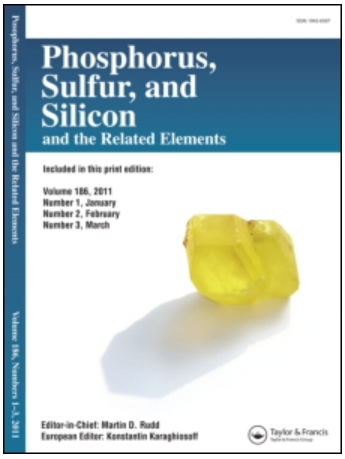

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SYNTHESIS AND EFFECT OF GAMMA RADIATION ON SOME SULFUR CONTAINING 3-SUBSTITUTED-4-OXO-2,4,5,6,7,8-HEXAHYDROBENZO [b]THIENO-[2,3-d]PYRIMIDINES OF BIOLOGICAL INTEREST

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SYNTHESIS AND EFFECT OF GAMMA RADIATION ON SOME SULFUR CONTAINING 3-SUBSTITUTED-4-OXO-2,4,5,6,7,8-HEXAHYDROBENZO [b]THIENO-[2,3-d]PYRIMIDINES OF BIOLOGICAL INTEREST

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Condensation of 4-oxo-3,4,5,6,7,8-hexahydrobenzo [b]thieno [2,3-d]-pyrimidine (**I**) with allyl bromide or ethyl chloroacetate gave (**IIa, b**). Interaction of the ester derivative **IIb** with hydrazine hydrate furnished the hydrazide derivative **III** which was used as starting material for the synthesis of pyrazoles, oxadiazoles, thiosemicarbazide and hydrazone derivatives **IV**, **V**, **VI**, **VII**, **VIII**, **IX**, and **XI** respectively. Cyclodehydration of thiosemicarbazide derivative **IX** with sodium hydroxide resulted in the formation of N-phenyl-mercaptotriazole derivative **X**. The thiazolidenones (**XIIa–d**) were obtained through the interaction of the hydrazone derivatives **XI** with mercaptoacetic acid. The obtained compounds have been characterized on the basis of their spectral (IR, PMR and Mass) data and elemental analysis. Most of these compounds have been found to exhibit good antibacterial and antifungal activities. The stability of some biologically active compounds towards gamma radiation have been investigated.

Key words: Synthesis of thienopyrimidinones, biological activity, gamma-radiation.

INTRODUCTION

A literature survey has revealed that the thienopyrimidines are long known to exhibit antithyroid activity, antibacterial and diuretic action.[1–4] In addition, oxadiazoles, triazoles and thiazolidenones are of great biological importance as potent drugs.[5–8] In view of this, we have now undertaken the synthesis of some new thienopyrimidine derivatives having collectively the above mentioned moieties and study their biological activities.

MATERIAL AND METHODS

Melting points were taken on an electrothermal melting point apparatus and are uncorrected. Microanalysis were carried out at the microanalytical data unit Cairo

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University on a heraeus instrument. IR spectra were recorded on a Pye Unicam SP 1000 Spectrophotometer in KBr. UV absorption spectra were recorded using a Beckman double beam spectrophotometer model 25, ranging from 190–700 nm (λ max in nm). PMR spectra were measured on a VARIAN GEMINI 200 (200 MHz, ^{1}HNMR) using TMS as internal standard chemical shift (δ in ppm). The mass spectra were run using HP MODEL: 5988. The irradiation process was carried out at the National Centre for Radiation Research and Technology, Nasr City, Cairo Egypt. The irradiation facility used was Egypt's Industrial Mega. gamma-I, Type. J.6600 irradiator, the source used is Cobalt-60. The average dose rate at the auxiliary conveyor was 0.0227 Gy/sec. at the time of the experiment.

Formation of (**IIa, b**)

A mixture of (**I**; 0.01 mol), allyl bromide or ethyl chlorocetate (0.01 mol) and anhydrous K_2CO_3 (2 g) in dry acetone (50 ml) was refluxed for 24 hr. The reaction mixture was filtered while hot and the product that obtained after concentration of filtrate was recrystallized to give (**IIa, b**; Table I).

Reaction of **IIb** *with Hydrazine Hydrate: Formation of Hydrazide Derivative* **III**

To a solution of (**IIb**; 0.01 mol) in ethanol (50 ml), hydrazine hydrate (0.012 mol) was added and the reaction mixture was refluxed for 1 hr. The product obtained after concentration was separated and recrystallized to give (**III**, Table I).

