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Synthesis of New Xanthenone Derivatives of Expected Antibilharzial Activity

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A new series of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles incorporated directly and/or indirectly into a xanthenone moiety at position-2 were synthesized. Some of the newly prepared compounds were biologically tested as schistosomicides in experimental animals.

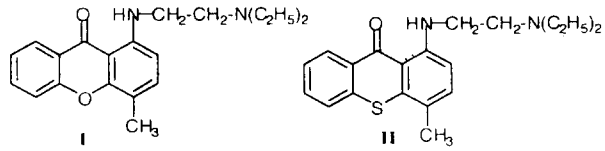
Key words : 1,3,4-Oxadiazole, 1,3,4-Thiadiazoles, 1,2,4-Triazoles, Antischistosomal activity

INTRODUCTION

A great deal of interest has been shown in the structure-activity relationship of the xanthenone derivative **1** (Moustafa *et al.*, 1963) and its analogue, the thiaxanthenone **II** (Archer *et al.*, 1988) due to their antibilharzial and antitumor activities (Archer *et al.*, 1988; Nabih, 1966; Nabih, 1973; Bailey *et al.*, 1970; Mattoccia *et al.*, 1981).

The particular activity of **I** and **II** may be explained by the presence of the polarizable carbonyl group and the heteroatom (oxygen or sulfur) neighboring to the 4-position. As both heteroatoms bear two paris of free electrons, the structures of both molecules (**I** and **II**) permit, to different extents, extensive delocalization of the free electrons to be involved in the resonance hybride (Nabih, 1966; Nabih, 1973). On the other hand, it has been established that, most of the biological activity of the structure **I** and **II** is connected with its planar aromatic triple ring system which can bind with schistosomal DNA, probably by intercalating between base pair of the DNA double helix through electrostatic attraction of the phosphate part DNA backbone (Archer *et al.*, 1988; Mattoccia, *et al.*, 1981).

Based on these findings the purpose of the present work is to synthesize a variety of some new heterocycles, namely oxadiazoles, also thiadiazoles and triazols and other related structure incorporated directly or indirectly into the xanthenone moity at its position-2 hoping that the resultant compounds might exhibit a promising biological activity as antibilharzial agents. Introduction of these heterocyclic systems was based on their reported biological importance in variety of



antiparasite agents (Katritzky, 1966).

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 reference 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 compounds

1-[(2-Xanthenonyl)-3-(3-chlorophenyl)]urea (2a) and 1-[(2-xanthenonyl)-3-ethyl]thiourea (2b):

General method: To a solution of 2-aminoxanthone (**1**) (2.1 g, 0.01 mole) in methanol (20 ml) and 3-chlorophenylisocyanate (1.53 g, 0.01 mole) or ethylisocyanate 0.87 g, 0.01 mole) in methanol (5 ml) was added dropwise within 15 minutes. The reaction mixture was stirred for 2h at 60°C and the formed precipitate was filtered to give the compounds **2a** and **2b** respectively (Table I). IR (KBr, cm^{-1}) of **2a**: 3410 (NH), 1680 (2C=O), 1600 (C=C), **2b**: ^{1}H-NMR (DMSO-d_6) δ 1.10-1.50 (3H, t, CH_3 of C_2H_5), 3.30~3.40 (2H, q, CH_2 of C_2H_5), 3.80 (2H, br. s., 2NH) and 7.00~8.00 (7H, m, aromatic protons).

1-(3-Chlorophenyl)-3-(2-xanthenonyl)-2-oxo-imidazolidin-4,5-dione (3a): A mixture of **2a** (1.8 g, 0.005 mole) and oxalyl chloride (0.006 mole) in dry ben-

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zene (15 ml) was heated at 50°C for 6h. The solvent was evaporated and the solid residue was recrystallized to give compound **3a** (Table I). IR (KBr, cm^{-1}): 1710 (3C=O), 1660 (C=O), 1600 (C=C).

1-Ethyl-3-(2-xanthenonyl)-2-thioxoimidazolidin-4,5-dione (3b): The foregoing procedure was carried out except that compound **2a** was replaced by **2b** to afford **3d** (Table I). MS, m/z (%): 352, M^+ (66), 330 (20), 296 (18), 253 (37) and 237 (100).

N-(2-Xanthenonyl)rhodanine (4): To an ice cooled mixture of concentrated ammonium hydroxide solution (5 ml) and carbon disulfide (2 ml, 0.028 mole) was added slowly 2-aminoxanthone (**1**) (2.1 g, 0.01 mole). The reaction mixture was stirred for 15 minutes and then allowed to stand overnight at 25°C. The solid dithiocarbanalic acid ammonium salt was collected and washed with ether, dried and added to cold solution of sodium chloroacetate (0.01 mol) in water (5 ml) which was made slightly alkaline by addition of Na_2CO_3 solution, then left at 25°C for 2h. The mixture was treated with warm 70% HCl and heated at 90°C for 0.5h. The precipitate which was formed on cooling was collected and crystallized to give compound **4** (Table I). IR (KBr, cm^{-1}): 1700, 1660 (2C=O), 1600 (C=C), 1130 (C=S); ^{1}H-NMR (DMSO-d_6) δ 5.50 (2H, s, CH_2 of thiazol), 7.00~8.00 (7H, m, aromatic protons). MS, m/z (%):327, M^+ (7), 280 (11), 226 (18), 211 (100) and 196 (20).

