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Synthesis of 1-(Heterocyclic Substituted Anilino)-9*H*-Thioxanthon-9-ones and Their Antitumor Activity

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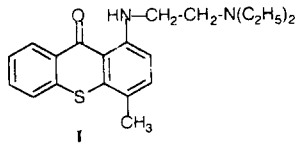
Some new 9H-thioxanthen-9-one incorporated into heterocyclic systems such as pyridone **8**, pyrazoline **9**, pyranone **11**, iminopyrane **12**, furopyrimidine **17**, imidazothiazole **19**, thiazole **21**, triazine **24** and other related compounds through a para imminophenyl grouping at position-1 of the thioxanthenone ring were synthesized and tested as antitumor agents against L 1210 leukemia in mice. Some of the new compounds showed considerable antitumor activity.

Key words : Pyranone, Furopyrimidine, Imidazothiazole, Triazine, Antitumor activity

INTRODUCTION

It has been well established that most of the biological activity of a potent drug against tumors (Henry, 1973), viruses, bacteria and parasites (Clayson, 1973) is connected with its ability of intercalate between base pair of the DNA double helix. This intercalation depends on a number of structural factors. It might be directly with the backbone of the molecule as in case of aminoacridines (Atwell *et al.*, Hansen *et al.*, 1983) or with a certain part of the molecule as in case of hycanthone **I** and oxamniquine **II** (Archer, 1985; El-Hamouly *et al.*, 1988) in which the benzylaminoalkyl part of the molecule is believed to enhance the binding to DNA by electrostatic attraction to the phosphate part of the DNA backbone (Peackock, 1973; Wilson and Jams. 1982; Archer, 1988).

Based on these findings and due to the promising biological activity of 9*H*-thioxanthen-9-one derivatives especially those incorporated into other moieties such as sulfa drugs (Ferguson, 1965), alkylaminoalkyl side chain (Burckhalter *et al.*, 1988) pyrazolines, pyridines, pyranes and others (Katritzky, 1966), it was of interest to synthesize some new 9*H*-thioxanthen-9-one derivatives for the purpose of biological evaluation as antitumor agents.



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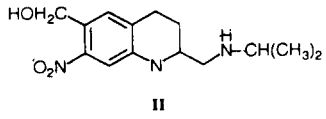

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MATERIALS AND METHODS

All melting points were determined on electrothermal capillary melting apparatus and were uncorrected. Infrared (IR) spectra were determined on KBr plates with Shimadzu IR 435 spectrometer. NMR spectra were recorded on JEOL EX-270 MHz with tetramethylsilane (TMS). as the internal references while the mass spectra with a Finnigan matt SSQ 7000 Spectrometer using electron impact (EI) method. Microanalysis were performed at Cairo University, Faculty of Science.

Synthesis of compouds

1-[N-4-(Substituted)sulfamoylanilino]-9*H*-thioxanthn-9-ones (2a-d): A mixture of **1** (0.7 g, 0.003 mole) and the appropriate sulfa drug, namely sulfanilamide, sulfathiazole, sulfisoxazole or sulfadiazin (0.003 mole). was refluxed in absolute ethanol (15 ml) containing few drops of concentrated hydrochloric acid for about 5 h. The reaction mixture was concentrated, cooled and the separated solid was filtered and then recrystallized from the proper solven affording **2a-d**, respectively (Tables I, II).

***N,N'*-Bis(9*H*-thioxanthen-9-on-1-yl)piperazine (3):** A mixture of **1** (1.4 g, 0.006 mole), pyridine (10 ml) and piperazine (0.003 mole) were heated under reflux for 24 h. The reaction mixture was poured onto water (100 ml) and the solid obtained was stirred for sometime, then filtered, dried and crystallized to give the pure product **3**.

