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Synthesis and Biological Evaluation of New Thiazolopyrimidines

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In this study, a series of 4-amino-5-cyano-3-substituted-2,3-dihydrothiazol-2-thiones **(1a-c)**, as well as their triazolo and triazinopyrimidine derivatives such as 8-substituted-3-benzyl-5-methylthiazolo[5,4-*e*][1,2,4] triazolo[1,5-*c*]pyrimidin-2-thiones **(4-6, 10)** and 3-benzyl-5-methyl thiazolo[5,4-*e*]pyrimidino[3,4-*b*][1,2,4]triazin-2-thiones **(7a-b)** were prepared as potential antimicrobial and antitumor agents. Some of the tested compounds showed promising antimicrobial activity and non of them showed any appreciable antitumor activity.

Key words: Thiazolopyrimidines, Antimicorbial activity, Antitumor activity

INTRODUCTION

Fused pyrimidines are an important class of compounds that attracted the attention of medicinal chemists as chemotherapeutic agents. The antibacterial (Bayomi *et al.*, 1993; Holla *et al.*, 1994) antimicrobial (El-Sherbeny *et al.*, 1995; Hozien *et al.*, 1997, Ghorab and El-Batal, 2002), antiviral (Kharizomenova *et al.*, 1982; Erik De Clereq, 1986; El-Sherbeny *et al.*, 1995) and cytotoxic properties (Ogawa *et al.*, 1986; Moharram *et al.*, 1990; Rizk *et al.*, 1993) are well documented. Recently, we have prepared and evaluated a new series of heterocyclic compounds containing a pyrimidine nucleus (Mouneer *et al.*, 2002) which has been reported to possess promising antimicrobial activity. In our on going efforts for finding new compounds for the antimicrobial activity and cancer chemotherapy, a new series of 3-benzyl-5-methylthiazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-2-thiones and 3-benzyl-5-methylthiazolo[5,4-*e*]pyrimidino[3,4-*b*][1,2,4]triazin-2-thiones have been synthesized to explore their antimicrobial and antitumor activity.

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MATERIALS AND METHODS

Chemistry

Melting points were determined on a Griffen melting point apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Unit of Cairo University. Infrared spectra were recorded using the Shimadzu IR 435 Spectrometer with KBr discs. Proton magnetic resonance was obtained in DMSO-d_6 using TMS as internal standard using the Jeol FX 90 Q (90 MHz) Spectrometer. Mass spectra were recorded on the HP Model-MS-5988 Mass Spectrometer. Thin layer chromatography was performed on pre-coated silica gel F-254 plates and visualized by the UV lamp.

3-Substituted-4-amino-5-Cyano-2,3-dihyrothiazol-2-thiones (1a-c)

A mixture of malononitrile (0.05 mmol), substituted isothiocyanate (0.05 mmol), finely divided sulphur (0.05 gm/atom) in dimethylformamide (6 mL) and triethylamine (6 mL) was heated up to 50 °C for 1 h. Then the mixture was poured onto ice cold water; the solid was filtered, washed and crystallized with the proper solvent (Table I, II).

3-Benzyl-5-cyano-4-(α-ethoxyethylidene-aminothiazolin-2-thione (2)

A mixture of compound **1a** (2 mmol), triethyl orthoacetate

(1.5 mL) and acetic anhydride (6 mL) was heated under reflux for 6 h. The reaction mixture was concentrated *in vacuo* and residue obtained was triturated with petroleum ether. The separated solid was filtered and recrystallized with the appropriate solvent (Table I, II).

6-Amino-3-benzyl-7-imino-5-methyl-2,3,6,7-tetrahydrothiazolo[4,5-d] pyrimidin-2-thione (3)

Hydrazine hydrate (1 mL) was added to a solution of 3-benzyl-5-cyano-4-(α-ethoxyethylideneaminothiazolin-2-thione (**2**) (10 mmol) in ethanol (25 mL). The reaction mixture was stirred for 4 h below 30 °C. The separated solid was filtered, washed with water, dried and recrystallized from the appropriate solvent (Table I, II).