N-(2-Xanthenonyl)glycine ethyl esters (5): A mixture of 1 (2.10 g, 0.01 mole) and ethyl bromoacetate (1.70 g, 0.01 mole) in dry DMF (20 ml) and anhydrous K_2CO_3 (2.5 g) were refluxed for 3h. After cooling, the reaction mixture was poured into ice water and neutralized with HCl. The formed precipitate was filtered, washed with cold water and crystallized to give the ester compound **5** (Table I). IR (KBr, cm^{-1}): 3400 (NH), 1720 (C=O), 1680 (C=O); ^{1}H-NMR (DMSO-d_6) δ 1.10~1.15 (3H, t, CH_3 of ester), 3.35~3.45 (2H, q, CH_2 of ester), 4.50 (2H, s, NCH_2), 7.00~8.00 (7H, m, aromatic protons), 8.60 (1H, s, NH).

N-(2-Xanthenonyl)glycine hydriazide (6): A mixture of the ester **5** (8.4 g, 0.04 mole) and hydrazine hydrate (0.05 mole) in absolute ethanol (100 ml) was refluxed for 6h. The reaction mixture was concentrated and the separated solid was filtered, dried and then crystallized to afford a pale yellow crystals of compound **6** (Table I). IR (KBr, cm^{-1}): 3420, 3300 (NH, NH_2), 1710 (C=O), 1670 (C=O); ^{1}H-NMR (DMSO-d_6) δ 4.20 (2H, s, NH_2), 4.40 (2H, s, NCH_2), 7.00~8.00 (7H, m, aromatic protons), 8.60 (1H, s, NH), 9.40 (1H, s, NH); MS, m/z (%): 283, M^+ (82), 242 (17), 211 (100), 196 (11).

2-(2-Xanthenonylamino)methyl-1,3,4-oxadiazol-5-thione (7): It was prepared according to a reported method (Young and Wood, 1955), by heating the hydrazide **6** (2.80 g, 0.01 mol), carbon disulfide (20 ml) and KOH (0.82 g, 0.015 mole) in absolute ethanol (20 ml) for 18h. After removal of the solvent, the residual solid was dissolved in water, neutralized with HCl and the resulting solid was collected, washed with water and crystallized from the proper solvent to give compound **7** (Table I). IR (KBr, cm^{-1}): 2380, 1120 (SH, S=C), 1640 (C=0), 1620 (C=N), 1070 (C-O-C); ^{1}H-NMR (DMSO-d_6) δ 4.45 (2H, s, NCH_2), 7.0~8.0 (7H, m, aromatic protons), 8.60 (1H, s, NH), 14.00 (1H, s, SH).

4-(Morpholinomethyl or diethylaminomethyl)-2-(2-xanthenonylamino)-methyl-1,3,4-oxadiazol-5-thione (8a and 8b):

General Method: A mixture of paraformaldehyde (0.01 mole) and the appropriate secondary amines namely morpholine or diethylamine (0.03 mole) in absolute ethanol (30 ml) was refluxed for 30 minutes until complete solubility of paraformaldehyde. A solution of compound **7** (0.01 mole) in absolute ethanol (10 ml) was added to the reaction mixture and refluxed for a further 3h, concentrated and the separated product was filtered, dried and than recrystallized from the proper solvent to give the compounds **8a** and **8b**, respectively. IR (KBr, cm^{-1}) of **8a**: 3400 (NH), 1650 (C=O), 1620 (C=N), 1130 (C=S), 1070 (C-O-C); ^{1}H-NMR (DMSO-d_6) δ 2.60 (4H, t, $2CH_2$ of morpholine), 3.40 (4H, t, $2CH_2$ of morpholine), 4.40 (2H, s, NCH_2), 4.90 (2H, s, NCH_2N), 7.00~8.00 (7H, m, aromatic protons), 8.50 (1H, s, NH); MS, m/z (%): 424, M^+ (7), 330 (16), 269 (18), 238 (10) and 224 (100). IR (KBr, cm^{-1}) of **8b**: 3350 (NH), 1710 (C=O of ester), 1640 (C=O), 1130 (C=S).

5-[2-(2-Xanthenonylamino)methyl-1,3,4-oxadiazol-5-yl]thioglycolic acid (9): To solution of 7 (1.6 g, 0.005 mole) in ethanolic NaOH (30 ml ethanol, 0.3 g NaOH), monochloroacetic acid (0.007 mole) was added. The reaction mixture was refluxed for 4h., cooled and diluted with water, acidified with HCl. The separated precipitate was filtered and the solid products was crystallized to yield compound **9**. IR (KBr, cm^{-1}): 3300 (NH, OH), 1700 (C=O), 1660 (C=O), 1620 (C=N), 1090 (C-O-C); ^{1}H-NMR (DMSO-d_6) δ 4.10 (2H, s, CH_2-COOH), 4.45 (2H, s, NCH_2), 7.00~8.00 (7H, m, aromatic protons), 8.60 (1H, s, NH), 10.60 (1H, s, OH); MS, m/z (%): 383, M^+ (6), 330 (28), 281 (15), 211 (70) and 105 (100).