Reaction of **III** *with Acetylacetone, Ethyl Acetoacetate or Diethylmalonate: Formation of Pyrazole Derivatives* **IV, V** *and* **VI**

A solution of (**III**; 0.01 mol) in ethanol (30 ml) was treated with acetylacetone, ethyl acetoacetate or diethylmalonate (0.01 mol) and the solution was refluxed for 6 hr. Ethanol was distilled off and the solid was filtered and purified by recrystallization to give (**IV, V** and **VI**, Table I).

Reaction of **III** *with Benzoic Acid: Formation of 2-phenyl-1,3,4-oxadiazole Derivative* **VII**

A mixture of (**III**, 0.01 mol), benzoic acid (0.02 mol) and phosphorus oxychloride (5 ml) was refluxed on a water bath for 5 hr. The resulting solid was recrystallized to give (**VII**; Table I).

Condensation of **III** *with Carbondisulfide: Formation of 2-mercapto-1,3,4-oxadiazole Derivative* **VIII**

A mixture of (**III**; 0.01 mol), KOH (0.01 mol) and CS_2 (0.01 mol) in absolute ethanol (30 ml) was heated under reflux for 8 hr. The solvent was removed under reduced pressure and the residue was dissolved in water, acidified with dil HCl and the separated solid was recrystallized to give (**VIII**, Table I).

TABLE I

Physico-chemical and analytical data of compounds, **IIa–XIIa–d**

Compd No.	M.P °C	Solv. cryst	Yield (%)	Mol- formula	analysis Found (calcd) %		
					C	H	N
IIa	110	E	81	$C_{13}H_{14}N_2OS$	63.40(63.41)	5.60(5.69)	11.40(11.38)
b	115	E	88	$C_{14}H_{16}N_2O_3S$	57.50(57.53)	5.40(5.47)	9.60(9.58)
III	>280	A	78	$C_{12}H_{14}N_4O_2S$	51.80(51.79)	5.10(5.03)	20.10(20.14)
IV	218	E	69	$C_{17}H_{18}N_4O_2S$	59.50(59.64)	5.30(5.26)	16.30(16.37)
V	168	B	72	$C_{16}H_{16}N_4O_3S$	55.90(55.81)	4.60(4.65)	16.40(16.27)
VI	230	A	65	$C_{15}H_{14}N_4O_4S$	52.00(52.02)	3.90(4.04)	16.10(16.18)
VII	171	E	76	$C_{19}H_{16}N_4O_2S$	62.50(62.63)	4.50(4.39)	15.30(15.38)
VIII	220	E	84	$C_{13}H_{12}N_4O_2S_2$	48.80(48.75)	3.60(3.75)	17.40(17.50)
IXa	216	A	65	$C_{14}H_{17}N_5O_2S_2$	47.70(47.86)	4.90(4.84)	19.80(19.94)
b	222	A	71	$C_{15}H_{19}N_5O_2S_2$	49.20(49.31)	5.10(5.20)	19.10(19.17)
c	142	E	68	$C_{19}H_{19}N_5O_2S_2$	55.10(55.20)	4.50(4.60)	16.90(16.94)
X	231	A	65	$C_{19}H_{17}N_5OS_2$	57.60(57.72)	4.40(4.30)	17.80(17.72)
XIa	245	A	72	$C_{19}H_{18}N_4O_2S$	62.40(62.29)	4.90(4.91)	15.40(15.30)
b	252	A	68	$C_{20}H_{20}N_4O_2S$	63.00(63.15)	5.20(5.26)	14.80(14.73)
c	>280	A	65	$C_{19}H_{17}N_5O_4S$	55.60(55.47)	4.10(4.13)	16.90(17.03)
d	246	A	71	$C_{19}H_{17}FN_4O_2S$	59.50(59.37)	4.30(4.42)	14.40(14.58)
e	260	A	69	$C_{19}H_{17}ClN_4O_2S$	57.00(56.92)	4.10(4.24)	13.80(13.98)
f	272	A	76	$C_{19}H_{17}BrN_4O_2S$	51.30(51.23)	3.90(3.82)	12.70(12.58)
g	248	A	72	$C_{18}H_{17}N_5O_2S$	58.70(58.85)	4.60(4.63)	19.00(19.07)
k	269	A	65	$C_{17}H_{16}N_4O_2S_2$	54.90(54.83)	4.20(4.30)	15.00(15.05)
XIIa	>280	E	61	$C_{21}H_{20}N_4O_3S_2$	57.10(57.27)	4.50(4.54)	12.60(12.72)
b	246	A	59	$C_{22}H_{22}N_4O_3S_2$	58.20(58.14)	4.90(4.84)	12.20(12.33)
c	202	A	65	$C_{20}H_{19}N_5O_3S_2$	54.50(54.42)	4.20(4.30)	15.80(15.87)
d	252	A	61	$C_{19}H_{18}N_4O_3S_3$	51.00(51.12)	4.10(4.03)	12.50(12.55)

A= Acetic acid B = Benzene E= Ethanol

Reaction of **III** *with Isothiocyanate: Formation of Thiosemicarbazide Derivatives (***IXa–c***)*

A mixture of (**III**, 0.01 mol), methyl isothiocyanate, ethyl isothiocyanate or phenyl isothiocyanate (0.01 mol) in dry dioxan (50 ml) was refluxed for 4 hr. The excess solvent was removed and the solid was recrystallized to give (**1Xa–c**; Table I).

