610 cm^{-1} (C=N).

Condensation of (1) with phthalimide gave 2-(5,6,7,8-tetrahydro-4-oxo-4H-3,1-benzothienoxazine-2-yl)-3,4-benzo-5-pyrrolidone (21a),which was reacted with 4-chloroaniline to give 2-[5,6,7,8-tetrahydro-3-(4-chlorophenyl)-4-oxo-2-benzothieno[2,3-d]pyrimidinyl]-3,4-benzo-5-pyrrolidone (21b). IR spectrum of (21a) showed bands at 3250 cm^{-1}(NH), 1750, 1680 cm^{-1} (2C=O). The ^{1}H-NMR spectrum of (21b, in DMSO-d_6) showed signals at 1.8–2.4 [8H, 2s, 4 CH_2 cyclo], 6.3 [1H, s, CH]; 7.3–8.2 [8H, m, Ar-H], 10.2 ppm [1H, s, NH].

Finally, aromatic aldehydes condensed with (1) by fusion at 170°C in the presence of anhydrous zinc chloride yielded 5,6,7,8-tetrahydro-2-styryl-4H-3,1-benzothienoxazine-4-one (23). IR spectrum of (23) showed bands at 1700 cm^{-1} (C=O). The ^{1}H-NMR spectrum of (23b; in DMSO-d_6) showed signals at 1.7, 2.5 [8H, 2s, 4CH_2 cyclo], 6.6 [2H, s, CH=CH]; 7.0–7.5 [3H, m, thiophene ring].

EXPERIMENTAL

Melting points reported are uncorrected. Elemental analyses were performed in Microanalytical Laboratory, Cairo University, Egypt. IR spectra (KBr) on a FT-IR 1650 spectrophotometer (γmax in cm^{-1}) and ^{1}H-NMR spectra in (DMSO-d_6) solution with TMS as internal standard (δ, ppm) were recorded on a JEOL FXQ 90 MHz NMR spectrometer. Mass spectra were recorded on a GCMS-QP 1000 EX by direct inlet (source temp-90–300 beem energy 70eV).

2-Methyl-3-cyano-5,6,7,8-tetrahydrobenzothienopyridine (2)

A mixture of (1, 0.01 mol); sodium ethoxide and malononitrile (0.01 mol) in (50 ml) ethanol was heated under reflux for 22 hr, the reaction mixture was poured into ice-cold dilute HCl. The product was crystallized from ethanol to give (2, Table I).

Formation of (6a,b).

Method (A)

A suspension of an equimolar amount (0.01 mol) of (2) and the appropriate amount of arylidenemalononitrile (3a,b; 0.01 mol) in ethanol (40 ml) was refluxed with piperidine (1 ml) for 3 hr. The solid product was collected by filtration and crystallized from ethanol to give (6a,b; Table I).

Method (B)

A suspension of (8; 0.01 mol) in ethanol (30 ml) was treated with malononitrile or ethyl cyanoacetate (0.01 mol) and dry pyridine (1 ml). The mixture was refluxed for 3 hr and the solvent was concentrated into vacuo and crystallized from ethanol (m.p and m.m.p as 6a,b).

Condensation of (2) with aromatic aldehydes

A solution of (2; 0.01 mol) and appropriate aromatic aldehydes (0.01 mol) in ethanol (30 ml) with (0.1 ml) piperidine was refluxed for 5 hr. The solvent was removed in vacuo and the remaining products were triturated with a little water. The resulting solid, obtained on standing was collected by filtration and crystallized from ethanol to give (8a,b; Table I).

Reaction of (1) with active methylene compounds

A solution of (1 ; 0.01 mol) and active methylene compounds namely ethyl acetoacetate; diethylmalonate and/or ethyl cyanoacetate (0.02 mol) in (50 ml) pyridine was heated under reflux for 17 hr. The reaction mixture was poured into ice-cold dilute HCl to give product which was crystallized from ethanol to give (9; Table I).