***N,N'*-Bis(4-hydroxymethyl)-9*H*-thioxanthen-9-on-1-yl)piperazine (4):** A solution of **3** (1 g, 0.002 mole), 20

Table I. Physical and analytical data of the newly prepared compounds

Cpd. No.	m.p. °C Solvent	Yield %	Formula (M. wt).	Analysis (%) Calcd/Found C	H	N	M^+ m/z (%)
2a	210 dil EtOH	60	$C_{19}H_{14}N_2O_3S_2$ (382.10)	59.70 59.85	3.65 3.73	7.33 7.60	
2b	187 dil EtOH	75	$C_{22}H_{15}N_3O_3S_3$ (433.22)	61.00 61.10	3.46 3.50	9.70 9.95	
2c	200	65	$C_{24}H_{19}N_3O_4S_2$ (477.24)	60.40 60.25	4.00 3.90	8.80 8.95	
2d	170 dil EtOH	70	$C_{23}H_{16}N_4O_3S_2$ (460.23)	60.00 60.15	3.45 3.60	12.16 12.40	
3	177 MeOH	82	$C_{30}H_{22}N_2O_2S_2$ (506.3)	71.15 71.30	4.35 4.50	5.53 5.75	
4	183 MeOH	70	$C_{32}H_{26}N_2O_4S_2$ (566.32)	67.85 67.75	4.60 4.45	4.95 5.20	566 (53), 506 (47), 296 (23), 212 (100)
5	213 MeCN	77	$C_{24}H_{24}N_2O_2S$ (404.24)	71.30 71.40	5.95 6.10	6.95 6.60	
6	180 EtOH	90	$C_{21}H_{15}NO_2S$ (345.21)	73.05 73.15	4.35 4.50	4.05 3.80	345 (27), 330 (30), 302 (18), 227 (100)
7	125 EtOH	70	$C_{28}H_{18}NO_2SCl$ (467.78)	71.90 71.75	3.85 3.70	3.00 3.35	
8	230 AcOH	75	$C_{31}H_{18}N_3O_2SCl$ (531.81)	70.00 70.15	3.38 3.55	7.90 7.65	331 (67), 420 (21), 303 (100), 227 (17)
9	140 EtOH	55	$C_{30}H_{21}N_3O_2SCl$ (522.80)	68.79 68.95	4.20 4.05	8.02 7.60	522 (15), 491 (20), 485 (40), 393 (100)
10	oil	85	$C_{23}H_{17}NO_3S$ (387.23)	71.35 71.50	4.39 4.65	3.61 3.20	
11	120 MeOH	80	$C_{26}H_{16}N_2O_3S$ (430.26)	72.57 72.30	3.72 3.55	6.50 6.75	
12	145 EtOH	60	$C_{26}H_{17}N_3O_2S$ (435.26)	71.75 72.00	3.90 4.15	9.65 9.30	435 (10), 402 (40), 376 (45), 356 (100)
13	90 EtOH	78	$C_{23}H_{17}N_3OS$ (383.23)	72.07 72.20	4.45 4.60	10.95 10.70	
14	105 EtOH	0	$C_{21}H_{14}NO_2SBr$ (424.21)	59.45 59.60	3.30 3.40	3.30 3.15	
15	190 EtOH	75	$C_{24}H_{15}N_3O_2S$ (409.24)	70.43 70.65	3.65 3.75	10.25 10.00	
16	169 benzene	70	$C_{24}H_{15}N_3O_2S$ (409.24)	70.43 70.20	3.65 3.45	10.25 10.55	409 (8), 392 (55), 378 (30), 361 (100)
17	172 EtOH	68	$C_{25}H_{15}N_3O_2S_3$ (458.25)	61.88 61.65	3.10 3.00	8.65 8.90	
18	gum	75	$C_{22}H_{15}N_3OS_2$ (449.22)	65.85 66.10	3.75 3.90	10.46 10.05	
19	123 EtOH	64	$C_{30}H_{17}N_3OS_2$ (501.30)	71.88 72.10	3.80 4.05	8.38 8.00	501 (50), 498 (100), 487 (15), 466 (40)
20	160 benzene	96	$C_{22}H_{14}N_2O_2S_2$ (402.22)	65.70 65.90	3.50 3.75	6.95 6.55	
21	174 MeOH	90	$C_{22}H_{14}N_2O_2S_2$ (402.22)	65.70 65.60	3.50 3.35	6.95 7.10	
22	180 EtOH	65	$C_{21}H_{13}NO_3S$ (359.21)	70.20 70.35	3.62 3.80	3.90 3.60	
23	185 EtOH	80	$C_{27}H_{17}N_3OS$ (431.27)	75.19 74.90	3.94 3.65	9.74 10.20	
24	150 EtOH	70	$C_{23}H_{16}N_4SO_2$ (428.23)	64.50 64.65	3.73 3.90	13.08 12.80	428 (15), 375 (40), 274 (100), 208 (10)
25	165 Bz	90	$C_{22}H_{16}N_6OS$ (412.22)	64.10 64.25	3.90 4.05	20.38 20.10	

Table I. Continued

Cpd. No.	m.p. °C Solvent	Yield %	Formula (M. wt).	Analysis (%) Calcd/Found C	H	N	M^+ m/z (%)
26	250 AcOH	80	$C_{30}H_{18}N_6O_3S$ (542.30)	66.44 66.70	3.32 3.50	15.50 15.25	
27	110 oil	85	$C_{22}H_{15}NO_4S$ (389.22)	67.90 68.15	3.85 4.00	3.60 3.20	389 (60), 370 (20), 350 (10), 343 (100)
28	198 benzene	65	$C_{27}H_{16}N_3O_2S$ (452.27)	72.66 72.85	3.58 3.80	9.41 9.10	452 (70), 378 (100), 300 (10), 275 (30)

% acetic acid (5 ml) and 37% formaldehyde (20 ml) was kept at 80°C for 72 h, the reaction mixture was coold and made basic with 10% Na_2CO_3. It was extracted with chloroform, evaporated and the gum residue was crystallized to give the desired product **4** (Tables I, II).

1-[(4-Hydroxy-3-diethylaminomethyl)anilino]-9*H*-thioxanthen-9-one (5): A solution of **1** (0.7 g, 0.003 mole) in benzene (10 ml) was added dropwise to a stirred solution of 4-amino-2-(diethylaminomethyl)phenol dihydrochloride (Omar, 1995) (0.005 mole) in benzene (15 ml). The reaction mixture was stirred at room temperature for 18 h, filtered and the benzene filtrates were washed with dilute sodium hydroxide followed with water, dried and concentrated to yield a yellow solid **5**.

1-(4-Acetyl)anilino-9*H*-thioxanthen-9-one (6): A mixture of **1** (5 g, 0.021 mole) and p-aminoacetophenone (2.7 g, 0.021 mole) in absolute ethanol (30 ml) containing few drops of concentrated hydrochloric acid was refluxed for 4 h. After cooling, the formed precipitate was filtered, washed with dilute ammonium hydroxide followed with water and the solid product was than recrystallized to give **6** (Table I, II).

1-[(9*H*-Thioxanthen-9-on-1-yl)amino]phenyl-2-(4-chlorophenyl)propen-1-one(7): To a mixture of **6** (2.9 g, 0.008 mole) and p-chlorobenzaldehyde (1.4 g, 0.01 mole) in ethanol (15 ml), 10% NaOH (8 ml) was added. The reaction mixture was left overnight with stirring at 25°C, then warmed at 40°C for 30 minutes. The formed precipitate was crystallized to give **7**.