Heating **1Xc** *with sodium hydroxide: Formation of N-phenyl-3-mercapto-1,2,4-triazole derivative* **X**

A mixture of (**1Xc**; 0.01 mol) and sodium hydroxide solution (25 ml, 8%) was refluxed for 5 hr. The reaction mixture was poured into water and filtered. The filtrate on acidification gave a solid which was recrystallized to give (**X**; Table I).

Reaction of **III** *with Aldehydes: Formation of Hydrazone Derivatives (***XIa–k***)*

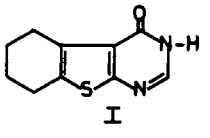
A mixture of (**III**; 0.01 mol) and the appropriate aldehyde (0.01 mol) in *n*-butanol (20 ml) was refluxed for 2 hr. The solvent was evaporated and the obtained solid was recrystallized to give (**XIa–k**; Table I).

Cyclization of **XI** *with Mercaptoacetic Acid: Formation of Thiazolidenone Derivatives (***XIIa–d***)*

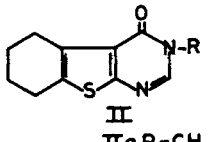
Mercaptoacetic acid (0.015 mol) was added to a well stirred solution of schiff bases (**Xa, b, g, k**; 0.01 mol) in dry benzene and refluxed for 20 hr. The solvent was evaporated by vacuum distillation and the residue treated with sodium bicarbonate and recrystallized to give (**XIIa–d**; Table I).

RESULTS AND DISCUSSION

The reaction of (**I**)[9] with allyl bromide or ethyl chloroacetate in acetone in the presence of anhydrous K_2CO_3 caused alkylation in the 3-position to give -3-substituted thienopyrimidine derivatives (**IIa, b**). This was confirmed with IR(**IIa**) which showed a strong peak at 1690 cm^{-1} corresponding (C=O) group. PMR spectrum of (**IIb** in DMSO-d_6) showed signals at 1.230 [t, 3H, CH_3, ethyl], 1.794, 2.764, 2.859 [2s, 8H, $4CH_2$ (cyclo)], 4.20 [q, 2H, CH_2 ethyl], 4.796 [s, 2H, N—CH_2—CO] and 8.327 [s, 1H, CH—N].



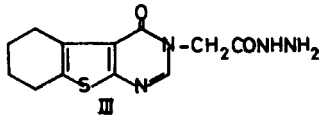
I



II

IIa; $R=CH_2-CH=CH_2$
b; $R=CH_2COOC_2H_5$

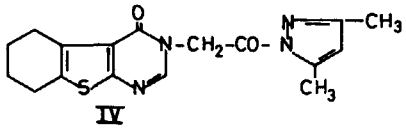
The required hydrazide derivative (**III**) was prepared through interaction of the ester (**IIb**) with hydrazine hydrate in ethanol. The assignment of this structure was inferred by analytical data and IR spectrum which showed bands at 3350; 3200 cm^{-1} (NH_2, NH) and 1700, 1680 cm^{-1} (2C=O). PMR spectrum of (**III** in DMSO-d_6) exhibited characteristic signals at 1.791, 2.776, 2.865 [2s, 8H, 4 CH_2 (cyclo)] 2.50 [s, 2H, NH_2, D_2O exchangeable], 4.717 [s, 2H, N—CH_2—CO], 8.298 [s, 1H, CH=N], 10.60 [s, 1H, NH, D_2O exchangeable].



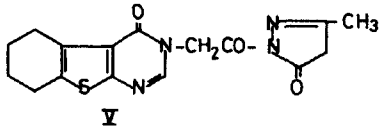
III

The pyrazole ring system has important and versatile biological activities.[10–12] As a part of our work on the synthesis of the biologically active compounds, we now wish to report the synthesis of pyrazolo thienopyrimidine derivatives. Condensation of the hydrazide (**III**) with acetylacetone, ethyl acetoacetate or diethylmalonate in ethanol[13] furnished products which gave analytical data compatible