Table I. Physical, analytical and IR spectral data of the synthesized compounds

Comp. No.	m.p. (°C) Solvent of crystallization	Yield %	Mol. Form. (Mol. Wt.)	Elememtal analysis % calcd./found			IR KBr (cm^{-1})
				C	H	N	
1a	210 (ethanol)	56	$C_{11}H_9N_3S_2$ (247)	53.44 53.40	3.64 3.60	17.00 17.00	3200-3300 (NH), 3050 (CH aromatic), 2950-2850 (CH aliph.), 2205 (C=N), 1590-1450 (C=C str. of aromatic ring)
1b	183 (ethanol)	58	$C_{10}H_6BrN_3S_2$ (312)	38.46 38.40	1.92 1.90	13.46 13.41	3200-3300 (NH), 3050 (CH aromatic), 2950-2850 (CH aliph.), 2205 (C=N), 1590-1450 (C=C str. of aromatic ring)
1c	285 (ethanol)	50	$C_{10}H_{13}N_3S_2$ (239)	50.20 50.10	5.43 5.42	17.57 17.50	3200-3300 (NH), 3050 (CH aromatic), 2950-2700 (CH aliph.), 2205 (C=N)
2	178(pet. ether/ methylene chloride)	56	$C_{15}H_{15}N_3OS_2$ (317)	56.78 56.76	4.73 4.70	13.24 13.20	3050 (CH aromatic), 2950-2850 (CH aliph.), 2200 (C=N), 1590-1450 (C=C str. of aromatic ring)
3	220 (ethanol/methylene chloride)	61	$C_{13}H_{13}N_5S_2$ (303)	51.48 51.30	4.29 4.10	23.10 23.00	3300-3100 (NH, NH_2), 3050 (CH aromatic), 2950-2850 (CH aliph.), 1590-1450 (C=C str. of aromatic ring)
4	143 (ethanol)	57	$C_{15}H_{13}N_5S_2$ (327)	55.04 54.90	3.97 3.80	21.40 21.40	3050 (CH aromatic), 2950-2850 (CH aliph.), 1590-1450 (C=C str. of aromatic ring)
5	180 (chloroform)	64	$C_{14}H_{11}N_5S_2$ (313)	53.67 53.50	3.51 3.40	22.36 22.10	3050 (CH aromatic), 2950-2850 (CH aliph.), 1590-1450 (C=C str. of aromatic ring)
6	238 (ethanol/DMF	64	$C_{20}H_{16}N_6S_2$ (404)	59.40 59.30	3.96 3.80	20.79 20.60	3280 (NH), 3050 (CH aromatic), 2950-2850 (CH aliph.), 1590-1450 (C=C str. of aromatic ring)
7a	138 (ethanol)	61	$C_{21}H_{17}N_5S_2$ (403)	62.53 62.40	4.21 4.20	17.36 17.30	3050 (CH aromatic), 2950-2850 (CH aliph.), 1590-1450 (C=C str. of aromatic ring)
7b	145 (ethanol)	60	$C_{21}H_{16}BrN_5S_2$ (482)	52.28 52.20	3.31 3.30	15.52 14.50	3050 (CH aromatic), 2950-2850 (CH aliph.), 1590-1450 (C=C str. of aromatic ring)
8	232 (pet. Ether)	76	$C_{16}H_{17}N_5S_2$ (343)	55.97 55.70	4.95 7.80	20.40 20.20	3250 (NH), 3050 (CH aromatic), 2950-2850 (CH aliph.), 1635 (C=N), 1590-1450 (C=C str. of aromatic ring)
9a	236 (ethanol)	80	$C_{20}H_{16}BrN_5S_2$ (470)	51.06 51.00	3.40 3.30	14.89 14.70	3250 (NH), 3050 (CH aromatic), 2950-2850 (CH aliph.), 1630 (C=N), 1590-1450 (C=C str. of aromatic ring)
9b	261 (ethanol)	85	$C_{20}H_{16}ClN_5S_2$ (425.5)	56.40 56.30	3.76 3.70	16.45 16.30	3250 (NH), 3050 (CH aromatic), 2950-2850 (CH aliph.), 1630 (C=N), 1590-1450 (C=C str. of aromatic ring)
9c	>300 (ethanol)	79	$C_{20}H_{16}N_6O_2S_2$ (436)	55.04 55.00	3.66 3.50	19.26 19.10	3250 (NH), 3050 (CH aromatic), 2950-2850 (CH aliph.), 1630 (C=N), 1590-1450 (C=C str. of aromatic ring)
10a	265 (ethanol)	60	$C_{20}H_{14}ClN_5S_2$ (423.5)	56.67 56.50	3.30 3.20	16.52 16.40	3050 (CH aromatic), 2950-2850 (CH aliph.), 1590-1450 (C=C str. of aromatic ring)
10b	288 (ethanol)	64	$C_{20}H_{14}FN_5S_2$ (407)	58.96 58.80	3.43 3.30	17.19 17.00	3050 (CH aromatic), 2950-2850 (CH aliph.), 1590-1450 (C=C str. of aromatic ring)
10c	270 (ethanol)	62	$C_{20}H_{14}N_6O_2S_2$ (434)	55.29 55.10	3.22 3.10	19.35 19.20	3050 (CH aromatic), 2950-2850 (CH aliph.), 1590-1450 (C=C str. of aromatic ring)
10d	279 (ethanol)	60	$C_{18}H_{13}N_5S_3$ (395)	54.68 54.50	3.29 3.20	17.72 17.60	3050 (CH aromatic), 2950-2850 (CH aliph.), 1590-1450 (C=C str. of aromatic ring)