3-Cyano-6-[9*H*-thioxanthen-9-on-1-yl)amino]phenyl-4-(4-chlorophenyl)-2-(1H)-pyridone (8): a- A mixture of **6** (1.4 g, 0.004 mole), ethyl cyanoactate (0.005 mole), p-chlorobenzaldehyde (0.005 mole) and ammonium acetate (0.035 mol) in n-butanol (30 ml) was heated under reflux for 3 h. The formed precipitate was filtered, washed with water followed with ether, dried and recrystallized to give the corresponding pyridone **8** in good yield (75%) (Table I, II).

b- A mixture of the chalcone analogue **7** (1.5 g, 0.003 mole), ethyl cyanoacetate (0.004 mole) and ammonium acetate (0.04 mole) in n-butanol (20 ml) was refluxed for 10 h, where a crystalline precipitate was separated. This was filtered after cooling to give pyridone compound **8** in low yield (>30%).

1-Acetyl-5-(4-chlorophenyl)-3-[9*H*-thioxanthen-9-on-1-yl)amino]phenyl-Δ^2-pyrazoline (9): A solution of **7** (1.2 g, 0.002 mole), hydrazin hydrate (0.25 g, 0.005 mole) in acetic acid (20 ml) was heated under reflux for 5 h, then left to cool and poured onto ice water. The obtaind precipitate was filtered, washed with water several times and then recrystallized to give **9** (Tables I, II).

4-[(9*H*-Thioxanthen-9-on-1-yl)amino]benzoylactone (10): A solution of **6** (4 g, 0.01 mole) in ethyl acetate (30 ml) was slowly added to small pieces of sodium metal (2 g). When the initial vigorous reaction subsided, the reaction mixture was refluxed for 5 h, the left to cool. Methanol (5 ml) was added to destory excess sodium. The the mixture was poured onto water and acidified with acetic acid. The separated oily layer was extracted with chloroform and dried over anhydrous sodium sulphate to give **10** (as an oil product).

3-Cyano-4-methyl-6-[(9*H*-thioxanthen-9-on-1-yl)amino]phenyl-2(H)-pyranone (11): A mixture of **7** (1.5 g, 0.003 mol), malononitrile (0.004 mole) and ammonium acetate (0.015 mole) in glacial acetic acid (15 ml) was refluxed for 3 h. The reaction mixture was allowed to cool and the separated solid was filtered off and crystallized from methanol to yield **11**.

3-Cyano-4-methyl-6-[(9*H*-thioxanthen-9-on-1-yl)amino]phenyl-2-imino-pyrane (12): The foregoing procedure was carried out except that the reaction was carried out in boiling ethanol instead of glacial acetic acid to give **12** (Tables I, II).

3-Methyl-5-[(9*H*-thioxanthen-9-on-1-yl)amino]phenylpyrazole (13): A mixture of **7** (1.2 g, 0.0025 mole) and 99% hydrazine hydrate (0.003 mole) in acetic acid (10 ml) was refluxed for 5 h. The reaction mixture was concentrated to 1/4 its volume and left to cool. The obtained precipitate was filtered off and crystallized to give **13** (Table I, II).

1-(4-Bromoacetylanilino)-9*H*-thioxanthen-9-one (14): A solution of **6** (10.35 g, 0.03 mole) in acetic acid (40 ml) was stirred at 0°C, while a solution of bromine (0.03 mol) in glacial acetic acid (20 ml) was added dropwise during 30 min, with continous stirring. The reaction mixture was left at room temperature for 1 h. The formed solid was filtered off and crystallized to

Table II. Spectral data for compounds listed in Table I.