2-(2-Xanthenonyl)-5-methylthio-1,3,4-thiadiazole (11): Carbon disulfide (1 ml, 0.014 mole) was added to a suspension of **6** (2.8 g, 0.01 mole) in methanol (20 ml). Potassium hydroxide (0.01 mole) was added and the reaction mixture was stirred at 0°C for 30 min and then at 25°C for 5h. Iodomethane (0.01 mole) was added with continous stirring overnight. The solution was concentrated in vacuo and the solid product which was obtained after addition of dry ether in nearly quantitative yield of the intermediate **10** (m.p. 165°C) A. solution of **10** (0.005 mole) and *p*-to-

luenesulfonic acid (0.005 mol) in toluene (20 ml) was refluxed for 2h. The solution was concentracted in vacuo, the residue was diluted with water and neutralized with HCl. The separated solid was filtered, washd with water and crystallized to yield compound **11**. IR (KBr, cm^{-1}): 3400 (NH), 1650 (C=O), 1620 (C=N), 1600 (C=C); ^{1}H-NMR (DMSO-d_6) δ 2.50 (3H, s, CH_3), 4.40 (2H, s, NCH_2), 7.00~8.00 (7H, m, aromatic protons), 8.40 (1H, s, NH); MS, m/z (%): 355, M^+ (85), 323 (43), 309 (17), 248 (23) and 224 (100).

2-(2-Xanthenonylanmino)methyl-5-(p-anilino)-1,3,4-oxadiazole (12): A mixture of the hydrazide **6** (1.6 g, 0.005 mole) and p-aminobenzoic acid (0.005 mole) in $POCl_3$ (5 ml) was refluxed for 2h. The reaction mixture was slowly added to ice water. The formed precipitate was filtered, washed with water and recrystallized to give the desired product **12**. IR (KBr, cm^{-1}): 3400, 3200 (NH, NH_2), 1660 (C=O), 1625 (C=N), 1130 (C-O-C).

3-Mercapto-5-(2-xanthenonylamino)methyl-1,2,4-triazole (13): Equimolecular amounts of hydrazide **6** and thiourea (0.01 mole) were fused together at 195°C in oil bath for 0.5 h. On cooling, the solid mass was dissolved in 8% NaOH and filtered. The filtrate was neutralized with HCl to pH 7 and the precipitate solid was filtered, washed with water and recrystallized to give the compound **13** (Table I). IR (KBr, cm^{-1}): 3420 (NH), 2370 (SH), 1650 (C=O), 1630 (C=N); ^{1}H-NMR (DMSO-d_6) δ 4.50 (2H, s, NCH_2), 7.00~8.00 (7H, m, aromatic protons), 8.60, 9.80 (2H, s, 2NH) and 14.0 (1H, s, SH).

3-Mercapto-4-amino-5-(2-xanthenonylamino) methyl-1,2-,4-triazole (14): To an ice-cooled mixture of hydrazide **6** (2.8 g, 0.01) mole) and KOH (0.85 g, 0.015 mole) in absolute ethanol (10 ml), carbon disulphide (8 ml) was added dropwise. After the addition was complete, absolute ethanol (10 ml) was added and the reaction mixture stirred at 25°C for 24h. After addition of dry ether (50 ml), the solid product which was obtained in nearly quantitative yield (m.p. 203°C) was treated with 99% hydrazine hydrate (0.02 mole) and water (4 ml) with stirring and heating at 60°C for 0.5h. The reaction mixture was then diluted with water (10 ml) and neutralized with HCl. The separated solid was filtered, washed with water and crystallized to yield the compound **14**. IR (KBr, cm^{-1}): 3450, 3300 (NH, NH_2), 2370 (SH), 1640 (C=O), 1620 (C=N); ^{1}H-NMR (DMSO-d_6) δ 4.40 (2h, S, NCH_2), 5.40 (2H, s, NH_2), 7.0~8.0 (7H, m, aromatic protons), 9.20 (1H, s, NH) and 14.0 (1H, s, SH); MS, m/z (%): 339, M^+ (78), 323 (15), 283 (17), 224 (65) and 211 (100).

2-Methyl-5-(2-xanthenonylamino)methyl-S-triazolo [3,4-b]-1,3,4-thiadiazole (15): Compound 14 (1.7 g, 0.005 5 mol) in acetic anhydride (10 ml) was heated under reflux for 2 h. The reaction mixture was neutralized with ammonium hydroxide solution and the

