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SYNTHESIS AND RADIATION STABILITY OF NOVEL THIAZOLOPYRIMIDINES WITH EXPECTED ANTIFUNGAL ACTIVITY

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SYNTHESIS AND RADIATION STABILITY OF NOVEL THIAZOLOPYRIMIDINES WITH EXPECTED ANTIFUNGAL ACTIVITY

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A number of thiazolopyrimidines (II–VII) were prepared through interaction of 6-methyl-4(4'-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (**Ia**) with many reagents. The antifungal activity of all prepared compounds have been determined using Dithane M-45 as a standard fungicide. Some compounds showed a high fungicidal activity equivalent to that of the standard towards *Aspergillus niger* and *Aspergillus ochraceus*. Also some biologically active compounds were subjected to gamma irradiation and the structures are stable.

Key words: Thiazolopyrimidines, antifungal activity, gamma irradiation.

INTRODUCTION

Hydropyrimidines and their derivatives are reported to possess diverse biological and pharmacological properties.^{1–6} Thiazole derivatives in general are largely used as antifungal,⁷ antibacterial,⁸ insecticidal,⁹ herbicidal¹⁰ and local anaesthetic.¹¹ It is reported that many sulfur containing compounds have a radioprotective capacity.¹² We have undertaken the synthesis of some fused thiazolopyrimidine derivatives for screening as antifungal agents. The effect of gamma irradiation as a sterilizing tool on some biologically active synthesized thiazolopyrimidines was studied.

EXPERIMENTAL

The melting points were determined in open capillaries and are uncorrected. Elemental analysis were carried out in the microanalytical center of the Faculty of Science, Cairo, University. UV and visible absorption spectra were recorded using Perkin-Elmer Lambda 3B. IR spectra (KBr) were measured on FT-IR 1650 (PERKIN ELMER). ¹H-NMR was carried out in the Faculty of Pharmacy, Cairo University, using a JEOL FXQ 90 MHZ NMR spectrometer. Mass spectra were run using HP MODEL: MS. 5988. Irradiation source is GAMMA-CHAMPER 4000 A, at dose rate 2.7 Rad/sec.

6-Methyl-4-substituted-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl esters (Ia–e)

A mixture of thiourea (0.01 mol), required aldehydes (0.01 mol), ethyl acetoacetate (0.015 mol) and (50 ml) of ethanol containing 10 drops of concentrated hydrochloric acid was refluxed for 3 hr. The solution was allowed to stand at 20°C for several hours and the solid obtained was recrystallized from ethanol



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TABLE I
Characterization data for newly synthesized compounds (Ia–XIc)