Compd. No.	IR (KBr), cm^{-1} (selcted bands)	^{1}H-NMR (DMSO-d_6) δ (ppm)
2a	3400, 3300 (NH_2 and NH), 1720 (C=O), 1350 (SO_2)	3.70~3.90 (br.s, 2H, NH_2), 6.90~7.80 (m, 11H, Ar-H), 8.30 (s, 1H, NH)
2b	3400 (NH), 1700 (C=O), 1350 (SO_2)	5.30~5.60 (dd, 2H of thiazole), 7.00~8.00 (m, 11H, Ar-H), 8.20 (s, 1H, NH), 8.50 (s, 1H, NH)
2c	3390 (NH), 1680 (C=O), 1345 (SO_2)	2.25 (s, 6H, $2CH_3$), 7.00~8.00 (m, 11H, Ar-H), 8.30 (s, 1H, NH), 8.60 (s, 1H, NH)
2d	3450 (NH), 1700 (C=O), 1340 (SO_2)	7.00~8.00 (m, 14H, Ar-H), 8.30 (s, 1H, NH), 8.60 (s, 1H, NH)
3	1640 (C=O), 1600 (C=C)	3.40~3.60 (m, 8H, of piperazine), 7.40~8.00 (m, 14H, Ar-H)
4	3340 (OH), 1640 (C=O), 1600 (C=C)	3.30~3.60 (m, 8H, of piperazine), 4.50 (s, 4H, $2CH_2$-OH), 7.20~8.00 (m, 12H, Ar-H)
5	3450 (NH and OH), 1650 (C=O), 1660 (C=C)	3.30~3.60 (m, 8H, of piperazine), 4.50 (s, 4H, $2CH_2$-OH), 7.20~8.00 (m, 12H, Ar-H)
5	3450 (NH and OH), 1650 (C=O), 1660 (C=C)	1.0~1.5 (t, 6H, $2CH_2\underline{CH_3}$), 2.40~2.60 (q, 4H, $2\underline{CH_2}CH_3$), 3.40 (s, 1H, OH), 3.70 (s, 2H, CH_2N), 7.0~8.1 (m, 10H, Ar-H), 8.60 (s, 1H, NH)
6	3400 (NH), 1680 (C=O), 1640 (C=O)	2.40 (s, 3H, $COCH_3$), 7.00~8.10 (m, 11H, Ar-H), 8.50 (s, 1H, NH)
7	3320 (NH), 1690 (C=O), 1640 (C=O), 1600 (C=C)	6.50~6.70 (dd, 2H, CH=CH), 7.10~7.80 (m, 15H, Ar-H), 9.20 (s, 1H, NH)
8	3420 (NH), 2220 (C≡N), 1700 (C=O), 1610 (C=C)	6.80 (s, 1H of pyridone), 7.00~7.80 (m, 15H, Ar-H), 8.50, 8.80 (2s, 2H, 2NH)
9	3300, 3200 (NH), 1700 (C=O), 1640 (C=O)	2.40 (s, 3H, $COCH_3$), 3.35~3.50 (2dd, 2H of pyrazoline), 2.60~3.70 (t, 1H, of pyrazoline), 6.90~7.85
10	3420 (NH), 1730, 1710 (tautomeric keto-enol form), 1600 (C=C)	2.50 (s, 3H, $COCH_3$), 3.40 (s, 2H, CH_2), 7.00~8.00 (m, 11H, Ar-H), 8.40 (s, 1H, NH)
11	3400 (NH), 2210 (C≡N), 1670 (2C=O)	2.50 (s, 3H, CH_3), 6.60 (s, 1H of pyranone) 7.20~7.70 (m, 11H, Ar-H), 9.60 (s, 1H, NH)
12	3350, 3100 (NH, =NH), 2215 (C≡N), 1660 (C=O)	2.40 (s, 2H, CH_3), 6.60 (s, 1H of iminopyrane) 7.20~7.80 (m, 12H, Ar-H), 8.40, 8.60 (2s, 2H, 2NH)
13	3380, 3090 (NH and NH of pyrazole), 1660 (C=O)	2.30 (s, 3H, CH_3), 7.40 (s, 1H of pyrazole), 7.50~8.00 (m, 11H, Ar-H), 9.00, 9.20 (2s, 2H, 2NH)
14	3300 (NH), 1660 (2C=O), 1600 (C=C)	3.40 (s, 2H, $COCH_2$, 7.10~8.00 (m, 11H, Ar-H), 8.40 (s, 1H, NH)
15	3400 (NH), 2220 (C≡N), 1690 (2C=O)	3.80~3.90 (dd, 2H, CH_2), 4.50~4.55 (t, 1H, CH), 7.10~7.80 (m, 11H, Ar-H), 8.60 (s, 1H, NH)
16	3360, 3100 (NH, NH_2), 2220 (C≡N), 1640 (C=O)	4.80 (s, 1H, furane ring), 5.10 (s, 2H, NH_2), 7.00~7.80 (m, 11H, Ar-H), 9.30 (s, 1H, NH)
17	3350~3250 (NH), 1660 (C=O), 1620 (C=N)	7.20~8.0 (m, 12H, Ar-H and one proton of furane), 8.20, 8.60, 9.80 (3s, 3H, 3NH)
18	3400, 3100 (NH, NH_2), 1665 (C=O), 1590 (thiazole ring)	4.30 (s, 2H, NH_2), 6.70 (s, 1H of imidazole), 7.00~7.80 (m, 11h, Ar-H), 8.20 (s, 1H, NH)
19	3400 (NH), 1680 (C=O), 1620 (C=N)	5.40 (s, 1H of thiazole), 6.70 (s, 1H of imidazole), 6.90~7.80 (m, 16H, Ar-H), 8.30 (s, 1H, NH)
20	3400 (NH), 2240 (C≡N), 1660 (C=O), 1600 (C=C)	3.40 (s, 2H, CH_2), 6.90~7.70 (m, 11H, Ar-H), 8.30 (s, 1H, NH)
21	3400 (NH), 3100 (OH), 1660 (C=O), 1590 (thiazole ring),	6.90~7.80 (m, 11H, Ar-H), 8.20 (s, 1H, NH), 10.30 (s, 1H, OH)
22	3400 (NH), 1690 (C=O), aldehydic group), 1660 (C=O), 1620 (C=O)	6.90~7.70 (m, 11H, Ar-H), 8.40 (s, 1H, NH), 10.40 (s, 1H, CHO)
23	3350 (NH), 1670 (C=O)	7.00~8.00 (m, 16H, Ar-H), 8.50 (s, 1H, NH)
24	3400 (NH), 1660 (C=O), 1630 (C=N)	2.70 (s, 3H, SCH_3), 7.10~7.90 (m, 12H, Ar-H), 9.30 (s, 1H, NH)
25	3330, 3210 (NH, NH_2), 1660 (C=O), 1620 (C=N)	7.00~7.80 (m, 12H, Ar-H), 8.30 (br. s, 3H, NH, NH_2), 9.20 (s, 1H, NH)

Table II. Continued

Compd. No.	IR (KBr), cm^{-1} (selcted bands)	^{1}H-NMR (DMSO-d_6) δ (ppm)
26	3200 (NH), 1780, 1740 (2C=O), 1660 (C=O)	6.90~7.80 (m, 16H, Ar-H), 8.30~8.50 (2s, 2H, 2NH)
27	3350 (NH), 1740, 1710 (2C=O), 1660 (C=O)	2.30 (s, 3H, CH_3), 6.90~7.80 (m, 11H, Ar-H), 8.30 (s, 1H, NH)
28	3400 (NH), 1700 (C=O), 1615 (C=O), amide)	7.00~7.80 (m, 15H, Ar-H), 8.35 (s, 1H, NH)

give a pale yellow powder of **14** (Tables I, II).

4-[[(9*H*-Thioxanthen-9-on-1-yl)amino]benzoyl]]methylmalononitrile (15): A solution of equimolar amounts (0.01 mol) of each of **14** and malononitrile in ethanol (20 ml) was treated with a solution of sodium hydroxid (2 g in 20 ml H_2O) dropwise with constant stirring. After complete addition, the reaction mixture was diluted with water (30 ml) and the formed solid was collected and crystallized to give **15** (Tables I, II).