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

Compd. No.	m.p. °C Solvent	Yield %	Formula (M.wt).	Analysis (%) Calcd/Found C	H	N
2a	155 E	84	$C_{20}H_{13}N_2O_3Cl$ (364.7)	65.85 65.60	3.55 3.30	7.65 7.95
2b	192 E	85	$C_{16}H_{14}N_2O_2S$ (298.16)	64.45 64.30	4.70 4.50	9.40 9.75
3a	210 M	76	$C_{22}H_{11}N_2O_5Cl$ (418.72)	63.10 63.30	2.60 2.75	6.70 6.45
3b	198 M	72	$C_{18}H_{12}N_2O_4S$ (352.18)	61.40 61.55	3.40 3.60	7.95 7.60
4	182 aq. E	34	$C_{16}H_9NO_3S_2$ (327.16)	58.75 58.94	2.75 3.00	4.30 3.95
5	110 E	68	$C_{17}H_{15}NO_4$ (297.17)	68.70 68.90	5.05 5.20	4.70 4.35
6	201 E	88	$C_{15}H_{13}N_3O_3$ (283.15)	63.65 63.50	4.60 4.40	14.85 15.20
7	174 E	84	$C_{16}H_{11}N_3O_3S$ (325.16)	59.10 59.35	3.40 3.65	12.90 12.55
8a	170 M	73	$C_{21}H_{20}N_4O_4S$ (424.21)	59.45 59.25	4.70 4.55	13.20 13.55
8b	162 M	66	$C_{21}H_{22}N_4O_3S$ (410.21)	61.50 61.75	5.35 5.55	13.65 13.30
9	193 M	53	$C_{18}H_{13}N_3O_5S$ (383.18)	56.40 56.55	3.40 3.50	10.95 10.60
11	180 E	57	$C_{17}H_{13}N_3O_3S_2$ (355.17)	57.85 58.00	3.65 3.75	11.80 11.50
12	231 E	63	$C_{22}H_{16}N_4O_3$ (384.22)	68.75 68.90	4.15 4.35	14.55 14.30
13	202-4 E	44	$C_{16}H_{12}N_4O_2S$ (324.16)	59.30 59.55	3.70 3.90	17.30 17.00
14	185 E	58	$C_{16}H_{13}N_5O_2S$ (339.16)	56.65 56.80	3.85 4.00	20.65 20.30
15	125 E	85	$C_{18}H_{13}N_5O_2S$ (363.18)	59.50 59.40	3.60 3.45	19.30 19.65
16	110 AcOH	79	$C_{23}H_{16}N_5O_2SCl$	59.80 60.00	3.45 3.60	15.15 14.90
17	150 E	94	$C_{22}H_{17}N_4O_3SCl$	58.35 58.25	3.75 3.55	12.35 12.60
18	115 E	76	$C_{22}H_{15}N_4O_2SCl$	60.80 60.65	3.45 3.30	12.90 13.25
19	145	81	$C_{22}H_{15}N_4O_2SCl$	60.80 60.70	3.45 3.35	12.90 13.15
20	155 E	85	$C_{20}H_{17}N_3O_3$ (347.20)	69.20 69.35	4.90 5.10	12.09 12.80
21	150 E	82	$C_{19}H_{15}N_3O_4$ (349.19)	65.35 65.50	4.30 4.45	12.05 11.80
22	166 E	79	$C_{18}H_{13}N_3O_5$ (351.18)	61.55 61.75	3.70 3.80	11.60 11.25
23	148 M	80	$C_{20}H_{15}N_3O_4$ (361.20)	66.50 66.35	4.15 4.00	11.60 11.95
24	141 M	65	$C_{22}H_{17}N_3O_5S$ (435.22)	60.70 60.90	3.90 4.05	9.65 9.30
25	178 E	55	$C_{23}H_{15}N_3O_5$ (413.23)	66.85 66.55	3.60 3.50	10.15 10.35

E=Ethanol; M=methanol

precipitated product was filtered, washed with water, derid and recrystallized to furnish the title compound **15**. IR (KBr, cm^{-1}): 3400 (NH), 1660 (C=O), 1630 (C=N); ^{1}H-NMR (DMSO-d_6) δ 2.40 (3H, s, CH_3), 4.40 (2H, s, NCH_2), 7.00~8.00 (7H, m, aromatic protons) and 8.60 (1H, s, NH); MS, m/z (%): 363, M^+ (14), 333 (100), 305 (8), 253 (23) and 211 (50).

3-Mrcapto-4-(p-chlorobenzylidinimino)-5-(2-xanthenonylamino)methyl-1,2,4-triazole (16): A mixture of **14** (1.79 g, 0.005 mole) and p-chlorobenzaldehyde (0.01 mole) in acetic acid (10 ml) was refluxed for 3 h. On cooling the precipitated solid was filtered, washed with cold acetic acid, dried and recrystallized to afford compound **16**. Ir (KBr, cm^{-1}): 3350 (NH), 1660 (C=O), 1630 (C=N); ^{1}H-NMR (DMSO-d_6) δ 4.40 (2H, s, NCH_2), 7.00~8.00 (7H, m, aromatic protons), 8.60 (1H, s, CH=N), 9.60 (1H, s, NH) and 14.0 (1H, s, SH).

N^4-3-Chlorophenyl-N^1-[(2-xanthenonylamino)] methylcarbonyl)thiosemicarbazide (17): A solution of **6** (3.4 g, 0.01 mole) and 3-chlorophenylisothiocyanate (0.01 mole) in ethanol-water mixture (30 ml) was refluxed for 6 h, left to cool, filtered, dried and crystallized to give compound **17** (Table 1). IR (KBr, cm^{-1}): 3400 (NH), 1700, 1660 (2C=O), 1630 (C=N), 1130 (C=S); ^{1}H-NMR (DMSO-d_6) δ 4.30 (2H, s, NCH_2), 7.00~8.00 (11H, m, aromatic protons) and 8.80, 9.80 (4H, 4s, 4NH).

