Quinolones Substituted by Different Moieties III. Reactions of 1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde with Some Cyclic Active Methylene Compounds

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1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde has been reacted with some cyclic active methylene compounds, *viz.* 1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline, 1-substituted 2-thiobarbituric acids, and 2-phenylimino-3-oxothiazolidine. The obtained exocyclic enone systems were reacted with hydrazine hydrate giving rise to the 3-pyrazolinylquinoline derivatives. All the given structures were verified by elemental analyses and spectral data.

2-Pyrazolines are well known for their considerable biological activity [1—3], and also pyrazoloquinolines [4, 5]. Therefore, it was of interest to combine pyrazoline and quinoline moieties within a molecular framework with a view to study their synergic effects on their biological properties. In continuation of our previous work on reactions of 1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde (*II*) with some active methylene compounds [6], we report herein on the reaction of the aldehyde *II* with some cyclic active methylene compounds and consequent cyclization of them to the target pyrazolinylquinolines.

1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinoline (*I*) showed a reactivity as an active methylene compound similar to the known cyclic 1,3-diones, such as dimedones, indandiones, barbituric acids, *etc.* This can be attributed to the tautomerism of *I* into 2,4-dioxo-1-methyl-1,2,3,4-tetrahydroquinoline, in solutions, which is concluded from the fact that it could be 3,3-dialkylated [7], 3,3-dihalogenated [8], and condensed with aldehydes [9]. Reacting of the aldehyde *II* with compound *I* at the ratio w_r = 1:1 in the presence of piperidine as a catalyst yielded 3-(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinylmethylene)-2,4-dioxo-1-methyl-1,2,3,4-tetrahydroquinoline (*III*). IR spectrum of compound *III* revealed additional two peaks specific for both the carbonyl group and exocyclic olefinic bond at positions 4 and 3, respectively. Both these absorptions disappeared in the spectrum of 3-(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinyl)-5-methyl-4-oxo-3,3a,4,5-tetrahydro-2*H*-pyrazolo[4,3-*c*]quinoline (*IV*) which was prepared by reacting *III* with hydrazine hydrate in boiling glacial acetic acid (Scheme 1). Characterization data of the new compounds are listed in Table 1.

Due to the previously mentioned biological importance of pyrazolines, another pyrazolino fused system was synthesized as substituted to quinoline moiety at position 3, that is by condensation of *II* with 1-phenyl(or allyl)-2-thiobarbituric acids *Va, Vb* under Knoevenagel conditions to afford 5-(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinylmethylene)-4,6-dioxo-1-phenyl(or allyl)-2-thioxoperhydropyrimidines (*VIa, VIb*). Reaction of *VIa* (R = Ph) with hydrazine hydrate afforded a mixture of the mercaptopyrazolopyrimidine *VII* and the hydrazinopyrimidine *VIII*. However, on using of excess hydrazine hydrate the hydrazinopyrazolopyrimidine *IX* was obtained. For obtaining compound *VIII* only the following reaction sequence was carried out, compound *VI* was methylated using dimethyl sulfate and sodium hydroxide affording the 2-methylthiopyrimidine derivative *X*. This reaction supports the existence of a thione—thiol tautomeric equilibrium. The latter compound was hydrazinolyzed to *VIII* using hydrazine hydrate in cold methanol (Scheme 2).

Since thiazolidinones represent one of the most active classes of compounds possessing a wide spectrum of biological activity [10], compound *II* was condensed with 4-oxo-2-phenyliminothiazolidine (*XI*) to give 5-(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinylmethylene)-4-oxo-2-phenyliminothiazolidine (*XII*). Reaction of the thiazolidine *XII* with hydrazine hy-

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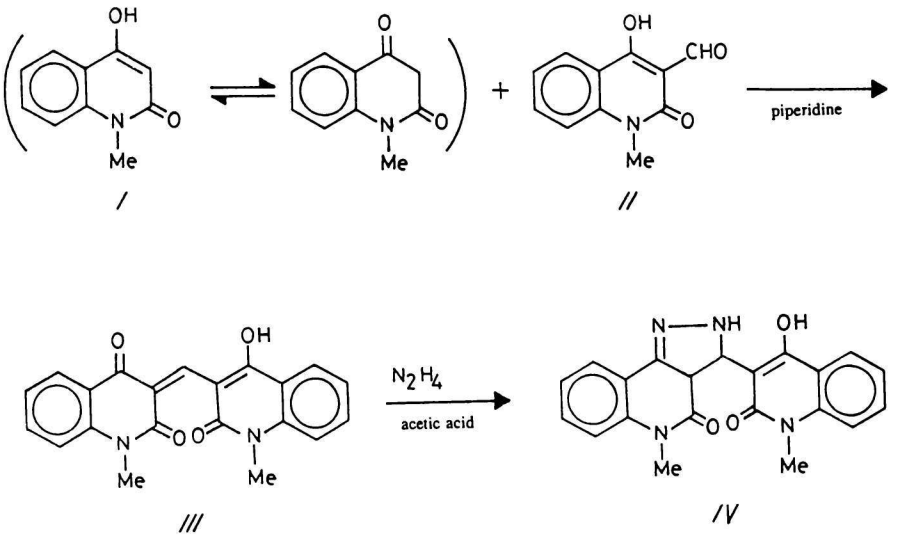
Table 1. Characterization of the New Compounds