Table II. ^{1}H-NMR and EIMS spectral data of the synthesized novel compounds

Compound No.	Spectral Data
1a	^{1}H-NMR (DMSO-d_6): δ2.8 (s, 2H, CH_2Ar), 3.6 (br, 2H, NH_2, D_2O, exchangeable), 7.3-7.6 (m, 5H, Ar-H). EIMS m/Z: 247M^+, (14.8%), 91 (100%).
1c	^{1}H-NMR (DMSO-d_6): δ2.1-2.3 (m, 6H, $3CH_2$) 2.4-2.5 (m, 4H, $2CH_2$), 2.7 (m, 1H, CH), 2.8 (s, 2H, CH_2Ar), 3.5 (br, 2H, NH_2, D_2O, exchangeable).
2	^{1}HNMR (DMSO-d_6): δ 0.6–0.9 (t, 3H, CH_2CH_3), 2.00 (s, 3H, CH_3), 2.8 (s, 2H, CH_2Ar), 3.1-3.2 (q, 2H, CH_2CH_3), 7.2-7.6 (m, 5H, Ar-H).
3	^{1}HNMR (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 2.8 (s, 2H, CH_2Ar) 3.3 (s, 2H, NH_2) D_2O, exchangeable), 6.1 (br, 1H, NH, D_2O exchangeable, 7.0-7.5 (m, 5H, Ar-H). EIMS m/Z: 303 M^+, (6.12%), 91.05 (100%).
4	^{1}H-NMR (DMSO-d_6): δ? 2.3 (s, 3H, CH_3), 2.8 (s, 2H, CH_2Ar), 3.1 (s, 3H, C_8-CH_3), 6.9-7.5 (m, 5H, Ar-H).
5	^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 2.8 (s, 2H, CH_2Ar) 6.8 (s, 1H, CH) 7.1-7.5 (m, 5H, Ar-H). EIMS m/Z: 313 M^+, (23.7%), 91 (100%).
6	^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 2.8 (s, 2H, CH_2Ar), 6.5 (s, 1H, NH, D_2O, exchangeable), 7.0-7.5 (m, 5H, Ar-H).
7a	^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 2.8 (s, 2H, CH_2Ar) 3.3 (s, 2H, CH_2) 6.9-7.5 (m, 10H, Ar-H).
8	^{1}H-NMR (DMSO-d_6): δ 1.3 (s, 6H, $2CH_3$), 2.3 (s, 3H, CH_3) 2.8 (s, 2H, CH_2Ar), 6.3 (s, 1H, NH, D_2O, exchangeable) 7.1-7.5 (m, 5H, Ar-H).
9a	^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 2.8 (s, 2H, CH_2Ar), 6.3 (s, 1H, NH, D_2O, exchangeable) 7.0-7.5 (m, 10H; 9H, Ar-H; 1H, N=CH).
9b	^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 2.8 (s, 2H, CH_2Ar), 6.4 (s, 1H, NH, D_2O, exchangeable) 7.0-7.5 (m, 10H; 9H, Ar-H; 1H, N=CH). EIMS m/Z: 425 M^+, 17.0%, 427 (8.3%), 91 (100%).
10a	^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 2.8 (s, 2H, CH_2Ar), 6.9-7.5 (m, 9H, Ar-H).
10b	^{1}H-NMR (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 2.8 (s, 2H, CH_2Ar), 6.9-7.4 (m, 9H, Ar-H). EIMS m/Z: 409 M^{+2}, (25.8%), 91 (100%).