2-(2-Xanthenonylamino)methyl-5-(3-chloroanilino)-1,3,4-thiadiazole (18): A solution of **17** (0.01 mole) in conc. sulfuric acid (10 ml) was cooled and allowed to stand for 30 minutes. The reaction mixture was then quenched with ice and treated with conc. ammonium hydroxide solution until neutral to litmus. The resulting precipitate was filtered, washed with water and recrystallized to give **18** (Table 1). IR (KBr, cm^{-1}): 3400 (NH), 1640 (C=O), 1620 (C=N); ^{1}H-NMR (DMSO-d_6) δ 4.40 (2H, s, NCH_2), 7.00~8.10 (11H, m, aromatic protons), 8.60, 9.80 (2H, 2s, 2NH); MS, m/z (%): 434, M^+ (5), 385 (7), 283 (17), 243 (10), 196 (8) and 169 (100).

3-Mercapto-4-(3-chlorophenyl)-5-(2-xanthenonyl-amino)methyl-1,2,4-triazole (19): A solution of **17** (0.01 mole) in 2N NaOH (10 ml) was refluxed for 2 h., the reaction mixture was cooled and acidified with HCl. The separated product was filtered, deried and recrystallized to give **19**. IR (KBr, cm^{-1}): 3400 (NH), 2370 (SH), 1650 (C=O), 1630 (C=N), 1600 (C=C); ^{1}H-NMR (DMSO-d_6) δ 4.40 (2H, s, NCH_2), 7.10~7.90 (11H, m, aromatic protons), 8.50 (1H, s, NH), 14.00 (1H, s, SH). MS, m/z (%): 434 (72), 398 (9), 336 (18), 269 (27), 239 (55) and 225 (100).

2-*N*-[(2-Xanthenonyl)glycyl]-3,5-dimethyl-1-pyrazoline (20): General Method: A mixture of the hydrazide **6** (1.4 g, 0.005 mole) and acteyl actone (0.07 mole) were heated on boiling water bath for 9 h. The reaction mixture was cooled and the separated solid was filtered, washed with water and crystallized to give the corresponding **20** (Table I).

The foregoing procdure was applied excpt that ethyl acetoacetate and diethylmalonate were used instead of acetyl acetone to give 2-N-[(2-xanthonyl)glycyl]-5-mthyl-1-pyrazolidin-3-one (**21**) and 2-*N*-[(2-xanthonyl)-glycyl]-1-pyrazolin-3,5-dione (**22**) respectively (Table I). ^{1}H-NMR (DMSO-d_6) of **20**: δ 2.00, 2.10 (6H, 2s, $2CH_3$ of pyrazole), 4.45 (2H, s, NCH_2), 5.30 (1H, s, CH, of pyrazole), 7.00~8.10 (7H, m, aromatic protons), 8.60 (H, s, NH). IR (KBr, cm^{-1}) of **22**: 3350 (NH), 1720 (3C=O), 1650 (C=O); MS, m/z (%): 351 (8), 330 (10), 325 (48), 280 (13), 224 (28) and 211 (100).

***N*-[(2-Xanthenonyl)glycin]furfurylidene)hydrazide (23):** A mixture of compound **6** (1.4 g, 0.00 5 mole) and furfural (0.5 g, 0.005 mol) in absolute ethanol (20 ml) containing 3 drops of piperidine was refluxed for 6 h, then concentrated under reduced pressure and cooled. The formed precipitate was filtered, dried and crystallized to give the product **23** (Table I). IR (KBr, cm^{-1}): 3400 (NH), 1660 (2C=O), 1620 (C=N), 1070 (C-O-C).

3-[*N*-(2-Xanthenonyl)glycinamido]-2-furfuryl] thiazolidin-4-one (24): Thioglycolic acid (0.005 mole) was added to a well stirred solution of the compound **23** (2.1 g, 0.005 mole) in dry benzene (20 ml) and refluxed for 5 h. The excess solvent was evaporated under reduced pressure. On cooling, the formed precipitate was dried and crystallized to afford the thiazolidinone derivative **24**. IR (KBr, cm^{-1}): 3350 (NH), 1740 (C=O) of five ring ketone), 1670 (C=O); ^{1}H-NMR (DMSO-d_6) δ 3.50 (1H, s, CH of thiazolidinone), 4.20 (2H, s, CH_2 of thiazolidinone), 4.40 (2H, s, NCH_2), 7.00~8.10 (10H, m, furan and aromatic protons), 8.40, 9.20 (2H, 2s, 2NH); MS, m/z (%): 435, M^+ (67), 281 (13), 211 (100) and 196 (18).

***N*-(2-Xanthenonyl)glycine hydrazido-*N*-phthalimide (25):** On addition of phthalic anhydride (0.01 mole) to a solution of the hydrazide **6** (0.01 mole) in dry xylene and the reaction mixture was refluxed for 2 h and a white precipitate was formed, filtered and crystallized to give the title compound **25** (Table I). IR (KBr, cm^{-1}): 3350 (NH), 1775, 1710 (2C=O at position 1.3), 1680 (C=O), 1640 (C=O); ^{1}H-NMR (DMSO-d_6) δ 4.40 (2H, s, NCH_2), 7.20~8.10 (11H, m, aromatic protons), 8.20, 8.40 (2H, 2s, 2NH); MS, m/z (%): 413, M^+ (9), 330 (15), 324 (18), 281 (23) and 224 (100).

Biology Part

Antischistosomal Activity

a-Infection of mice with cercariae: Laboratory-bred female albino mice [The Schisosome Biological Supply Program (SBSP), Theodor Bilharz Research Institute (TBRI, Cairo, Egypt) were used. They were fed with spe-

cial; (protein, carbohydrates and vitamin) diet pellet.