Formation of (11)

Method (A)

A solution of (2; 0.01 mol), phenyl isocyanate (0.01 mol) and triethylamine (0.5 ml) in dry benzene (50 ml) was refluxed for 48 hr. The obtained product was crystallized from benzene to give (11; Table I).

Method (B)

Compound (11) was also obtained by refluxing (2; 0.01 mol) with phenyl isocyanate (0.02 mol) in dry benzene (50 ml) in the presence of triethylamine (0.5 ml) for 48 hr (m.p and m.m.p).

Formation of (12)

Method (A)

To a solution of (2; 0.01 mol) and phenyl isocyanate (0.01 mol) in toluene (50 ml) in presence of triethylamine (0.5 ml) was refluxed for 48 hr. The obtained product was crystallized from ethanol to give (12, Table I).

Method (B)

Compound (12) was also obtained by refluxing (2; 0.01 mol), with phenyl isocyanate (0.02 mol) and triethylamine (0.5 ml) in toluene (50 ml) to give (12) (m.p and m.m.p).

Condensation of (1) with anhydrides, phthalimide or aldehydes

A mixture of (1; 0.01 mol); appropriate anhydride; phthalimide and/or aldehydes (0.015 mol) and anhydrous zinc chloride (0.5 g) was heated in an oil bath at 170°C for 4hr. After cooling the products was washed with water and crystallized from ethanol-acetic acid to give (13), (15), (16), (21a) and (23), respectively (Table I).

Formation of (14)

A mixture of (13a; 0.01 mol) and phenylacetic acid (0.05 mol), was heated in an oil bath for 6 hr. The reaction mixture was steam distilled to get rid off the excess of phenylacetic acid. The solid obtained was crystallized from ethanol-benzene to give (14; Table I).

Formation of (17), (19) and (22)

A mixture of (1; 0.01 mol); o-phenylenediamine, anthanilamide and/or thiosemicarbazide (0.01 mol) and fused sodium acetate (1 gm) was refluxed in glacial acetic acid for 12 hr. After cooling, the reaction mixture was

poured onto ice-cooled water (100 ml). The solid so-formed was isolated, dried and crystallized from ethanol to give (17), (19) and (22); respectively (Table I).

Formation of (20)

A mixture of (1; 0.01 mol) and anthranlic acid (0.012mol) was refluxed in ethanol (50 ml) for 12 hr. The solid product was crystallized from dioxane to give (20, Table I).

Formation of (21b)

A mixture of (21a; 0.01 mol) and 4-chloroaniline (0.012 mol) was refluxed in ethanol (50 ml) for 8 hr. The solid product was crystallized from dioxane to give (21b, Table I).

TABLE I Physico-chemical and analytical data of compounds (2–23)

Compd. No.	*M. .P. Degree Centigrade*	*Yield %*	*Mol.-formula*	*Analysis Required / (Found)*		
				C%	*H%*	*N%*
2	278–280	76	$C_{13}H_{12}N_2OS$	63.93	4.91	11.47
				(64.10)	(4.60)	(11.30)
6a	>340	65	$C_{23}H_{19}N_3O_2S$	68.82	4.73	10.47
				(68.60)	(4.50)	(10.20)
6b	>340	64	$C_{22}H_{16}N_3OSCl$	65.18	3.95	10.37
				(65.40)	(3.70)	(10.50)
8a	>340	77	$C_{21}H_{18}N_2O_2S$	69.61	4.97	7.73
				(69.40)	(5.10)	(7.90)
8b	>340	84	$C_{20}H_{16}N_2OSCl$	65.30	4.35	7.61
				(65.10)	(4.60)	(7.40)
9	218–220	81	$C_{15}H_{17}NO_3S$	61.85	5.84	4.81
				(62.10)	(5.50)	(4.50)
11	200–202	57	$C_{27}H_{22}N_4O_3S$	67.21	4.56	11.61
				(67.50)	(4.70)	(11.80)