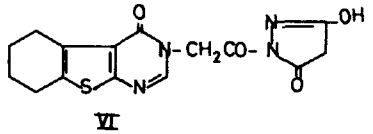
with 3,5-dimethylpyrazolo, 3-methyl-5-pyrazolono and 3-hydroxy-5-pyrazolono derivatives (**IV**, **V** and **VI**) respectively. IR measurements showed the disappearance of (NH_2, NH) and the presence of bands at 1780, 1730 cm^{-1} (2C=O) for compounds (**V**, **VI**) and a broad band at 3500 cm^{-1} (OH) for compound (VI). PMR spectrum of (**IV** in DMSO-d_6) showed signals at 1.794, 2.775, 2.856 [2s, 8H, $4CH_2$ (cyclo)], 2.261, 2.470 [2s, 6H, $2CH_3$], 5.527 [s, 2H, N—CH_2—CO], 6.314 [s, 1H, CH=C] and 8.942 [s, 1H, CH=N].



IV

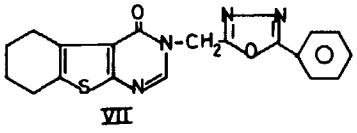


V

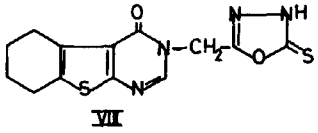


VI

The authors also thought to combine the thienopyrimidine nucleus with oxadiazole moiety on the hope of obtaining other new compounds of pronounced biological activities. Thus, interaction of (**III**) with benzoic acid in the presence of $POCl_3$[14] resulted in the formation of the 1,3,4-oxadiazole derivative (**VII**). IR spectrum of (**VII**) exhibited aromatic (CH) at 3100 cm^{-1} and 1690 cm^{-1} (C=O), while its mass spectrum showed a molecular ion peak at m/z 364 (57.37%) and the base peak at 205 (100%) which underwent fragmentation processes and clearly support the structure (Chart 1). However, Interaction of (**III**) with carbondisulfide in ethanolic potassium hydroxide gave rise to the corresponding oxadiazole derivative (**VIII**). IR measurement showed bands at 3180 (NH), 1690 (C=O) and 1280 (C=S) cm^{-1}.

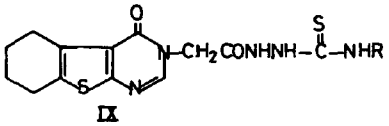


VII



VIII

Again (**III**) was reacted with isothiocyanates to afford the anticipated thiosemicarbazide derivatives (**1Xa–c**). The structure assigned for (**1Xb**) was confirmed by elemental analysis, IR spectrum which showed bands at 3460, 3320 (NH) and 1700, 1690 (2C=O) cm^{-1}. PMR spectrum of (**1Xb** in DMSO-d_6) showed signals at 1.115 [t, 3H, CH_3, ethyl], 1.795, 2.768, 2.872 [2s, 8H, $4CH_2$ (cyclo)], 3.485 [q, 2H, CH_2, ethyl], 4.675 [s, 2H, N—CH_2—CO], 8.282 [s, 1H, CH=N], 7.745 [s, 1H, NH, D_2O exchangeable], 9.415 [s, 1H, NH, D_2O exchangeable] and 10.346 [s, 1H, NH, D_2O exchangeable].