2-Amino-3-cyano-5-[(9*H*-thioxanthen-9-on-1-yl) amino]benzofurane (16): A mixture of **15** (2.3 g, 0.005 mol) in acetic acid (10 ml) and concentrated hydrochloric acid (5 ml) was refluxed for 1 h. The reaction mixture was cooled and diluted with water. The formed precipitate was filtered off and recrystallized to give **16** (Tables I, II).

4-[1-(9*H*-Thioxanthen-9-on-1-yl)aminophenyl]-2,4-dithioxo-1,2,3,4-tetrahydrofuro[3,2-d]pyrimidine (17): A solution **16** (1.5 g, 0.003 mole) in a mixture of dry pyridine (10 ml) and carbon disulphide (10 ml) was refluxed on a water bath for 4 h, then allowed to stand at room temperature for 4 days. The solution was then triturated with ethanol (100 ml). The precipitated solid was filtered off and recrystallized to yield **17**.

2-Amino-4-[(9*H*-Thioxanthen-9-on-1-yl)amino]benzothiazole (18): A mixture of **14** (3 g, 0.007 mole) and thiourea (0.008 mole) was refluxed in ethanol for 3 h. The reaction mixture was coold and then poured onto crushed ice. The precipitate was filtered and the dried product was crystallized to give **18** (Tables I, II).

2-Phenyl-4-[1-(9*H*-thioxanthen-9-on-1-yl-amino) phenyl]imidazo[2,1-b]-thiazole (19): A mixture of **18** (1.5 g, 0.003 mole) and phenacyl bromide (0.004 mol) in dry methanol (20 ml) was heated under reflux for 4 h, cooled and neutralized with KCO_3 solution. The solid thus obtained was purified (charcoal) and crystallized giving colourless shining flakes of **19** (Tables I, II).

1-[(4-Thiocyanatoacetyl)anilino]-9*H*-thioxanthen-9-one (20): A solution of compound **14** (2 g, 0.0047) in ethanol (30 ml) was added to a solution of potassium thiocyanat (0.005 mole) in ethanol (5 ml). The reaction mixture was heated for an hour with stirring on boiling steam bath. The precipitate was isolated by filteration and recrystallized to give **20**.

2-Hydroxy-4-[(9*H*-thioxanthen-9-on-1-yl)amino]benzothiazole (21): A soultion of **20** (1 g) in glacial actic acid (10 ml) and conc, sulphuric acid (2 ml) was heated with stirring for 30 min, on a steam bath and then cooled. The precipitate was filtered off and the formed solid was crystallized to give **21** (Tables I, II).

4-[(9*H*-Thioxanthen-9-on-1-yl)amino]phenylglyoxaldehyde (22): A solution of **14** (4.2 g, 0.01 mole) in dimethylsulphoxide (20 ml) was heated for 4 h on a steam bath and then allowed to stand overnight. After the addition of water (50 ml), the formed precipitate was crystallized to yield the title compound **22**.

1-[4-(2-Quinoxalinyl)]anilino-9*H*-thioxanthen-9-one (23): A solution of o-phenylenediamine (1.55 g, 0.005 mole) in ethanol (20 ml) was added to glyoxaldehyde derivative **22** (1.8 g, 0.005 mol) in ethanol (5 ml). The reaction mixture was heated on a steam bath for 30 min, and then diluted with water. The crystalline mass separated was filtered off and crystallized to give the product **23**.

3-Methylthio-5-[4-(9*H*-thioxanthen-9-on-1-yl)amino] phenyl-1,2,4-triazine (24): A solution of **22** (3.6 g, 0.01 mole) in 80% ethanol was added gradually to a stirred solution of methylthiosemicarbazide hydrogen iodide[32] (0.012 mole) and $NaHCO_3$ (0.01 mole) in 80% ethanol. The mixture was stirred for 5 h at 25°C. The formed precipitate was filtered off, washed with water and crystallized to afford **24** (Table I, II).

3-Hydrazino-5-[4-(9H-thioxanthen-9-on-1-yl)amino] phenyl-1,2,4-triazine (25): To a solution of **24** (3 g) in dioxane (20 ml) was added NH_2NH_2 (10 ml) dropwise. The reaction mixture was refluxed for 72 h with stirring (until the evolution of methyl mercaptan). The solution was concentrated and cooled, where a yellow percipitate was formed. The precipitate was filtered, washed with water and crystallized to give **25** (Tables I, II).

3-(1,2,3,4-Tetrahydro-naphth-6-yl)-5-[4-(9*H*-thioxanthen-9-on-1-yl)amino]-phenyl-1,2,4-triazine (26): To a solution of 25 (2 g, 0.005 mol) in absolute ethanol (20 ml), phthalic anhydride (0.006 mole) was added. The reaction mixture was refluxed for 10 h, cooled and the formed precipitate was filtered, washed with ethanol and then crystallized to give compound **26** (Tables I, II).

Methyl-4-[(9-*H*-thioxanthen-9-on-1-yl)amino]phenylglyoxylate (27): A mixture of compound **14** (2.1 g, 0.005 mole), selenium dioxide (0.005 mole) and absolute methanol (30 ml) was refluxed with stirring for 10 h. The seleium was removed and the filterate was evaporated leaving **27** as an oil (Tables I, II).

1-[4-(2-Oxo-1,2-dihydro-3-quinoxalinyl)anilino-9*H*-thioxanthen-9-one (28): A solution of o-phenylenediamine (0.55 g, 0.005 mole) in ethanol (20 ml) was added to the crude glyoxylate **27** (0.005 mole). The reaction mixture was heated on a steam bath for 30 min. After dilution with water, the formed precipitate was crystallized to give the tiltle compound **28** (Tables I, II).

Antitumor test *in vivo*

Some of the poreviously synthesized compounds were tested against L1210 leukemia in mice.