Compd. No.	M.P. °C	Yield %	Molecular Formula	Analysis Calculated/Found		
				%C	%H	%N
Ia	172	73	C ₁₄ H ₁₅ ClN ₂ O ₂ S	54.10	4.83	9.01
				54.20	4.90	8.90
b	190	65	C ₁₆ H ₂₁ N ₃ O ₂ S	60.18	6.58	13.16
				60.10	6.70	13.30
c	144	69	C ₁₆ H ₂₀ N ₂ O ₄ S	57.14	5.95	8.33
				57.30	5.80	8.20
d	177	71	C ₁₄ H ₁₄ Cl ₂ N ₂ O ₂ S	48.69	4.05	8.11
				48.80	4.00	8.20
e	201	76	C ₁₄ H ₁₅ BrN ₂ O ₂ S	47.32	4.22	7.88
				47.50	4.30	7.70
II	199	56	C ₁₆ H ₁₇ ClN ₂ O ₂ S	57.05	5.05	8.32
				57.10	4.90	8.40
III	130	61	C ₂₄ H ₁₇ ClN ₂ O ₄ S	62.00	3.65	6.02
				61.90	3.80	6.10
IV	184	65	C ₂₂ H ₁₇ ClN ₄ O ₂ S	60.48	3.89	12.82
				60.60	3.70	12.90
V	150	69	C ₁₆ H ₁₅ ClN ₂ O ₃ S	54.77	4.27	7.98
				54.70	4.20	7.80
VIa	212	72	C ₂₄ H ₂₁ ClN ₂ O ₄ S	61.47	4.48	5.97
				61.30	4.40	5.80
b	152	62	C ₂₃ H ₁₈ Cl ₂ N ₂ O ₃ S	58.35	3.80	5.91
				58.50	3.70	6.00
c	208	69	C ₂₃ H ₁₈ Cl ₂ N ₂ O ₃ S	58.35	3.80	5.91
				58.40	3.70	5.80
d	228	62	C ₂₅ H ₂₄ ClN ₃ O ₃ S	62.30	4.98	8.72
				62.20	4.90	8.60
e	196	68	C ₂₃ H ₁₇ Cl ₃ N ₂ O ₃ S	54.38	3.34	5.51
				54.50	3.40	5.60
VIIa	>300	75	C ₂₆ H ₂₀ Cl ₂ N ₄ O ₃ S	57.88	3.71	10.38
				57.80	3.60	10.50
b	>300	68	C ₂₆ H ₂₀ Cl ₂ N ₄ O ₃ S	57.88	3.71	10.38
				57.90	3.60	10.40
c	>300	62	C ₂₆ H ₁₉ Cl ₃ N ₄ O ₃ S	54.40	3.31	9.76
				54.30	3.20	9.60
IX	67	67	C ₁₅ H ₁₅ ClN ₂ O ₃ S	53.17	4.43	8.27
				53.30	4.30	8.40
X	187	61	C ₁₈ H ₁₅ ClN ₄ O ₂ S	55.88	3.88	14.48
				55.70	3.80	14.40
XIa	212	56	C ₁₂ H ₁₃ ClN ₄ OS	48.56	4.38	18.88
				48.40	4.50	18.80
b	187	69	C ₁₈ H ₁₅ FCIN ₃ OS	57.52	3.99	11.18
				57.60	3.80	11.30
c	191	65	C ₁₈ H ₁₅ Cl ₂ N ₃ OS	55.10	3.82	10.71
				55.20	3.70	10.80

to give (Ia–e; Table I). IR spectrum of (Ia) showed bands at 3350, 3300 cm^{−1} (NH), 1720 cm^{−1} (C=O). ¹H-NMR spectrum of (Ia in DMSO-d₆) exhibited signals at 1.4 [t, 3H, CH₃ ester], 2.5 [s, 3H, CH₃], 4.2 [q, 2H, CH₂ ester], 5.5 [s, 1H, CH]; 7.2–8.0 [m, 4H, Ar-H] and 10.0, 10.8 ppm [2s, 2H, 2NH; exchangeable—D₂O]. UV spectrum of (Ia in DMF) showed a band at 311 nm and log ε at 3.92.

5H-Thiazolo[3,2-*a*]pyrimidine (II), *naphthoquino*[2,3:4,5]thiazolo-[3,2-*a*]pyrimidine (III) and *pyrimidino*[1,2:3,2']thiazolo [4,5-*b*]quinoxaline (IV)

A mixture of (Ia; 0.01 mol); 1,2-dichloroethane; 2,3-dichloronaphthoquinone and/or 2,3-dichloroquinoxaline (0.012 mol) in dimethylformamide (20 ml) was refluxed for 12 hr. The reaction mixture was cooled

and the solid obtained was recrystallized from ethanol to give (II), (III) and (IV) respectively (Table I). IR spectra showed the disappearance of (NH) bands. Mass spectrum of (III) exhibited a molecular ion peak m/z 464 (6.0%) with a base peak at 342 (100%); other significant peaks appeared at 392 (42.9%); 313 (65.5%); 286 (19.3%); 256 (22.9%); 228 (21.7%); 126 (14.5%); 104 (41.5%) and 76 (61.6%). UV spectrum of (III in DMF) showed bands at 266, 311, 407 nm and $\log \epsilon$ at 4.02, 4.21, 3.53.