IX

IX a;R=CH_3
b;R=C_2H_5
C;R=C_6H_5

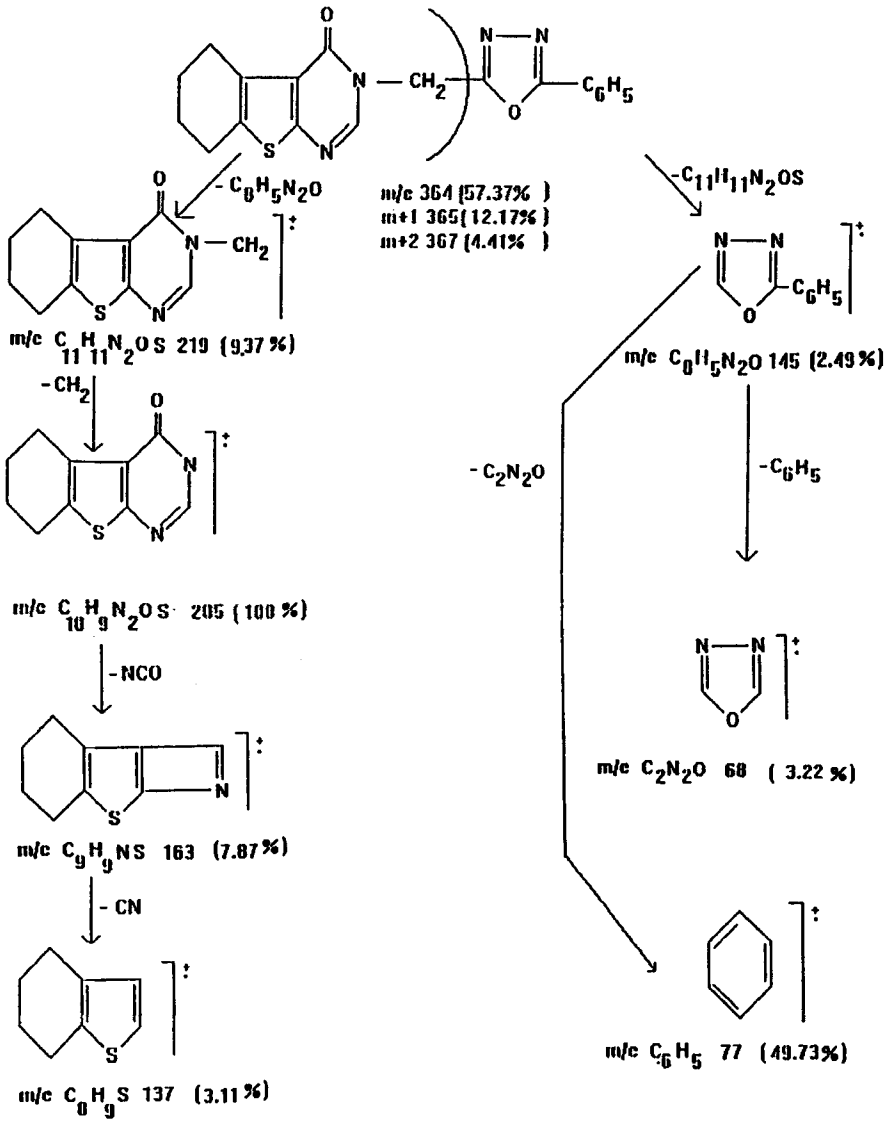
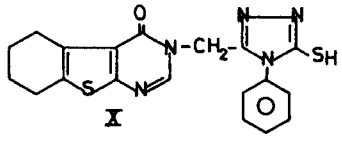


CHART 1 Mass fragmentation pattern of compound (**VII**).

Heating (**1Xc**) in 8% sodium hydroxide[15] solution yielded the triazolo derivative (**X**). The mass spectral fragmentation pattern of compound (**X**) has been presented in (Chart 2).



X

Condensation of (**III**) with various aldehydes afforded the hydrazones (**XIa–k**). The structure of (**XI**) was proved by analytical data and IR measurements which