Schistosoma mansoni cercaria sheded from infected Biomphalaria alexandrina snails (SBSP-TBRI), were used for infaction.

Thirteen Groups, each of ten mice, of the same generation and weight (≈20 g), were maintained under laboratory care. Mice in all groups, were exposed to ≈150 Schistosoma mansoni cercariae/mouse, using the tail submerging technique (Standen, 1963). Six to eight weeks post infection, the stools of mice were examined for the presence of schistosome eggs. This is an indication that the parasite adult-stage has reached.

b-Preparation of chemical compounds for biological screeing: Compounds **3a**, **4**, **8a**, **9**, **11**, **15**, **16**, **18~21** and **24** were screened for their antischistosomal activity. These compounds are illustrated in Schemes 1, 2, 3 and 4.

c-Measurement of LD_{50} of the tested compounds: The LD_{50} of the compounds under study was determined. The dose used was estimated to be ≈80 mg/kg body weight for all compounds.

d-Chemical treatment of mice: 12 Groups of mice were orally given the tested compounds, while the 13th group were identically given praziquantelas a referece compound. A 14th group was served as control. Two weeks later, mice in all groups were subjected to the following techniques:

1-Estimation of eggs/24 h stools.

2-Counting of adult worms using the liver perfusion techniques

3-Egg count/gram liver tissue.

Biological Activity

The results of the antischistosomal activity of the tested compounds were illustrated in Table II.

It was found that compound **20** and **21** showed the highest degree of adult worms and eggs reduction (65~76%). This may be due to the presence of pyrazoline moiety, this may have increased the activity of the newly synthesizd compounds leading to its biological effects. This could be in accordance with the structural anthelmintic activity of praziquantel which is attributed to its pyrazino-isoquinoline moiety (Abo-Ghalia and Soliman, 1996).

Table II. Antischistosomal activity of the new preapred compounds (% reduction in worms and eggs count)

Compound No.	Adult worms recored from liver	Eggs/24 h collcted stool	Egg/sgram liver tissue
Control	56	62	53
3a	34	32	35
4	42	46	45
8a	36	34	38
9	42	46	39
11	37	41	38
15	61	58	57
16	72	65	68
18	42	44	46
19	46	49	47
20	23	25	21
21	21	24	22
24	56	52	54

It can be concluded that the incorporation of active moieties may increase the efficiency of the chemical compounds. On the other hand, the antischistosomal activity of the tested compounds needs more detailed studies in order to attain a suitable active drug without toxicity or side effects, prophylactic, curative, safe, and also having chemical stability in solution or tables under all storage conditions, and finally efficient in small doses and inexpensive.

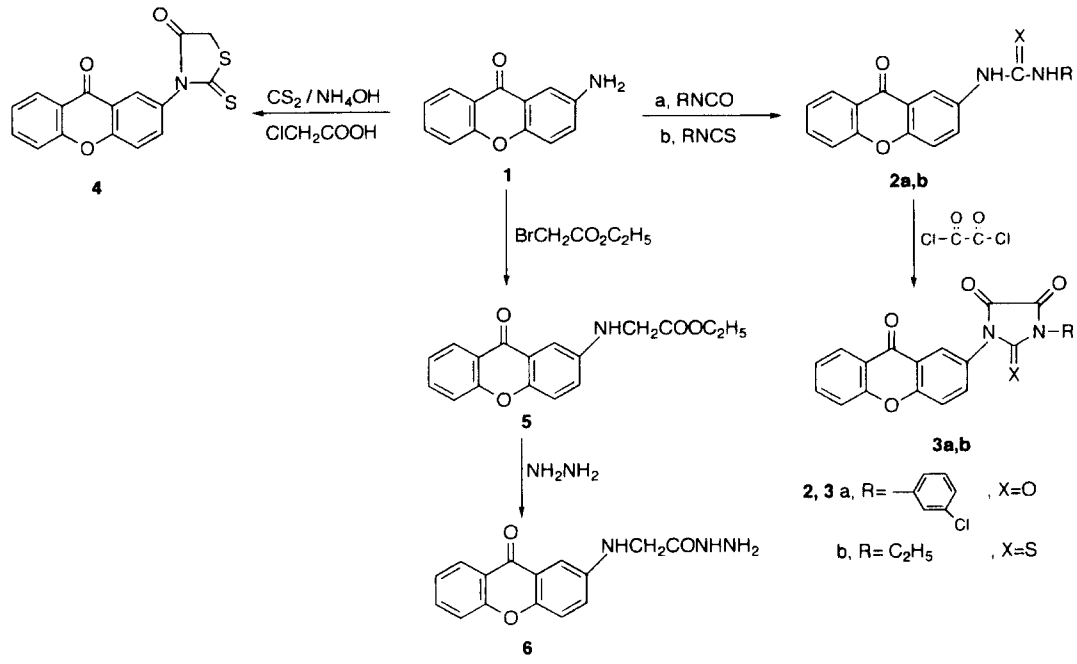
RESULTS AND DISCUSSION

The new compounds were obtained through different routes of chemical reactions and transformations starting with 2-aminoxanthenone (**1**) and *N*-(2-xanthenonyl)glycine hydrazide (**6**) as shown in Schemes (1-4).