3-Benzyl-5,8-dimethyl-2,3-dihydrothiazolo[5,4-e] [1,2,4]triazolo[1,5-c] pyrimidin-2-thione (4)

A mixture of 6-amino-3-benzyl-7-imino-5-methyl-2,3,6,7-tetra hydrothiazolo[4,5-d]pyrimidin-2-thione (3) (2.5 mmol), glacial acetic (4 mL) and acetic anhydride (4 mL) was heated under reflux for 4 h. The separated solid was collected and recrystallized from the appropriate solvent (Table I, II).

3-Benzyl-5-methyl-2,3-dihydrothiazolo[5,4-e] [1,2,4] triazolo[1,5-c]pyrimidin-2-thione (5)

A solution of compound **3** (2.5 mmol) in formic acid (5 mL) was heated under reflux for 10 h. The reaction mixture was concentrated under reduced pressure, water (20 mL) was added and the solution was neutralized with sodium carbonate. The obtained solid was filtered, washed with water and recrystallized with the proper solvent (Table I, II).

3-Benzyl-5-methyl-8-phenylamino-2,3-dihydrothiazolo[5,4-e][1,2,4]triazolo [1,5-c]pyrimidin-2-thione (6)

A mixture of compound **3** (1 mmol) and phenyl isothiocyanate (1 mmol) in absolute ethanol (20 mL) was heated under reflux for 12 h. The product thus formed was collected by filtration and recrystallized from the appropriate solvent (Table I, II).

8-Aryl-3-benzyl-5-methyl-2,3,9,10-tetrahydrothiazolo [5,4-e]pyrimidino[3,4-b] [1,2,4] triazin-2-thiones (7a & b)

A mixture of compound **3** (5 mmol), the appropriate α-bromoacetophenone (5 mmol) and sodium bicarbonate (5 mmol) in ethanol (10 mL) was heated under reflux for 8 h. After cooling, the separated solid was filtered, washed with water, dried and recrystallized from the appropriate solvent (Table I, II).

6-(Acetone-2-ylidenamino-3-benzyl-7 imino-5-methyl) -2,3,6,7-tetrahydrothiazolo [4, 5-d]pyrimidino-2-thione (8)

A mixture of compound **3** (1 mmol) and acetone (20 mL) was heated under reflux for 4 h. After cooling, the reaction mixture was concentrated to one third of the volume. The product obtained was filtered and recrystallized from the appropriate solvent (Table I, II).

6-Arylidineamino-3-benzyl-7-imino-5-methyl-2,3,6,7-tetrahydrothiazolo[4,5-d]pyrimidin-2-thiones (9a-c)

A mixture of compound **3** (1 mmol), selected aromatic aldehydes (1 mmol) was refluxed in absolute ethanol (20

mL) for 5 h. After cooling, the product was filtered and recrystallized from the proper solvent (Table I, II).

8-Aryl-3-benzyl-5-methyl-2,3-dihydrothiazolo[5,4-e] [1,2,4]triazolo[1,5-c] pyrimidin-2-thiones (10a-d)

Method A:

A mixture of **3** (5 mmol) and the appropriate aldehydes (5 mmol) in acetic acid (15 mL) was heated under reflux for 12 h. The separated solid, upon cooling, was filtered, dried and recrystallized from the proper solvent (Table I, II).

Method B: (for compounds **10b** and **10c**)

A mixture of **9b** or **9c** (5 mmol) in acetic acid (10 mL) was heated under reflux for 7 h. After cooling, the separated solid was filtered, dried and recrystallized from the appropriate solvent to afford **10b** and **10c** respectively. (Table I, II).