Synthesis of thiazolidinone derivative (V)

A mixture of (Ia; 0.01 mol); chloroacetic acid (0.01 mol), acetic anhydride (12 ml) in acetic acid (20 ml) was refluxed for 4 hr. The solid obtained was recrystallized from acetic acid to give (V; Table I). IR spectrum of (V) exhibited bands at 1730; 1700 cm^{-1} ($2\text{C}=\text{O}$). UV spectrum of (V in DMF) showed bands at 266, 335 nm and $\log \epsilon$ at 3.65, 3.89.

Synthesis of arylidine derivatives (VIa–e)

Method A: A mixture of (V; 0.01 mol); required aldehydes (0.01 mol) in acetic acid (20 ml) in the presence of fused sodium acetate (0.5 g) was refluxed for 2 hr. The solid obtained was recrystallized from acetic acid to give (VIa–e; Table I). IR spectrum of (VIc) exhibited bands at 2900 cm^{-1} (CH aliphatic); 1720, 1680 cm^{-1} ($2\text{C}=\text{O}$), $^1\text{H-NMR}$ spectrum of (VIa in $\text{DMSO-}d_6$) exhibited signals at 1.5 [t, 3H, CH_3 ester]; 2.5 [s, 3H, CH_3]; 4.0 [s, 3H, OCH_3]; 4.2 [q, 2H, CH_2 ester]; 6.3 [s, 1H, $\text{S}-\text{C}=\text{CH}$], 7.2–8.0 [m, 8H, Ar-H] and 8.1 ppm [s, 1H, N-CH]. $^1\text{H-NMR}$ spectrum of (VIc in $\text{DMSO-}d_6$) showed signals at 1.4 [t, 3H, CH_3 ester]; 3.2 [s, 3H, CH_3]; 4.2 [q; 2H, CH_2 ester]; 6.2 [s, 2H, 2CH] and 7.2–8.2 ppm [m, 8H, Ar-H]. UV spectrum of (VIc in DMF) showed bands at 265, 382 nm and $\log \epsilon$ at 3.31, 3.95.

Method B: A mixture of (Ia; 0.01 mol); chloroacetic acid (0.01 mol), required aldehydes (0.01 mol); acetic anhydride (12 ml) and acetic acid (20 ml) in the presence of fused sodium acetate (0.5 g) was refluxed for 2 hr. The solid obtained was recrystallized from acetic acid to give (VIa–e; m.p and mixture m.p).

Synthesis of pyranothiazolopyrimidine derivatives (VIIa–c)

A mixture of (VIb,c,e, 0.01 mol); malononitrile (0.01 mol) in ethanol (25 ml) in the presence of 3 drops of piperidine was refluxed for 3 hr. The solid obtained was recrystallized from ethanol to give (VIIa–c; Table I). IR spectra exhibited bands at 3400, 3300 cm^{-1} (NH_2); 2220 cm^{-1} ($\text{C}\equiv\text{N}$); 1650 cm^{-1} ($\text{C}=\text{O}$). UV spectrum of (VIIb in DMF) showed bands at 264, 317 nm and $\log \epsilon$ at 4.16, 4.23.

Synthesis of formyl derivative (IX)

To a solution of (Ia; 0.01 mol) in (30 ml) of dry dimethylformamide; phosphorus oxychloride (0.02 mol) was added under stirring in an-ice-bath. Stirring was continued at room temperature for another 15 minutes and then the solution was poured into 400 ml of ice-water, filtered; dried and recrystallized from ethanol to give (IX, Table I). UV spectrum of (IX in DMF) showed bands at 255, 331 nm and $\log \epsilon$ at 3.55, 4.12.