Animals: In this study, we used the syngenic female Balb/C mice weighing 22~23 g obtained from the nursery of laboratory animals (The Egyptian Organization of Serum and Vaccines). They were kept in plastic cages where they fed on special food pellets consisting of proteins, essential amino acid, minerals and vitamins.

Induction of ascitic leukemia: Eleven groups, each of ten mice were used *in vivo* studies. Mice recieved an i.p. injection of 1×10^6 ascitic L1210 cells and were routinely used in experiments when bearing approximately 1×10^8 cells (7 days post injection). The 11^{th} group served as control.

Treatments: Leukemic mice were given i.p. injection with 0.2 ml of the tested compounds using different concentration to study the growth inhibition effect of these compouds.

BIOLOGICAL ACTIVITY

Results of the *in vivo* antitumor activity of the tested compounds against L1210 leukemia in mice are listed in Table III.

In this test system, only two compounds showed moderate antitumor activity against L1210 leukemia in mice, while the rest of compounds were inactive (i.e. T/C <125). The antitumor activity of 1-acetyl-5-(4-chlorophenyl)-3-[9*H*-thioxanthen-9-on-1-yl)amino]phenyl-Δ^2-pyrazoline (**9**) was higher than the activity of 2-amino-4-[(9*H*-thioxanthen-9-on-1-yl)amino]benzothiazole (**18**).

The results reported herein are in agreement with results showed by Archer *et al.*, 1983, 1987, 1988, who investigated the antitumor activity of 9*H*-thioxanthen-9-one derivative I.

Table III. Antitumor activity of some newly synthesized compounds

Compound No.	*In vivo* antitumor activity against L1210 leukemia in mice	
	dose, mg/kg	T/C
2	52	98
3	44	103
5	32	112
8	27	97
9	14.25	148
12	36	84
17	55	89
18	20.5	133
19	38	96
26	18	87

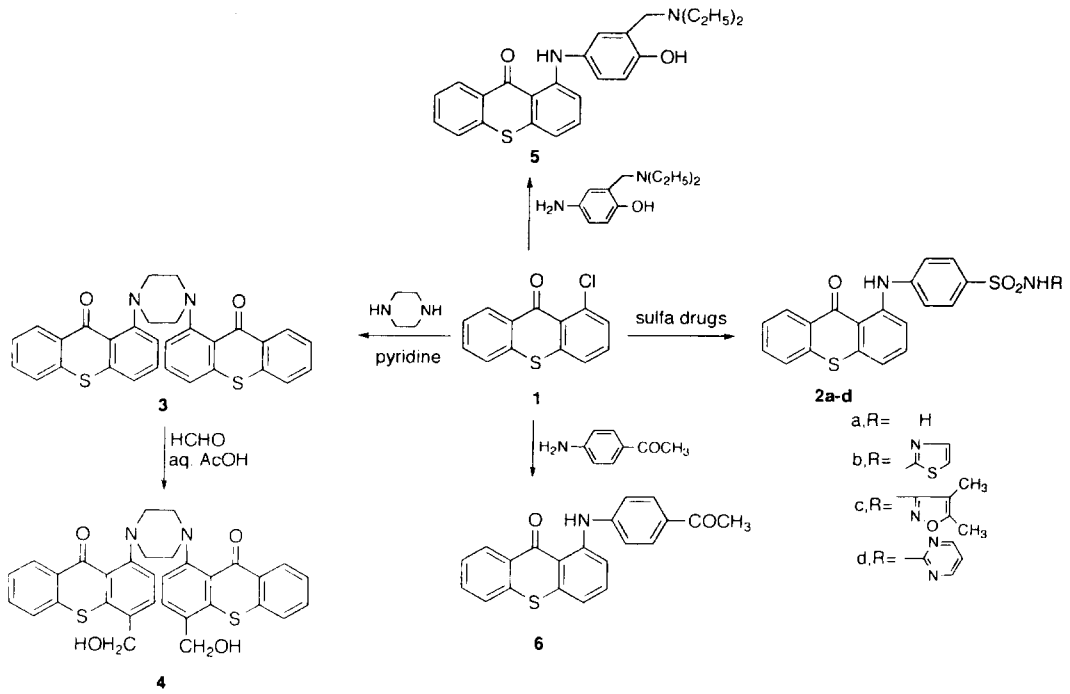
RESULTS AND DISCUSSION

Synthesis of 1-[*N*-4-(substituted)sulfamoylanilino]-9*H*-thioxanthen-9-ones (**2a-d**) was achieved by allowing 1-chloro-9H-thioxanthen-9-one (**1**) (Archer, 1985) to reflux with different sulfa drugs namely sulfanilamide, sulfathiazole, sulfisoxazole and sulfadiazine (El-Marzabani *et al.*, 1976), respectively in ethanol.