Compd. No.	*M. .P. Degree Centigrade*	*Yield %*	*Mol.-formula*	*Analysis Required / (Found)*		
				C%	*H%*	*N%*
12	220–22	61	$C_{20}H_{17}N_3O_2S$	66.11	4.68	11.57
				(66.40)	(4.90)	(11.80)
13a	258–60	78	$C_{19}H_{13}NO_4S$	64.95	3.70	3.98
				(64.60)	(3.50)	(3.70)
13b	270–72	83	$C_{19}H_9NO_4SBr_4$	34.18	1.34	2.09
				(34.50)	(1.50)	(2.20)
14	130–32	64	$C_{26}H_{19}NO_3S$	73.41	4.47	3.29
				(73.60)	(4.60)	(3.40)
15	>340	73	$C_{15}H_{13}NO_4S$	59.40	4.29	4.62
				(59.20)	(4.50)	(4.80)
16	>340	71	$C_{15}H_{11}NO_4S$	59.80	3.65	4.65
				(59.50)	(3.50)	(4.40)
17	>340	72	$C_{17}H_{15}N_3S$	69.62	5.11	14.33
				(69.40)	(5.30)	(14.10)
19	210–212	68	$C_{18}H_{15}N_3OS$	67.28	4.67	13.08
				(67.10)	(4.90)	(13.20)
20	>340	79	$C_{18}H_{16}N_2O_3S$	63.52	4.70	8.23
				(63.30)	(4.40)	(8.50)
21a	230–32	62	$C_{19}H_{14}N_2O_3S$	65.14	4.00	8.00
				(65.40)	(4.20)	(7.80)
21b	198–200	67	$C_{25}H_{18}N_3O_2SCl$	65.35	3.92	9.15
				(65.60)	(3.60)	(9.40)
22	253–55	75	$C_{12}H_{12}N_4S_2$	52.17	4.34	20.28
				(52.40)	(4.50)	(20.10)
23a	220–22	86	$C_{18}H_{15}NO_2S$	69.90	4.85	4.53
				(69.60)	(4.70)	(4.70)
23b	>340	81	$C_{16}H_{13}NO_2S_2$	60.95	4.12	4.44
				(61.10)	(4.30)	(4.10)

Biological Screening

The compounds (6a, 11, 12, 17, 21b and 22) has been selected in view of the possible role as radioprotective and/or antineoplastic agents. The screening results are presented in (Table II–V).

TABLE II In-vitro antineoplastic activity of some new compounds

Compd. No.	6a	11	12	17	21b	22
non-viable %*	55	66	30	56	60	55

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

TABLE III In-vivo micronucleus test of antineoplastic activity of some new compounds

Compd. No.	Control	6a	11	12	17	21b	22
No. of mice	2	2	2	2	2	2	2
PE with micronuclei	1.5	3.1 *	2.8*	1.9	1.6	4.2**	1.7

* Significant > 0.05.
** Highly significant > 0.01.
(PE) micronucleated polychromatic mice erythrocytes.

I- In-vitro antineoplastic activity

The selected compounds were tested against Ehrlich Asites Carcinoma tumor cells, according to the reported method[23]. The tested compounds were suspended in tween 80 and distilled water at the concentration of 0.75 mg/ml.

II- In-vivo antineoplastic activity

A - Micronucleus test

Micronucleus test was carried out to investigate the antineoplastic activity of the tested compounds according to Schmid[24] (1973). The screening results are expressed as the avarege number of micronucleated polychromatic erythrocytes (PE) per 100 PE (%).

B - Radioprotection activity

In the present work twenty four female rats "80–120 gm" were used for each tested compound in addition to 6 rats representing the positive control group. The experimental animals were tested as follows :

i. A group of rats (contains 12 rat) treated with the tested compound alone at a concentration of 0.75 mg/kg body weight.

ii. A group of rats (contains 12 rat) treated with the tested compound pre-irradiation.