Antimicrobial activity

Microorganisms

In vitro antimicrobial activity of the tested compounds was determined by the serial agar micro dilution method (Ahmady *et al.*, 1985). Microorganisms used in the antimicrobial assay were; *Mycobacterium phlei, Bacillus subtilis, Staphylococcus aureus, Sarcina lutea, Escherichia coli, proteus vulgaris, Pseudomonas aeruginosa, Candida albicans, Candida tropicals* and *Tourulopsis glabrata.*

Culture media

The Mueller-Hinton agar was used for diluting the bacteria suspension and for two-fold agar dilution of the tested compounds and the Sabouraud liquid medium was used for the yeast-like fungi.

In vitro antimicrobial assay

A series of two-fold agar dilution for each compound was made by dispersing the stock solutions in the remaining wells. The inoculum was prepared by diluting the overnight culture of each microorganism to 10^6 CFU/mL, and 10 µL of each culture media were transferred on the surface of the died plates (10^4 CFU/inoculum). The bacterial plates were incubated for 24 h at 37 °C and yeast plates for 48 h at 25 °C. Ofloxacine (OFX) for bacteria and Amphotericin B (Amp. B) for yeast, were tested under the same conditions and were used as positive controls. The minimal inhibitory concentration (MIC) was determined for the selected compounds (**1a-c**, **3**, **7a**, **8**, **9a**, **10b**) and compared to that obtained using the positive control (Table III).

Table III. Antimicrobial activity of some synthesized compounds

	Compd. Minimal Inhibitory concentration (MIC, µg/LI)									
Microorganisms	**1a**	**1b**	**1c**	**3**	**7a**	**8**	**9a**	**10b**	OFX	AMP B
A	-	-	128	-	-	64	-	-	2	
B	-	-	64	128	128	32	128	128	2	
C	128	64	64	64	64	64	64	64	16	
D	128	32	32	64	-	32	-	-	8	
E	64	32	32	64	-	32	-	128	4	
F	32	32	32	64	64	32	-	128	2	
G	-	64	64	-	-	64	-	-	2	
H	128	64	16	128	-	64	-	-		8
I	64	64	32	64	-	64	-	-		4
J	128	64	32	64	-	64	-	-		4

Microorganisms selected: ***A*** *(Escherichia coli)* ATCC 10536, **B** *(Proteus vulgaris)* NCTC 4175, **C** *(Pseudomonas aurginosa)* CNCM A21, **D** *(Staphylococcus aureus)* ATCC 4175, **E** *(Sarcina lutea)**, **F** *(Bacillus subtilis)* NCTC 6633, **G** (*Mycobacterium pheli**) , **H** (*Candida albicans* ATCC 60193), **I** *(Candida tropicalis**), **J** *(Torulopsis glabrata**)
(-) no activity at MIC>128 µg/mL
OFX (Ofloxacin)
AMP B (Amphotericin B)
*Strains of laboratory collection.

Antitumor activity

Materials and methods

Animals: Weighing 18-22 g, female Swiss albino mice from the animal house of Cairo Cancer Institute, were used. Animals were sustained on standard pellet diet and water ad-lib.

Tumor: Ehrlich ascites carcinoma (EAC)

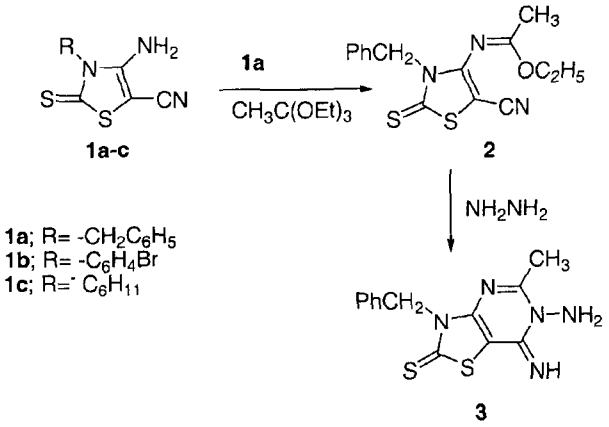
Experiment

A set of sterile test tubes was used, 2.5×10^5 tumor cells per mL (0.1 mL) were suspended in the phosphate buffer saline (0.8 mL). Each tested compound (10 mg) was dissolved in DMSO (0.5 mL) and then diluted with H_2O (9.5 mL). From this solution, 0.1 mL was taken and diluted with H_2O (0.9 mL) to give the required concentration used in the study. The test tubes were incubated for 2 h at 37 °C. The trypan blue exclusion test (Mclimans *et al.*, 1957) was then carried out to calculate the percentage of non viable cells and the activity was compared with Doxorubicin (40 µg/mL).