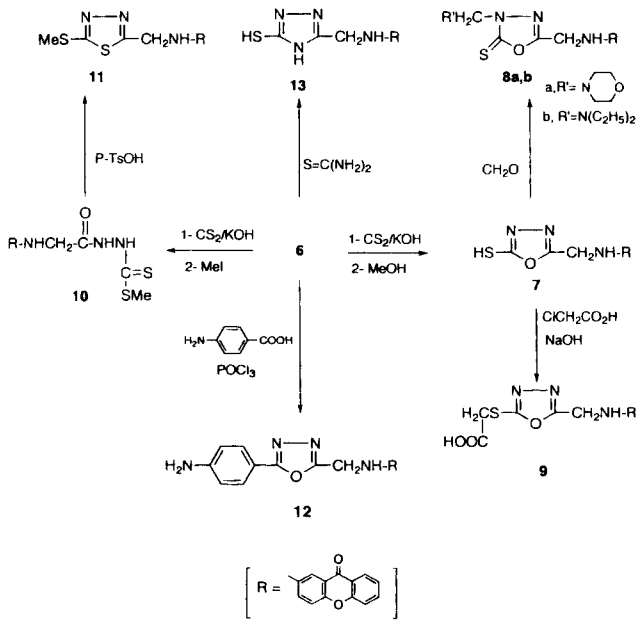
The 2-aminoxanthenone (**1**) was allowed to react with isocyanate and isothiocyanate (Abdou, 1993) in methanol to give the corresponding 2-xanthenonylurea **2a** and thiourea **2b**. Treatment of each **2a** and **2b** with oxalylchloride (Abdou, 1993) at 50°C furnished the hydantoin **3a** and the thiohydantoin **3b**, respectively. The *N*-(2-xanthenonyl)rahodanine (**4**) was obtained according to a reported method (Abdou, 1993) by allowing compound **1** to react with carbon disulfied in the presence of ammonium hydroxide solution at 0°C, yielded the intermediate dithiocarbanilic acid ammonium salt. Reaction of this salt with sodium chloroacetate afforded the desired compound **4**. Also, condensation of **1** with bromo ethylacetate and K_2CO_3/DMF yielded the corresponding ester **5**. The latter **5** was refluxed with hydrazine hydrate in ethanol to give the N-(2-xanthenonyl)glycine hydrazide (**6**) in good yield (Scheme 1).

On the other hand, the 2-substituted-1,3,4-oxadiazol-5-thione (**7**) was prepared (Abd El-Motti *et al.*, 1995), by heating the hydrazide **6** with CS_2 in the presnce of methanolic KOH. Mannich reaction was carried out by condensing compound **7** with paraformaldehyde and the appropriate amines (morpholine or diethylamine) (Sherman and Fach, 1962) to give the corresponding 4-substituted oxadiazole **8a** and **8b** respectively, while the 5-substituted acid **9** was prepared by refluxing compound **7** with monochloroacetic acid (Abd El-Motti *et al.*, 1995) in the presence of ethanolic sodium hydroxide.

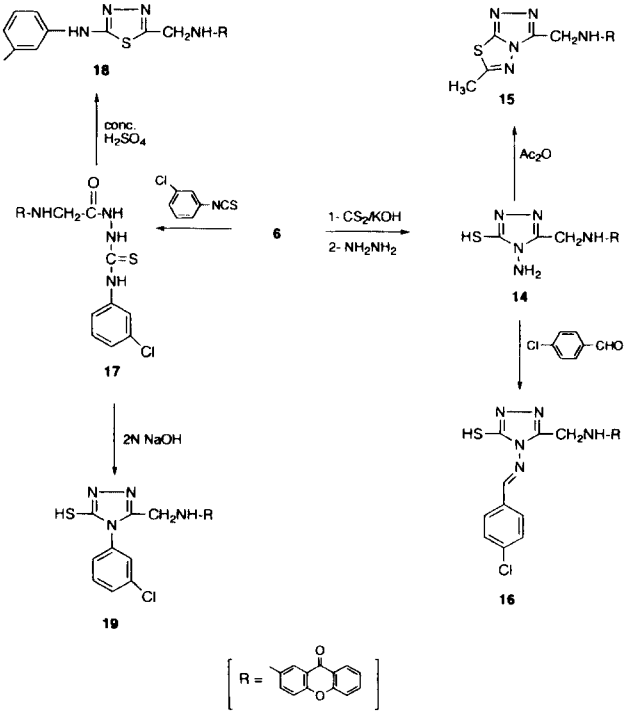
Reaction of the hydrazide **6** with CS_2 and methanolic KOH at 0°C, followed by addition of iodomethane (Boschelli *et al.*, 1993) gave the intermediated **10** in quantitative yield. Compound **10** was cyclized under



Scheme 1.



Scheme 2.