Blood samples were collected on the first and third days after treatment.

Irradiation technique

The irradiation tool was a Canadian Caesium 137 irradiation unit installed at the National Center for Radiation Research and Technology (NCRRT). The animals were subjected to whole body gamma irradiation at total dose level of 6.5 Gy. Dose rate is 1.2 rad/sec.

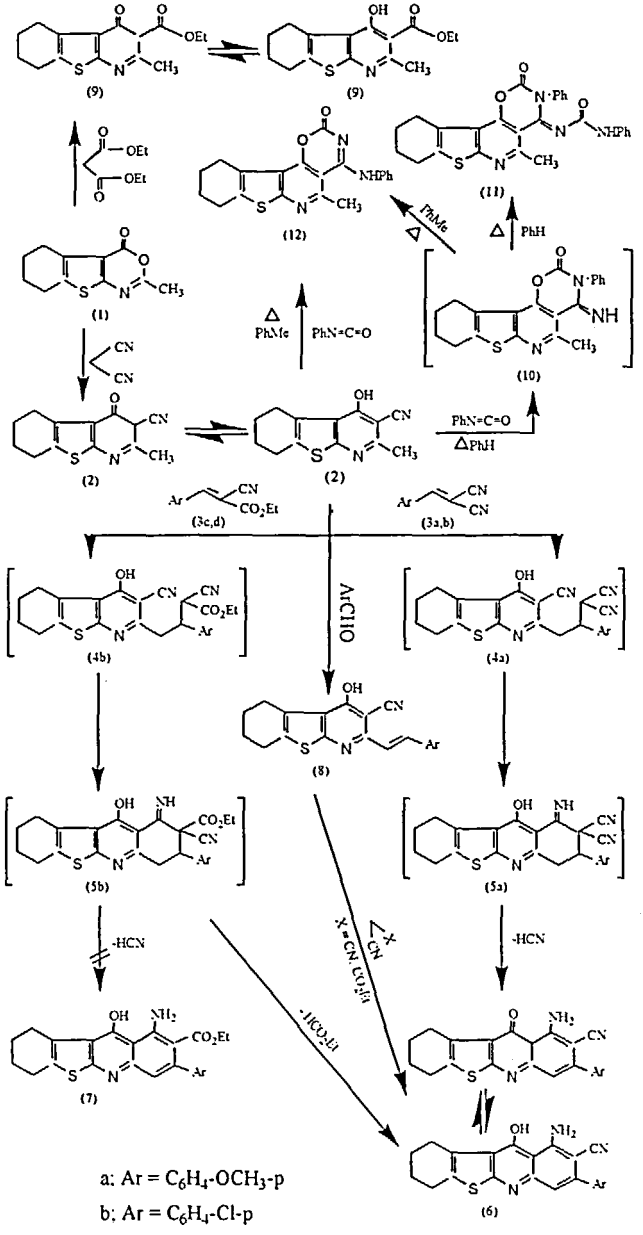
Biochemical Assays

a. Determination of reduced glutathione content (GSH); according to the reported method[25].
This method is based upon the development of a relatively stable yellow colour when 5,5-dithio-bis(2-nitrobenzoic acid) is added to sulfhydril compounds.

b. Determination of superoxide dismutase activity (SOD) by Minami and Yoshikawa[26].
This enzyme catalyses the determination of superoxide anions to hydrogen peroxide and molecular oxygen.

Antineoplastic activity

From the obtained results (Table II, III) compounds (6a, 11, 17 and 21b) revealed antineoplastic activity specially compound (21b) showed highly significant increased, this may be attributed to the combination of thienopyrimidine ring and pyrrolidone moiety.