RESULTS AND DISCUSSION

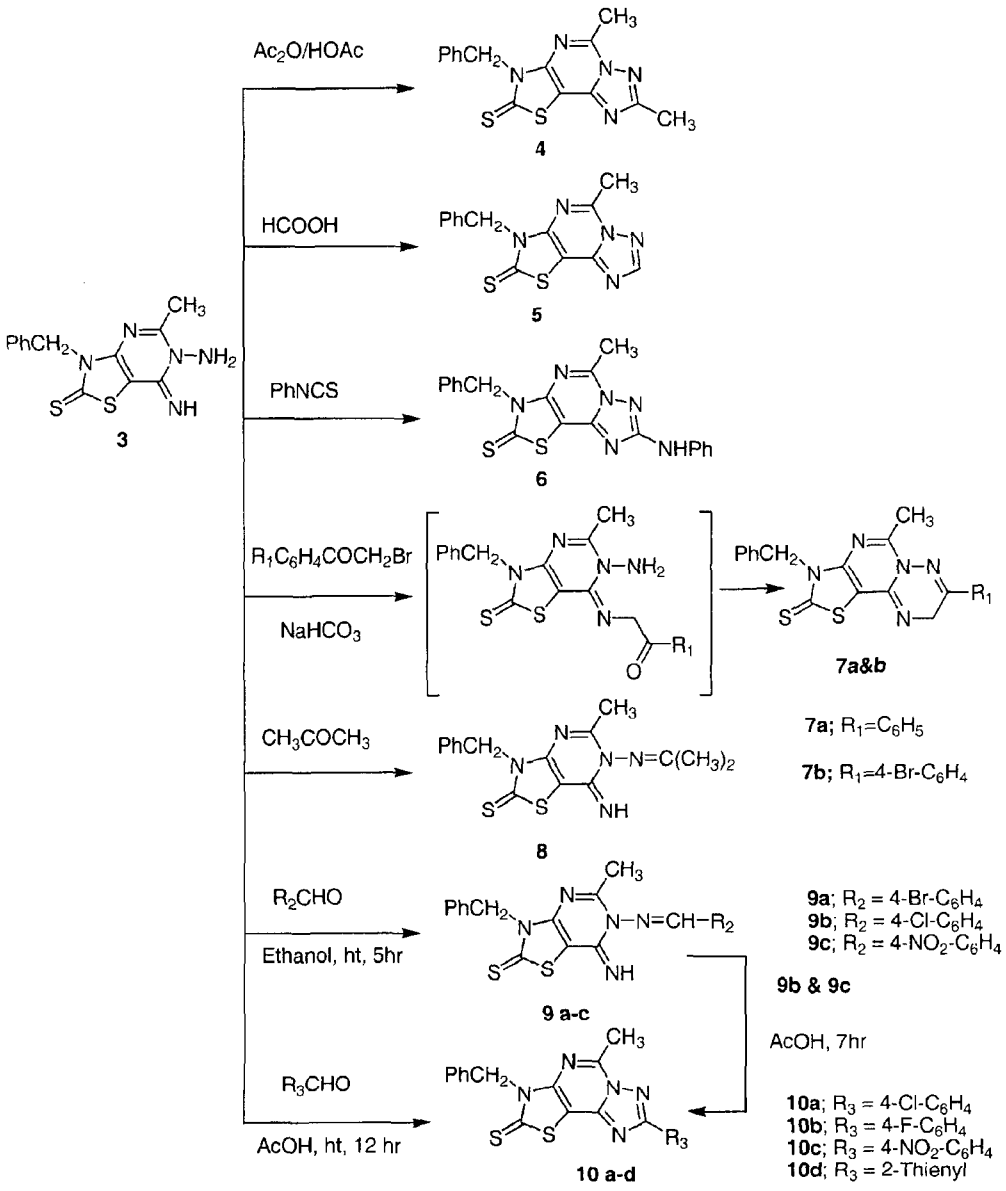
Chemistry

A series of 4-amino-5-cyano-3-substituted 2,3-dihydrothiazol-2-thiones (**1a-c**) was prepared according to the reported method (Gewald, 1966). 4-Amino-3-benzyl-5-cyano-2,3-dihydrothiazol-2-thione (**1a**) was reacted with triethyl orthoacetate in acetic anhydride to yield 3-benzyl-5-cyano-4-(α-ethoxyethylideneamino)thiazolin-2-thione (**2**). Subsequently, the latter was cyclocondensed with hydrazine hydrate to afford 6-amino-3-benzyl-7-imino-5-methyl-2,3,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidin-2-thione (**3**) (Scheme 1).



Scheme 1. Synthesis of compounds **3a-c**

Treatment of the latter with a mixture of acetic anhy-



Scheme 2. Sythesis of new thiazolopyrimidines from **3**

dride and glacial acetic acid under reflux yielded 3-benzyl-5,8-dimethyl 2,3-dihydrothiazolo[5,4-e][1,2,4]triazolo[1,5-c] pyrimidin-2-thione (**4**). On the other hand, when compound **3** was allowed to react with formic acid, it produced 3-benzyl-5-methyl-2,3-dihydrothiazolo[5,4-*e*][1,2,4]triazolo [1,5-c] pyrimidin-2-thione (**5**). Treatment of 3 with phenyl isothiocyanate, afforded 3-benzyl-5-methyl-8-phenylamino-2,3-dihydrothiazolo[5,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-2-thione (**6**).

8-Aryl-3-benzyl-5-methyl-2,3,9,10-tetrahydrothiazolo [5,4-*e*]pyrimidino[3,4-*b*][1,2,4]triazin-2-thiones (**7a** and **7b**), Scheme II, were obtained by reacting compound **3** with the appropriately 4-substituted α-bromoacetophenones in the presence of sodium bicarbonate. The latter reaction proceeds in basic medium, *via N*-phenacylimino intermediates which finally cyclized to the corresponding triazine derivatives **7a** and **7b**. Condensation of compound **3** with acetone in ethanol brought about 6-acetone-2-ylidenamino-3-benzyl-7-imino-5-methyl-2,3,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidin-2-thione (**8**) (Scheme II). On the other hand, reacting compound **3** with certain aldehydes in ethanol gave 6-arylidineamino-3-benzyl-7-imino-5-methyl-2,3,6,7-tetrahydrothiazolo[4,5-*d*]pyrimidin-2-thiones (**9a-c**).