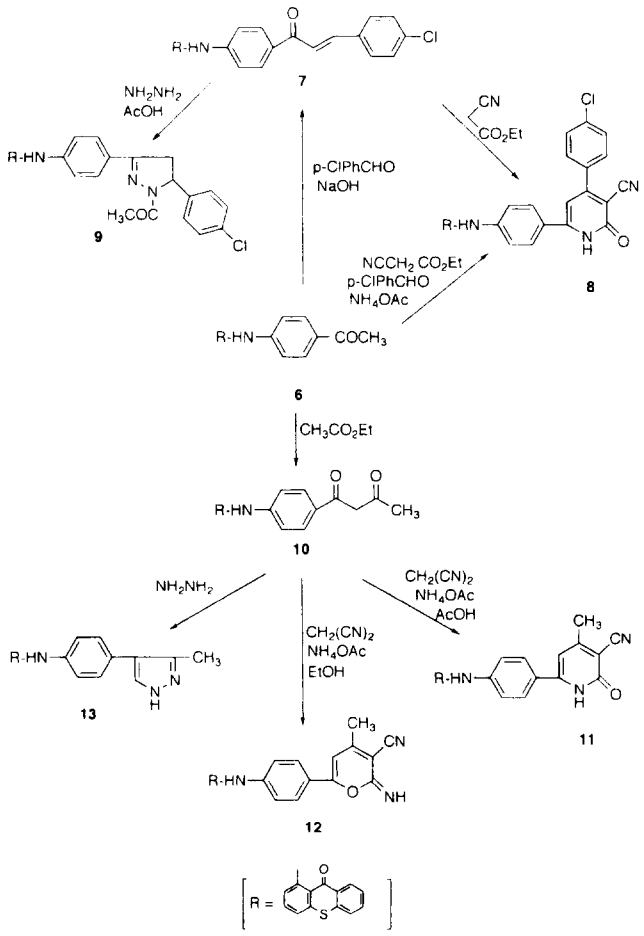
The dimeric compound **3** was prepared by selecting piperazine to bring the two monomeric molecules together in one compound. Condensation of **1** with piperazine in the presence of pyridine afforded the target compound *N,N*-bis(9*H*-thioxanthen-9-on-1-yl)piperazine (**3**), upon reaction of **3** with formaldehyde in aqueous acetic acid (Archer, 1988) it gave the corresponding *N,N*-bis(4-hydroxymethyl-9*H*-thioxanthen-9-on-1-yl)piperazie (**4**).

Condensation of **1** with 4-amino-2-(diethylaminomethyl)phenol dihydrochloride (Omar, 1995) afforded the thioxanthone-Mannich base **5** in good yield. Further, treatment of **1** with *p*-aminoacetophenone it afforded 1-(4-acetylanilino)-9*H*-thioxanthen-9-one (**6**) (Scheme 1).

The derivative **7** was obtained through Claisen-Schmidt condensation (Susan and Synden, 1958) of *p*-chlorobenzaldehyde with **6** in the presence of sodium hydroxide. Reaction of α,β-unsaturated ketone **7** with ethylcyano-acetate in excess ammonium acetate afforded the pyridone derivative **8** in low yield (<30%), using an alternative route, the one-pot reaction for the synthesis of compound **8** by heating a mixture of **6**, *p*-chlorobenzaldehyde and ethylcyanoacetate in the preseance of excess ammonium acetate, it afforded the pyridone derivative **8** in a high yield. Also, the chalcone derivative **7** was allowed to react with hydrazine hydrate (Eldrfield, 1957) in boiling acetic acid, the corresponding 1-acetyl-5-(4-chlorophenyl)[(9*H*-thioxanthen-9-on-1-yl)-amino]-phenyl-Δ^2-pyrazoline (**9**) was obtained. Synthesis of the pyranone **11** and the imminopyrane **12** were achieved via two different routes by allowing the acetyl derivative **6** to undergo further acetylation, by heating compound **6** with ethyl acetate (Kamel *et al.*, 1986) in presence of sodium metal to give 4-[(9*H*-thioxanthen-9-on-1-yl)-amino]benzoylacetone (**10**). Reaction of **10** with malononitrile in the presence of ammonium acetate afforded **11** or **12** according to the reaction condition (Kamel *et al.*, 1986). When the reaction was carried out in hot ethanol, the iminopyrane **12** was obtained. Further, reaction of **10** with hydrazine hydrate in acetic acid afforded



Scheme 1.

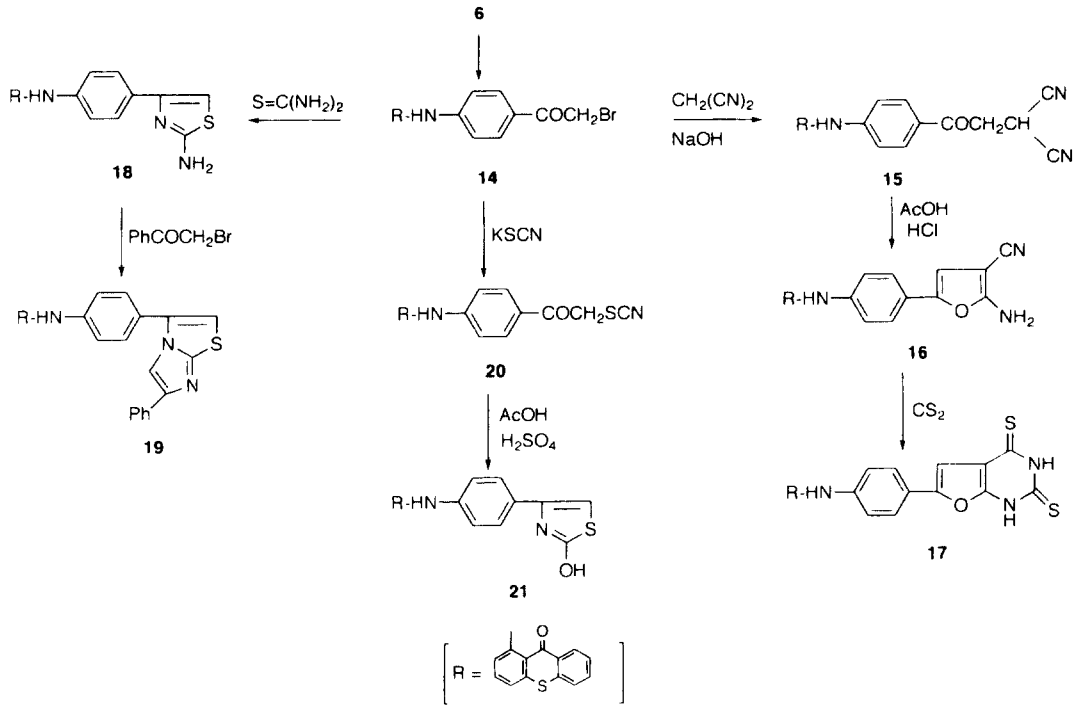


Scheme 2.