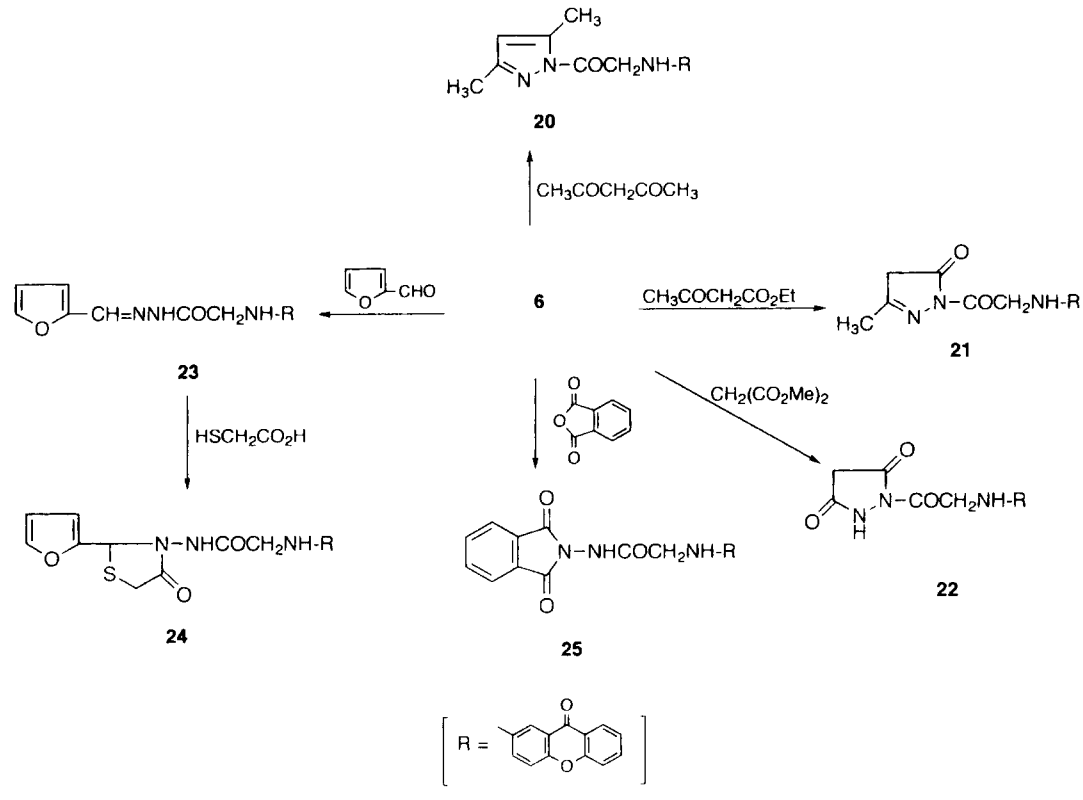


Scheme 3.

acidic condition to provide the desired thiadiazole derivative **11** in moderate yield.

The oxadiazole derivative **12** was prepared by refluxing the hydrazide **6** with p-aminobenzoic acid (Abd El-Motti *et al.*, 1995) and $POCl_3$, while upon fusion of equimolar amount of the hydrazide **6** and thioura (El-Feky *et al.*, 1994) at 195°C gave the corresponding triazole derivative **13** (Scheme 2).

Further, several synthetic procedures for the preparation of 2,5-disubstituted-S-triazolo[3,4-b]-1,3,4-thiadiazoles were reported (El-Ansary and Hassan, 1994) utilizing S-triazoles as starting matrials. The synthesis of 3-mercapto-4-amino-5-(2-xanthenonylamino) methyl-1,2,4-triazole (**14**) was synthsized from the corresponding hydrazide **6** by stirring with carbon disulfide and alcoholic KOH and cold and then at 25°C for 24 h. The solid obtained was treated with hydrazine hy-



Scheme 4.

drate (El-Ansary and Hassan, 1994). Reacting **14** with excess acetic anhydride under reflux condition afforded the 2-methyl-5-(2-xanthenonylamino)-methyl-S-triazolo-[3,4-b]-1,3,4-thia-diazole (**15**), while reacting the same compound **14** with *p*-chlorobenzaldehyde in acetic acid gave the corresponding arylidene triazole **16** in a good yield.

Refluxing a mixture of equimolar amounts of the hydrazide **6** with isothiocyanate (El-Ansary and Hassan, 1994) in ethanol-water mixture gave the corresponding thiosemicarbazide **17**. The latter **17** was reacted with sulfuric acid and underwent cyclization to give the 1,3,4-thiadiazole derivative **18** and also the same compound **17** afforded the S-triazol-5-thione **19** on treatment with 2N-NaOH in a good yield (Scheme 3).

Furthermore, it was of interest to synthesize some new pyrazolines (Katritzky, 1996) **20**, **21** and **22** incorporated into xanthenone moiety at its position-2 through a glycinamide linkage for biological activity that may act as enzyme inhibitors of the metabolism in bilharzia (Katritzky, 1996, Abdou, 1993). Reaction of the hydrazide **6** with acetyl acetone gave the corresponding 2-*N*-[(2-xanthenonyl)glycyl]-3,5-dimethyl-1-pyrazoline (**20**). In a similar mannar, compound **6** was allowed to react with acetoacetic ester and dimethylmalonate to give **21** and **22** respectively, in a good yields. The Schiff base (Kamdar *et al.*, 1987) **23** was obtained by allowing **6** to react with furfural to give the arylidene derivative **23**. Cyclocondensation of the latter **23** with thioglycolic acid gave the desired thiazolidinone derivative **24**. Finally, the *N*-imido derivative **25** was obtained from refluxing **6** with phthalic anhydride in dry xylene (Sechem 4).

The structures of all the new compounds wre confirmed on the basis of their elemental analysis, IR, ^{1}H-NMR and MS spectroscopy (experimental section, Table I).

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