SCHEME 1

Radioprotection activity

I-SOD level

From the data obtained in (Table IV) on the first day after treatment-irradiation (in group II) the SOD level revealed highly significant level for compounds (6a, 12, 17 and 22) in comparison with the control-irradiated group.

TABLE IV Blood Superoxide Dismutase Level (μg/ml of mixture)

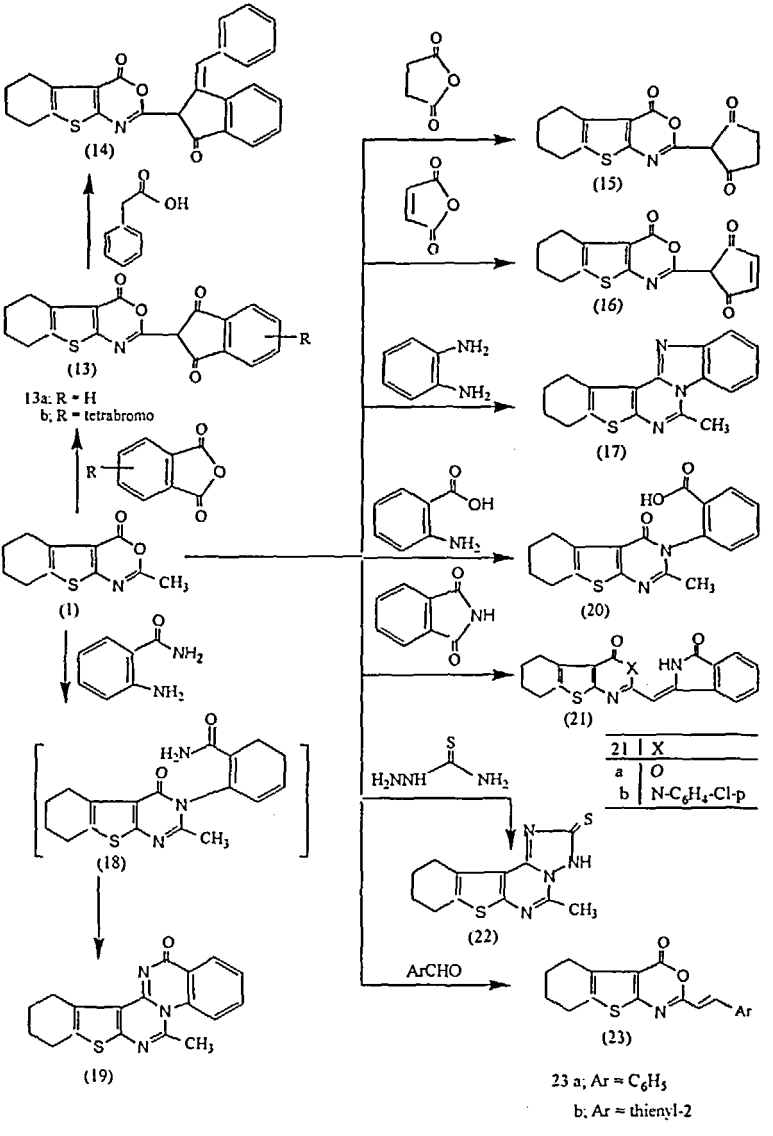
Treatment Compd.No.	*Treated alone I*		*Treated + Irradiated II*	
	1 day	*3 day*	*1 day*	*3 day*
6a	5.716±0.181	**6.416± 0.225	**6.790± 0.173	*8.016 ± 0,169
11	**2.533±0.133	**3.866±0.114	**4.461±0.113	*5.750 ±0.158
12	**4.628±0.151	5.416±0.107	**6.663±0.176	*7.200±0.232
17	**3.383±0.116	*4.383±0.181	**6.700±0.153	*7.783±0.107
21b	5.733 ±0.162	**6.233±0.057	5.826±0.117	*6.583±0.107
22	5.666±0.167	**6.266±0.149	6.700±0.158	*7.333±1.160
Control-irradiated group	5.878±0.113	5.158±0.114		

On the third day after treatment (in group I) the SOD level showed highly significance for compounds (6a, 21b, and 22), as well as most compounds (except compound 11) exhibited highly significance (in group II).