8-Aryl-3-benzyl-5-methyl-2,3-dihydrothiazolo[5,4-*e*][1,2,4] triazolo[1,5-*c*]pyrimidin-2-thiones (**10a-d**) were obtained by two pathways. The first pathway involved reflux of **3** with the appropriate aldehyde in acetic acid for 12 h. The second method involved heating compound **9a** or **9c** under reflux in the same solvent for 7 h. Compounds **10a** and **10c** obtained by the two pathways were identical and verified by spectral data. Compounds **10b** and **10d** were prepared as depicted in Scheme II.

Antimicrobial activity

The results of antimicrobial testing revealed that compounds (**1c**, **3**, and **8**) were the most active and also showed a broad spectrum antimicrobial activity against both Gram negative, Gram positive as well as fungal species. Both compounds **1c** and **8** showed moderate activity against mycobacterial species. On the other hand, compounds **1a** and 1**b** exhibit also moderate antimicrobial activity, of which was more active on Gram positive than on Gram-negative bacteria. On the other hand, products **7a**, **9a**, and **10b** showed little or no activity against the Gram-positive bacteria and moderate effect against the Gram negative ones. It was interesting to find out that all the tested compounds possessed anti-pseudomonal activity.

Antitumor activity

Some representative compounds (**1a-c**, **3**, **6**, **7a**, **8**, **9a**, **9c**, and **10a-c**) have been tested for their antitumor activity and they showed no actions against the growth of Ehrlich ascites carcinoma (EAC) cells even at high compound concentration levels.