Compound	Formula M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.	Solvent
		C	H	N	%	°C	
III	$C_{21}H_{16}N_2O_4$	70.00	4.44	7.78	78	> 300	DMSO
	360	69.72	4.30	7.50			
IV	$C_{21}H_{18}N_4O_3$	67.38	4.81	14.97	65	> 300	DMF
	374	67.20	4.50	14.65			
VIa	$C_{21}H_{15}N_3O_4S$	62.22	3.70	10.37	80	256—257	AcOH
	405	61.90	3.90	10.25			
VIb	$C_{18}H_{15}N_3O_4S$	58.54	4.07	11.38	55	290—292	DMF
	369	58.40	4.10	11.50			
VII	$C_{21}H_{17}N_5O_3S$	60.14	4.06	16.71	62	> 300	EtOH
	419	60.30	3.90	16.50			
VIII	$C_{21}H_{17}N_5O_4$	62.53	4.22	17.37	12[a]	253—254	MeOH
	403	62.30	4.30	17.25	74[b]		
IX	$C_{21}H_{19}N_7O_3$	60.43	4.56	23.50	64	> 300	DMF
	417	60.50	4.40	23.30			
X	$C_{22}H_{17}N_3O_4S$	63.01	4.06	10.02	75	157—158	EtOH
	419	62.80	4.00	9.85			
XII	$C_{20}H_{15}N_3O_3S$	63.66	3.98	11.14	82	253—254	AcOH
	377	63.42	3.91	11.30			
XIII	$C_{20}H_{17}N_5O_2S$	61.38	4.35	17.90	70	205—207	Dioxane
	391	61.20	4.32	17.70			
XIV	$C_{24}H_{21}N_3O_5S$	62.20	4.54	9.07	51	200—201	Acetone
	463	62.16	4.50	8.89			
XV	$C_{22}H_{17}N_5O_3S$	61.26	3.94	16.24	66	> 300	DMF
	431	61.10	3.76	16.45			

a) and *b*) yield/% of *VIII* from hydrazinolysis of *VI* and *X*, respectively.