Synthesis of thiazine derivative (X)

To a solution of (IX; 0.01 mol) in ethanol (25 ml); triethylamine (0.5 ml) was added and the mixture was refluxed for 6 hr. The reaction mixture was cooled and the solid obtained was recrystallized from ethanol to give (X; Table I). IR spectrum of (X) showed bands at 3330 cm^{-1} (NH), 3100 cm^{-1} (CH aromatic); 2220 cm^{-1} ($\text{C}\equiv\text{N}$) and 1670 cm^{-1} ($\text{C}=\text{O}$). UV spectrum of (X in DMF) showed band at 312 nm and $\log \epsilon$ at 4.02.

Synthesis of hydrazide derivative XIa

A mixture of (Ia; 0.01 mol), hydrazine hydrate (0.012 mol) in ethanol (50 ml) was refluxed for 18 hr. The solid obtained was recrystallized from ethanol to give (XIa; Table I). IR spectrum showed bands at 3400, 3380 cm^{-1} (NH_2).

Synthesis of amide derivatives (XIb,c)

A mixture of (Ia; 0.01 mol), and the required aromatic amines (0.01 mol) was fused at 180°C for 10 minutes. The solid obtained was recrystallized from ethanol to give (XIb,c; Table I). IR spectrum showed a band at 3250 cm^{-1} (NH).

RESULTS AND DISCUSSION

6-Methyl-4-substituted-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl esters (**Ia–e**) were prepared by condensation of an aldehyde, thiourea and ethyl acetoacetate according to the reported method.^{13–15}

Compound (**I**) can be considered as a cyclic thiourea derivative, and therefore can react with various dielectrophiles to yield fused pyrimidines. Two isomeric cyclization products may be expected Scheme I.

Thus, when (**Ia**) was refluxed with 1,2-dichloroethane gave 5H-thiazolo[3,2-a]pyrimidine (**II**). Also reaction of (**Ia**) with 2,3-dichloronaphthoquinone furnished naphthoquino[2,3:4,5]thiazolo[3,2-a]pyrimidine (**III**). Additionally upon heating (**Ia**) with 2,3-dichloroquinoxaline produced pyrimidino [1,2:3,2] thiazolo [4,5-b] quinoxaline (**IV**).

Reaction of (**Ia**) with chloroacetic acid in acetic anhydride and in the presence of fused sodium acetate led to the formation of thiazolopyrimidine derivative (**V**). Condensation of (**V**) with aromatic aldehyde yielded the corresponding arylidene derivatives (**VIa–e**). The same arylidene derivatives (**VIa–e**) were obtained in one step through the reaction of (**Ia**) with chloroacetic acid, aldehydes in acetic anhydride and in the presence of fused sodium acetate.

Interaction of (**V**) with α -cyanocinnamonnitriles in a trial for obtaining pyrano-thiazolopyrimidine derivatives, but instead the arylidene derivatives (**VI**) were obtained. The required pyranothiazolopyrimidines (**VII**) were obtained through interaction of (**VI**) with malononitrile in presence of piperidine.

When (**Ia**) was treated with phosphorus oxychloride in dimethylformamide at room temperature, intermediate (**VIII**) was readily formed, which upon hydrolysis gave 6-formyl-2-thioxo derivative (**IX**).

Condensation of (**IX**) with malononitrile caused cyclization to give 6H-pyrimido [2,3-b] thiazine (**X**).

Finally, condensation of (**Ia**) with hydrazine hydrate and aromatic amines produced the corresponding hydrazide and amide derivatives (**XIa–c**).