Antitumor activity of the tested drugsusing (EAC)

None of the tested compounds showed any appreciable activity on EAC.

REFERENCES

Ahmedy, A., Vidon D. J. M., Delmas, C. L. and Lett, M. C., Antimicrobial Susceptibles of food-isolated Strains of Yesrsinia enterocolitica, Y. intermedia, Y. Frederiksenii and Y. Kristensenii. *Antimicrobial Agents Chemother.*, 28, 351-353 (1985)

Bayomi, S. M., Amin, K. M., Al-Obaid, A. M., and Hares, N. G., Synthesis of pyrimido [1,2-a] benzimidazole-3-carboxylic acids and pyrrolo[2,3-*b*] pyridine-5-carboxylic acid as nalidixic acid analogues. *Egypt J. Pharm. Sci.*, 34, 117 (1993).

De Clercq, E. Chemotherapeutic approaches to the treatment of the acquired immune deficiency syndrome (AIDS). *J. Med. Chem.*, 29, 1561 (1986).

El-Sherbeny, M. A., El-Ashmawy, M. B., El-Subbagh, H. I., El-Eman, A. A., and Badria, F. A., Synthesis, antimicrobial and antiviral evaluation of certain thienopyrimidine derivatives. *Eur. J. Med. Chem.*, 30, 445 (1995).

Gewald, V. K., Reaktion von methylenaktiven nitrilen mit senfolen und sch wefel. *J. Fur. Prakt. Chem.*, 32, 26 (1966).

Ghorab, M. M. and El-Batal, A. I., Synthesis of some new thiazole derivatives, Antifungal activity and ultrastructure changes of some mycotoxine producing.fungi. *Boll. Chim. Farm.*, 141, 110 (2002).

Holla, B. S., Kalluraya, B., Sridhar, K. R., Drake, E., Thomas, L. M., Bhandary, K. K., and Levine, M. J., Synthesis, structure characterization, crystallographic analysis and antibacterial properties of some Nitrofuryl triazolo [3,4-b]-1,3,4-thiadiazines. *Eur. J. Med. Chem.*, 29, 301 (1994).

Hozien, Z. A., Abdel-Wahab, A. A., Hassan, Kh. M., Atta, F. M., and Ahmed, S. A., Synthesis of some biologically active agents derived from thieno[2,3-d] pyrimidine derivatives. *Pharmazie*, 52, 753 (1997).

Kharizomenova, I. A., Grinev, A. N., Samsonova, N. V., Panisheva, E. R., Kaplina, N. V., Nikolaeva, I. S., Pushkina, T. V., and Pershin, G. N., Functional derivatives of thiophene synthesis and antiviral activity of 3-aminothieno[2,3-d] pyrimidine. *Khim-Farm, Zh.*, 15(9), 40 (1981) through Chem. Abst. 96, 68930r (1982).

Mclimans, W. F., Davis, E. V., Gloves, F. L., and Rakes, G. W., The submerged cultures of mammalian cells; The spinner. Culture. *J. Immunol.*, 79, 424 (1957).

Moharram, H. H., Mansour, S. A., and Osman, A. N., Reactions with purine derivatives: Synthesis of arylamino purines of antitumor effects. *Egypt J. Pharm. Sci.*, 31, 487 (1990).

Mouneer, A. A., Abouzid, K. A. M., and Said, M. M., Synthesis

of certain thienopyrimidine derivatives as antimicrobial agents. *Al Azhar J. Pharm. Sci.*, 30, 150 (2002).

Ogawa, H. and Tanaka, N., 7-(1-piperidinyl)-1,2,3,5-tetrahydro-imidazo[2,1-b] quinazolin-2-one cancer metastasis inhibitor. Jpn. Kokai Tokkyo Koho Jp. 60, 152, 416 10 Aug. 1985; Through Chem. Abst. 62069d, 104 (1986).

Risk, M. S., Abdel-Hamid, A. Z., and Faddah, L. H., Effect of some synthesized purine analogues on nucleic acids in mice. *Egypt J. Pharm. Sci.*, 34, 57 (1993).