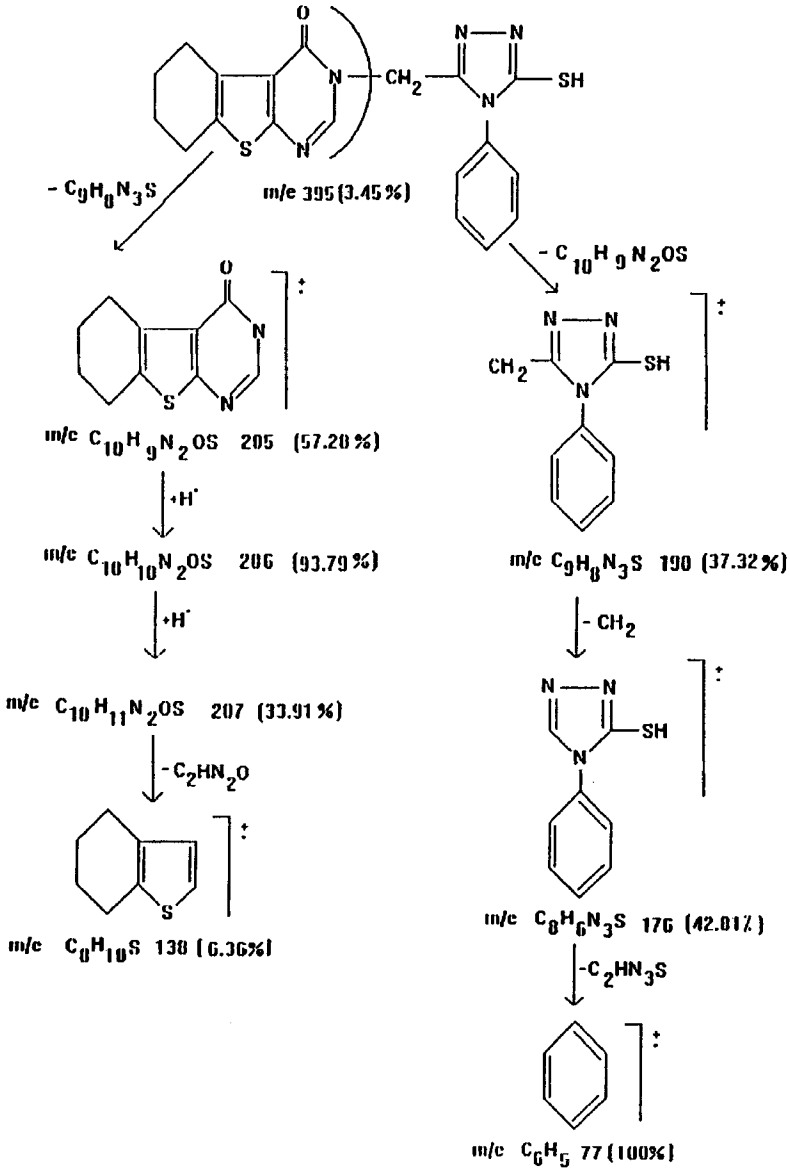


CHART 2 Mass fragmentation pattern of compound (X).

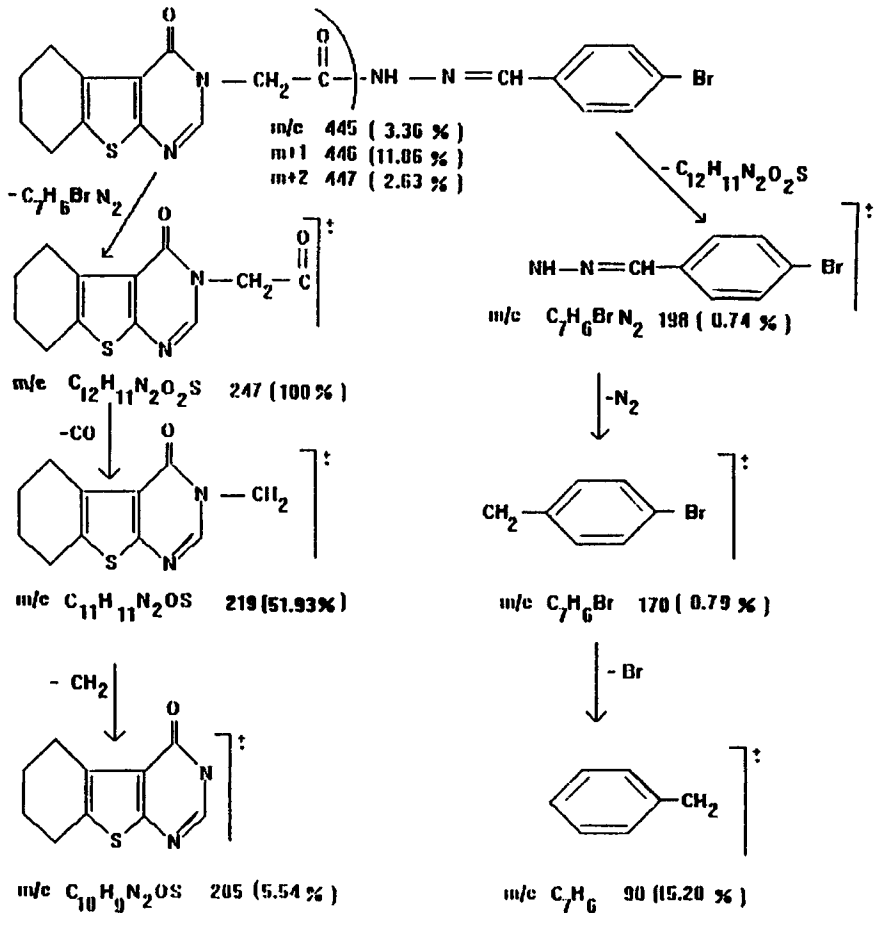
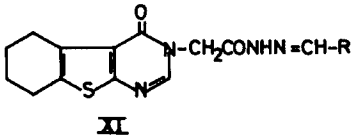


CHART 3 Mass fragmentation pattern of compound (**XIf**).

revealed the absence of NH_2 and the presence of bands at 3220 (NH), 1720, 1690 (2C=O) and 1620 (C=N) cm^{-1}. Mass spectrum of (**XIf**) showed a molecular ion peak at m/z 445 (3.36%) and the base peak at 247 (100%) which underwent fragmentation processes and clearly support the structure (Chart 3).