It must be taken into consideration that all the tested compounds (in group I) on the first day, showed significant decreased level of SOD.

II-GSH content

The GSH content in both group (I) and (II) on the first day exhibited significant to highly significant increased content for the tested compounds except for compound (17) as shown in (Table V) in comparison with the control-irradiated group.



SCHEME 2

On the third day after treatment alone (group I) compounds (6a, 12, 17, 21b and 22) revealed increased content of the GSH in comparison with the control-irradiated group. Meanwhile, on the third day in (group II), only

compounds (12 and 21b) showed highly significant amelioration of the GSH content compared with the control-irradiated group.

TABLE V Blood Glutathione Content (mg%)

Treatment Compd. No.	*Treated alone I*		*Treated + Irradiated II*	
	1 day	*3 day*	*1 day*	*3 day*
6a	**60.768±1.790	**44.066±1.250	**41.111±1.410	**28.078±1.320
11	**68.191±1.320	**22.042±1.370	**61.811±1.570	33.390±2.290
12	*40.545±1.502	**81.386±0.910	**40.601±1.350	*44.241 ±1.570
17	28.420±1.220	**45.588±1.490	37.510±1.542	36.928±1.310
21b	*39.231±1.740	**51.619±1.460	**40.596±1.310	**69.785±1.180
22	35.886±1.520	*40.910±0.980	26.063±1.366	25.916±2.660
Control-irradiated group	26.665±1.160	36.876±1.526		

* Significant > 0.05.
** Highly significant > 0.01

Radiation exposure is known to be able to impair the biological integrity of the living organisms (Yarmonenko 1988)[27]. As already known, irradiation induces direct and indirect effects. The indirect effect induce free radicals in water specially the superoxide radical, which is captured by superoxide dismutase in cells to protect them against their hazardous effects.

In the present study, irradiation alone induced significant decrease in glutathione content and superoxide dismutase enzyme level in-agreement with those of Witshi[28] (1976) and Barni et al[29] (1980).

The depletion of glutathione content as shown in the present results either by exposure to irradiation alone or by treatment with compound (17) in (Table V), was brought about by impaired glutathione-synthesis which is associated with an increase in oxidized glutathione due to the decreased transport activity of oxidized glutathione through cell membranes.

The significant amelioration of glutathione content by compounds (12 and 21b) (Table V) was in-agreement with results of Young et al[30](1985)

and Vaz et al[31] (1981) who reported increased glutathione content with compound containing (NH) group.

Since superoxide dismutase is present in all metabolizing cells, so it functions to provide a defense against the potentially damaging reactivities of the oxygen radical which is captured by SOD in cells. The decreased level of superoxide dismutase lead to disturbances in the metabolic consequences (Weisiger and Fridovich, 1973)[32]. This was presented in our results by the use of compound (11).

Compounds (6a, 12, 21b and 22) revealed significant amelioration in the level of SOD enzyme specially after exposure to gamma-irradiation, due to the presence of (NH and NH_2) group which donate electrons to metals to change their oxidation states, this was in-agreement with Buettner et al[33](1978).

Finally, compounds (12 and 21b) showed to be the most promising radioprotector ones, this may be attributed to the combined presence of (NH) and sulfur atom in their structures.In addition compound (21b) revealed to be the only one which showed both antineoplastic and radioprotection activity.

Acknowledgements

The authors wish to thank Dr. S.M. El-Sayed, Biology Department, National Center for Radiation Research and Technology, Cairo, Egypt and Dr. M.A. El-Sayed, Faculty of Science, Cairo University, Beni Sweaf Branch for plaining and performing the biological studies and for their great co-operation.

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