Antifungal Activity

All the synthesized compounds were tested in vitro for their antifungal activity against *Aspergillus niger* and *Aspergillus ochraceus* in DMF at a concentration of 1 mg/ml by the method of cup diffusion techniques.¹⁶ Dithane M-45 (a compound product of maneb 78%, Fig. 1 and 2% zinc ion)¹⁷ was used as a standard compound by a concentration of 0.25 mg/ml in DMF. The results (Table II) revealed that compounds (**Ia**), (**Ib**), (**III**), (**V**) and (**VIc**) showed a potent fungicidal activity equivalent to that of Dithane M-45 toward *Aspergillus niger* and *Aspergillus ochraceus*. In order to compare the relationship between the structure and activity, we found that compounds containing 2-thioxo-pyrimidines with chlorine atom or N-dimethyl group in the para-position (**Ia,b**), respectively showed a greater activity than other substituted derivatives (**Ic,d,e**). Introduction of P-naphthoquinone with thiazolopyrimidine as in (**III**) showed a potent fungicidal activity. The presence of thiazolodione and its arylidene derivative with chlorine atom in the para-position gave compounds possessing antifungal activity (**V** and **VIc**), respectively.

TABLE II
Antifungal activity of the newly synthesized compounds (Ia–XIc)

Compd. No.	<i>Aspergillus niger</i> (MIC)	<i>A. ochraceus</i> (MIC)
Ia	+	+
b	+	+
c	+	-
d	-	+
e	-	-
II	-	-
III	+	+
IV	+	-
V	+	+
VIa	-	-
b	+	-
c	+	+
d	-	-
e	-	-
VIIa	-	-
b	-	-
c	+	-
IX	-	-
X	-	-
XIa	+	-
b	-	+
c	-	-
DMF	-	-
Dithane M-45	+	+

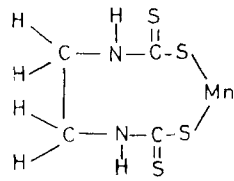


FIGURE 1

Radiation Stability of Some Biologically Active Compounds

The aim of the present work is to investigate the stability and fungicidal activity of the biologically active sulfur containing compounds (Ia), (III), (V) and (VIc), after exposure to gamma irradiation in case of sterilization. These compounds in the dry state, were exposed to doses of gamma irradiation ranging from 5–40 KGy at a dose rate of 2.7 Rad/sec. Spectrophotometric techniques (UV, IR, ¹H-NMR) and mass spectra were applied to identify any changes after irradiation. Ultra-violet spectra of non-irradiated and irradiated compounds in dimethylformamide as solvent are listed in (Table III).

The results showed that all the tested compounds remain radioresistant retaining their structure and antifungal activity unchanged up to 40 KGy.

This means that sterilization of these compounds in the dry form may prove to be applicable. These results are in agreement with the fact that sulfur compounds are widely used as anti-radiation drugs.

TABLE III
UV and visible data of studied biologically active compounds before and after
gamma-irradiation

Compd No.	Dose KGy	Conc. (Mol).	(1) λ max	Abs O.D	(2) λ max	Abs O.D	(3) λ max	Abs O.D
Ia	0	5×10^{-5}	311	0.833				
	5	"	311	0.847				
	10	"	311	0.899				
	15	"	311	0.911				
	20	"	311	0.988				
	25	"	311	1.052				
	40	"	311	1.197				
III	0	1×10^{-4}	266	1.053	311	1.635	407	0.340
	5	"	266	1.066	311	1.842	407	0.344
	10	"	266	1.069	311	1.887	407	0.345
	15	"	266	1.073	311	1.890	407	0.345
	20	"	266	1.080	311	1.960	407	0.340
	25	"	266	1.082	311	1.966	407	0.342
	40	"	266	1.086	311	2.002	407	0.346
V	0	1×10^{-4}	266	0.457	335	0.782		
	5	"	266	0.478	335	0.872		
	10	"	266	0.530	335	0.900		
	15	"	266	0.531	335	0.900		
	20	"	266	0.570	335	0.910		
	25	"	266	0.533	335	0.930		
	40	"	266	0.555	335	0.986		
VIc	0	5×10^{-5}	265	0.205	382	0.908		
	5	"	265	0.327	382	1.270		
	10	"	265	0.331	382	1.370		
	15	"	265	0.327	382	1.370		
	20	"	265	0.386	382	1.415		
	25	"	265	0.345	382	1.425		
	40	"	265	0.355	382	1.500		

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