XI

XI a;R= C_6H_5
b;R = C_6H_4-CH_3-p
c;R = C_6H_4-NO_2-p
d;R = C_6H_4-F-p
e;R = C_6H_4-Cl-p
f;R = C_6H_4-Br-p
g;R = Pyridinyl-4
k;R = Thienyl-2

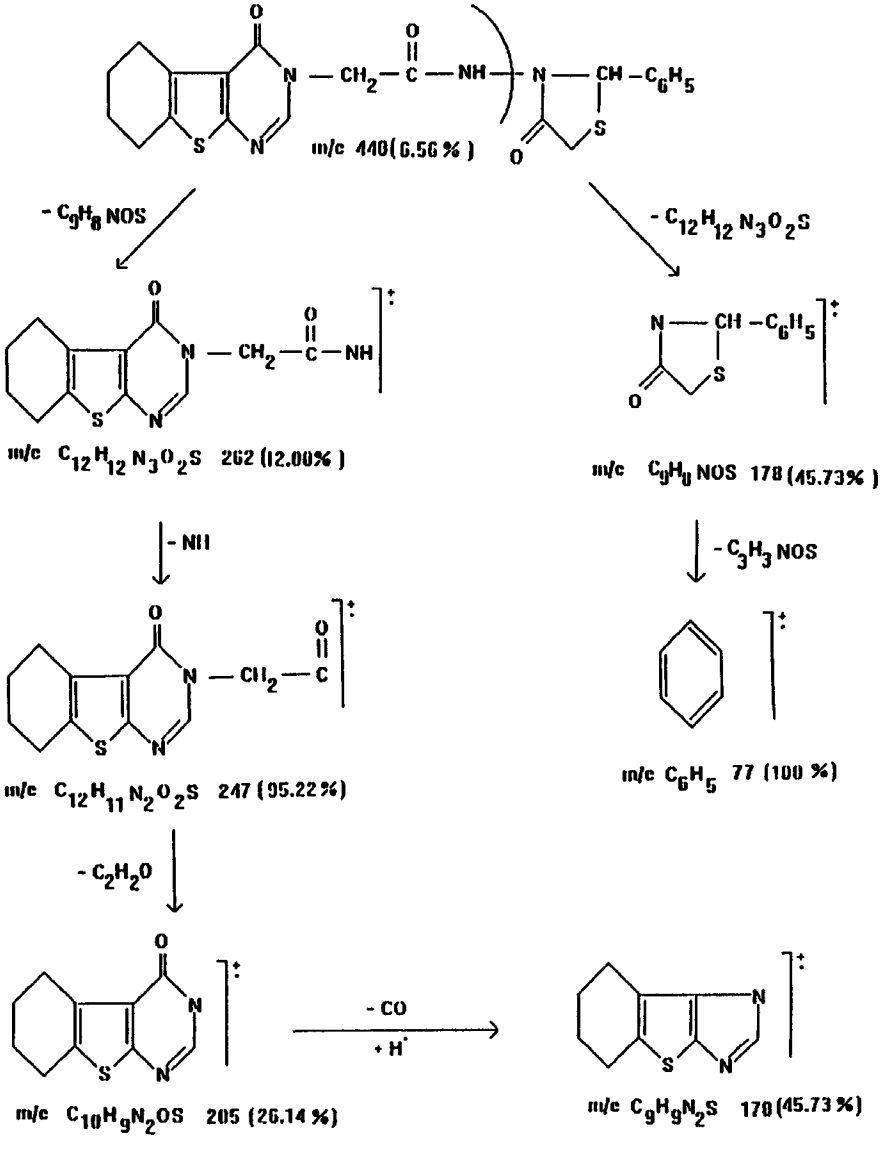
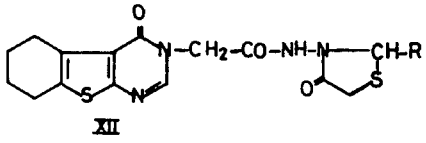


CHART 4 Mass fragmentation pattern of compound (**XIIa**).

The thiazolidinones (**XIIa–b**) were obtained via interaction of (**XI**) with mercaptoacetic acid.[16] The structure of (**XII**) was checked by analytical data and IR spectra which showed (C=O) at 1740 cm^{-1} corresponding for the thiazolidinone moiety. Mass spectrum of (**XIIa**) showed a molecular ion peak at m/z 440 (6.56%) and base peak at 77 (100%), (Chart 4).



XII

XII a;R = C_6H_5
b;R = C_6H_5–CH_3–p
c;R = Pyridinyl–4
d;R = Thienyl–2

Biological Activity

Antibacterial activity of the obtained products was assayed against *Bacillus cereus*, *Bacillus megaterium*; *Escherichia coli* and *Pseudomonas putida*, following the cup diffusion technique.[17] Antifungal activity was determined against *Aspergillus niger* and *Penicillium janthinellum* adopting a standard method.[17] The tested compounds in DMF as solvent showed a moderate effect towards all the tested organisms, where compounds (**IXc**) and (**XIg**) showed the highest antibacterial activity, while compounds (**XIg**) and (**XIk**) showed the highest antifungal activity (Table II). The presence of DMF caused no visible change in the bacterial and fungal growth. Ampicillin and Mycostatin were used as standard for the antibacterial and antifungal activities respectively.