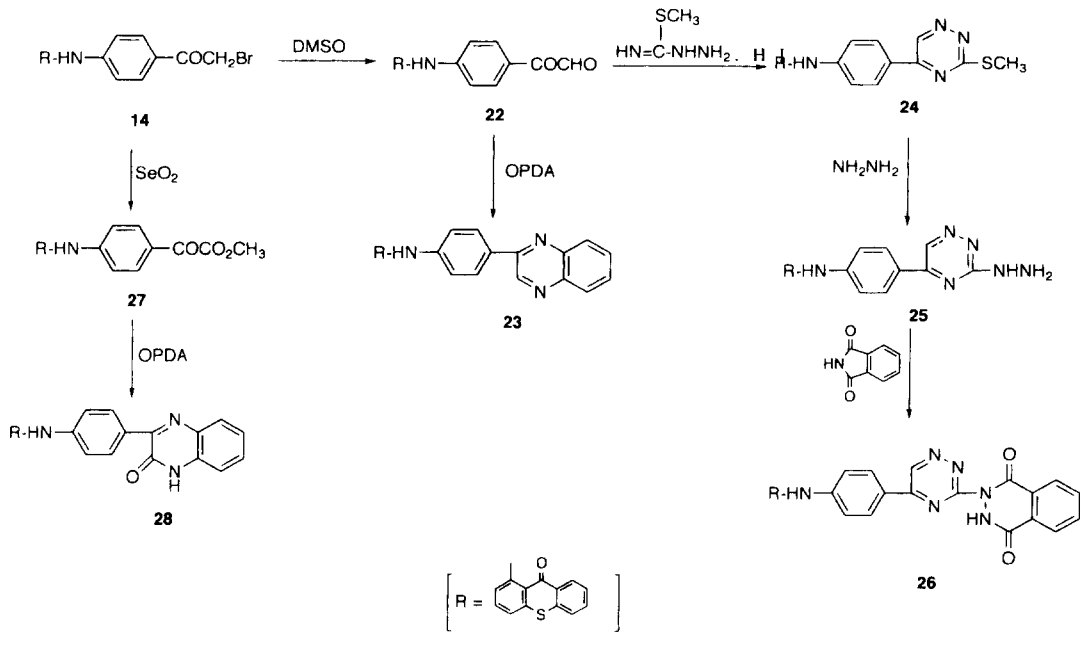
3-methyl-4-[(9*H*-thioxanthen-9-on-1-yl)amino]phenylpyrazole (**13**) according to a reported method (Kamel *et al.*, 1996) (Scheme 2).

Synthesis of 4-[1-(9*H*-thioxanthen-9-on-1-yl)aminophenyl]-2,4-dithioxo-1,2,3,4-tetrahydrofuro[2,3-d]pyrimidine (17) was achieved by allowing the acetyl derivative **6** to undergo bromination to give the bromo compound **14** according to a reported method (Ebeid *et al.*, 1991). Reaction of **14** with malononitrile in aqueous sodium hydroxide gave 4-[(9*H*-thioxanthen-9-on-1-yl)amino]-benzoyl]methylmalononitrile (**15**) in almost quantitative yield.

On the other hand, it is well known that polyfunctional nitriles are highyl reactive reagents that have been extensively used in heterocyclic synthesis. Accordingly, it was of interest to allow **15** to undergo cyclization by boiling in acetic acid and concentrated hydrochloric acid (Abdel-Hamid *et al.*, 1989) to give the enamino furan derivative **16**. The latter was condensed with carbon disulphide in dry pyridine (Abdelrazek and Nawwar, 1991) to give the furopyrimidine dithione derivative **17**. Reaction of **14** with thiourea in ethanol yielded the aminothiazole derivative **18** which underwent cyclization upon its reaction with α-haloketone in dry ethanol to give imidazo [2,1-b]thiazole derivative **19** according to a reported method (Nabih *et al.*, 1985; Mohan and Anjaneyulu, 1987). Condensation of **14** with potassium thiocyanate in ethanol gave the thiocyanatoacetyl derivative **20**. Treatment of **20** with glacial acetic acid and concentrated sulphuric acid affored the hydroxythiazole



Scheme 3.



Scheme 4.

derivative **21** according to a reported method (Zoorob *et al.*, 1980) in a good yield (Scheme 3).

Furthermore, the glyoxylaldehyde derivative **22** was prepared by heating the bromoacetyl derivative **14** with dimethylsulphoxide (Zoorob *et al.*, 198). Treatment of **22** with *o*-phenylenediamine (OPDA) gave 1-[4-(2-quinoxalinyl)anilino]-9*H*-thioxanthen-9-one **23**. Also, compound **22** was reacted with methylthiosemicarbazide hydrogen iodide (Nabih *et al.*, 1986), to give the corresponding thio-1,2,4-triazine derivative **24**. Upon reactionn of **24** with hydrazine hydrate, it gave the corresponding hydrazino-1,2,4-triazine **25** through nucleophilic displacement reaction. Reaction of **25** with phthalic anhydride in the presence of hydrochloric

acid afforded the corresponding 1,2-diazine derivative **26**. At the same time, the glyoxylate derivative **27** was synthesized by oxidation of the bromo compound **14** with selenium dioxyide in absolute ethanol. Compound **27** was condensed with *o*-phenylenediamine to give the corresponding 1-[4-(2-oxo-1,2-dihydro-3-quinoxalimyl)anilino]-9*H*-thoxanthen-9-one (**28**) according to a reported method (Zoorob *et al.*, 1980) (Scheme 4, Tables I, II).

All the new compounds were confirmed by elemental analyses, IR, ^{1}H-NMR and mass spctroscopy (c.f. experimental part, Tables 1 and 2).

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