Effect of Gamma Radiation

It was interesting to investigate the effect of gamma radiation on some biologically active compounds. The selected compounds **IIb** and **III** were irradiated in dimethylsulfoxide as solvent, at different dose levels ranging from 50 to 1000 Gy. The stability of their structures were followed using an ultra-violet spectrophotometer.

The UV spectra of the unirradiated compounds showed a Beta-band at 260 nm and a Para-band at 310 nm for compound **IIb** (Table III), while a Beta-band at 260 nm and a Para-band at 303 nm were observed for compound **III** (Table IV). After irradiation compound **IIb** showed a red shift in the Beta-band from 260 to 280 nm at doses over 50 Gy, where the Para-band was shifted from 310 to 315 nm at 100 Gy, then disappeared completely at higher doses. This compound is not stable toward gamma radiation (Table III).

A reduction in optical density was observed for compound **III** at doses over 50 Gy (Table IV). The reduction of the optical densities were estimated from the following relation:

$$\left(\frac{A_0 - A_i}{A_0} \times 100\right)$$

TABLE II

Biological activities results

Compd. No.	B. cereus (MIC)	B.megaterium (MIC)	E.coli (MIC)	Ps. putida (MIC)	Asp. nig (MIC)	P. janthenillum (MIC)
IIa	-	-	-	+	+	+
b	+	-	-	+	++	+
III	+	-	+	+	+	+
IV	-	-	+	+	++	-
V	+	-	++	+	+	+
VI	-	+	-	+	+	++
VII	-	-	+	+	+	++
VIII	-	-	++	-	+	+
IXa	-	-	+	+	+	++
b	+	-	++	++	-	-
c	-	-	+	+++	++	+
X	+	+	+	+	+	+
XIa	+	-	+	+	+	++
b	-	-	+	+	-	+
c	-	+	-	-	+	+
d	-	-	+	+	+	++
e	-	+	-	+	-	-
f	-	-	-	++	+	-
g	-	-	+	+++	+	+++
k	-	-	+	+	-	+++
XIIa	+	-	+	+	+	+
b	-	+	+	+	+	+
c	+	-	++	+	++	++
d	-	-	+	++	-	-
DMF	-	-	-	-	-	-
Ampicillin	-	-	+	+++++	-	-
Mycostatin	-	-	-	-	+	+

(MIC) Minimum inhibitory concentration calculated as 100 μ g / ml
(-) No activity
Number of (+) proportional with activity.

TABLE III

UV data of biologically active compound **IIb** before and after gamma irradiation

Conc. (M..)	Dose (Gy)	Beta-band	Abs O. D	ε	Para-band	Abs O.D	ε
$1X10^{-4}$	0	260	0.310	3100	310	0.853	8530
	50	260	1.042	-	310	1.180	
	100	280	1.120	-	315	0.250	
	200	280	1.160	-	-	-	
	400	280	1.116	-	-	-	
	600	280	1.150	-	-	-	
	800	280	1.230	-	-	-	
	1000	280	1.210	-	-	-	

where, A_0 and A_i are the optical density of the compound before and after irradiation.

The degradation yield Gd is presented by the number of molecules produced as a result of the absorption of 100 eV of energy. It is given by the following well known equation.

$$Gd = 9.647 \cdot 10^8 \frac{\Delta A}{\varepsilon \rho l} \frac{1}{D(rad)}$$

TABLE IV

UV data of biologically active compound **III** before and after gamma irradiation

Conc. (M..)	Dose (Gy)	Beta-band	Abs O. D	Δ A	Δ A/ A_0 %	ε	Para-band	Abs O.D	Δ A	Δ A/ A_0 %	ε
$1X10^{-4}$	0	260	0.787	-	-	7870	303	0.800	-	-	8000
	50	260	0.861	-	-		303	1.122	-	-	
	100	260	0.572	0.215	27.31		303	0.971	-	-	
	200	260	0.567	0.220	27.95		303	0.859	-	-	
	400	260	0.523	0.264	33.54		303	0.814	-	-	
	600	260	0.515	0.272	34.56		303	0.796	0.004	0.50	
	800	260	0.413	0.374	47.52		303	0.510	0.290	36.25	
	1000	260	0.279	0.508	64.54		303	0.506	0.294	36.75	

where: ε = molar extinction coefficient $1 \cdot mol^{-1} \cdot Cm^{-1}$ for the used solution, ρ = density of the solution g/Cm^3, I = optical path length (Cm), D = absorbed dose (rad).

From this equation the calculated Gd of compound (**III**) was 0.056. These results showed that the compounds **IIb** and **III** are sensitive toward gamma radiation.

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