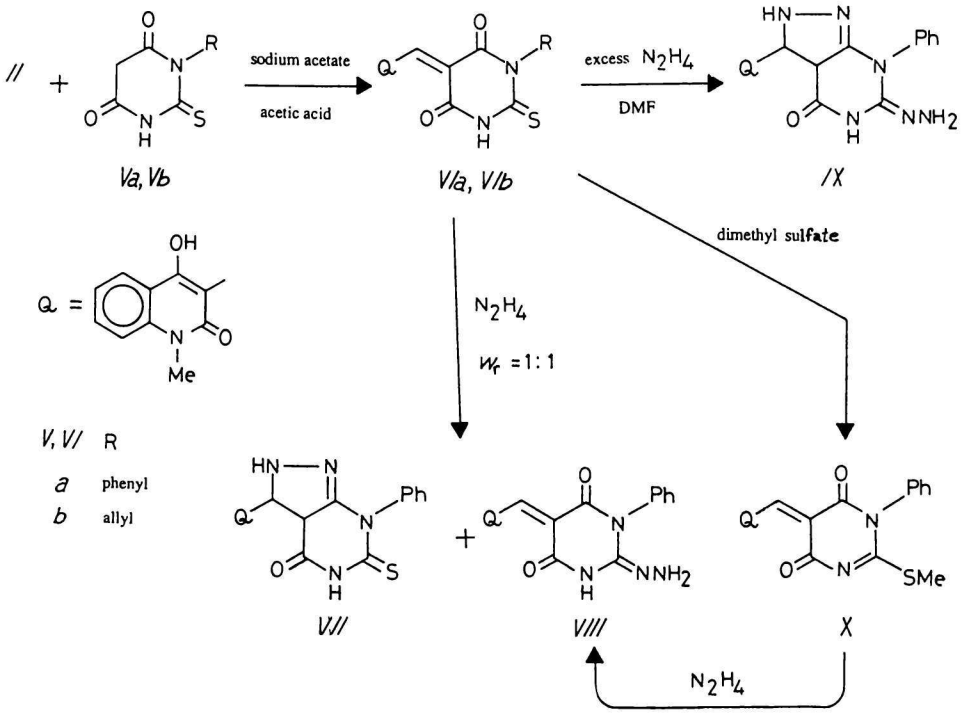


Scheme 1

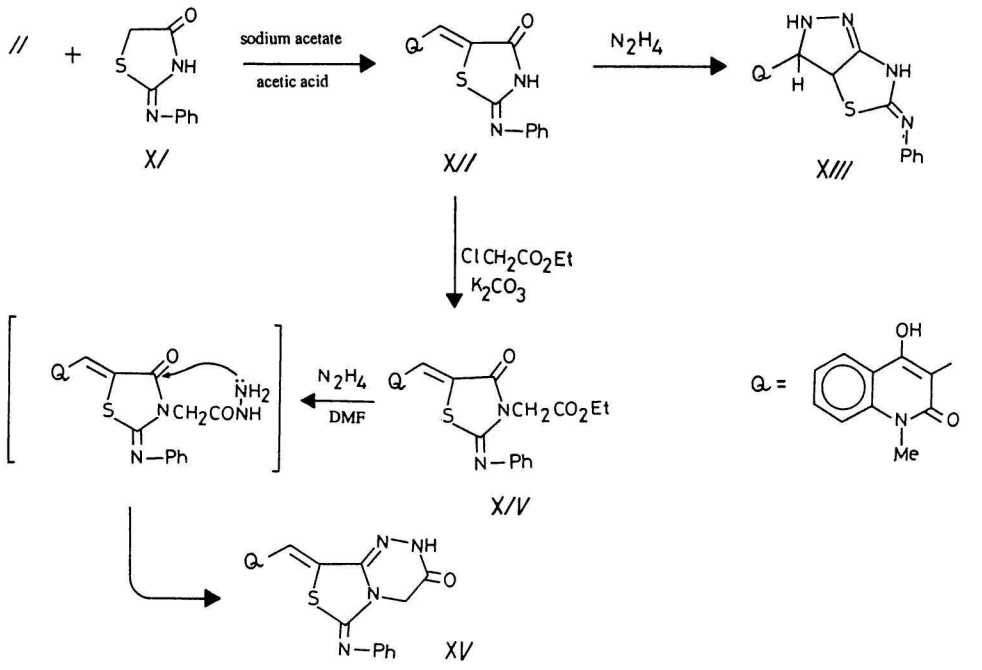
drate in ethanol, in the presence of few drops of acetic acid [11], gave the thiazolidinopyrazoline (*XIII*). Treatment of *XII* with ethyl chloroacetate in acetone, in the presence of potassium carbonate afforded the 3-carbethoxymethylthiazolidine derivative *XIV* which on cyclocondensation with hydrazine hydrate in boiling DMF gave the thiazolidinotriazine (*XV*). Compound *XV* may be formed *via* simple condensation of the ester *XIV* with a molecule of hydrazine followed by intramolecular cyclocondensation of the hydrazide amino group with the neighbouring carbonyl accompanied with the loss of a water molecule. The structure of *XV* was inferred from its correct elemental analysis and spectral data (Scheme 3).

EXPERIMENTAL

Melting points were determined in open capil-



Scheme 2



Scheme 3

lary tubes and are uncorrected. Infrared spectra were recorded on a Perkin—Elmer 598 spectrophotometer using samples in KBr disks. ^{1}H NMR spectra were taken on a Jeol FX-90 spectrometer (DMSO-d_6; 90 MHz), using TMS as an internal standard. Mass spectra were determined on a Hewlett—Packard Model MS-5988 by direct inlet (electron beam energy 70 eV). Elemental microanalyses were performed at the Microanalytical Centre, Cairo University. Compound *I* was prepared using the method described by *Mohamed* [12], and compound *II* was prepared according to the reported method [13]. Compounds *Va, Vb* were prepared using the reported method [14], and compound *XI* was prepared using the method described by *Naik et al.* [15].

3-(1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinylmethylene)-1-methyl-1,2,3,4-tetrahydroquinoline-2,4-dione (*III*)

A mixture of the compound *I* (0.005 mol), the aldehyde *II* (0.005 mol), and a few drops of piperidine was heated at boiling water-bath temperature for 1 h. The solid mass so formed was triturated with cold methanol (20 cm^3), filtered off, and crystallized. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1550, 1570 ν(C=C_{arom}), 1610 ν(C=$C_{exocyclic}$), 1640—1655 ν(C=O_{lactam}), 1678 ν(C=O), ≈ 2600 ν(H-bonded OH). Mass spectrum, m/z (I_r/%): 360 (30), 187 (56), 174 (55), 133 (78), 132 (62), 105 (45), 77 (42), 65 (100).

3-(1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinyl)-5-methyl-3,3a,4,5-tetrahydro-2*H*-pyrazolo[4,3-*c*]quinolin-4-one (*IV*)

A suspension of *III* (0.01 mol) in glacial acetic acid (25 cm^3) was treated with hydrazine hydrate (0.015 mol; w = 98 %) in one portion and then refluxed for 1 h. The solid so separated during the course of the reaction was filtered while hot, washed with methanol (20 cm^3) and diethyl ether (20 cm^3), and crystallized. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1130, 1155 ν(CH—N), 1372 ν(def $CH_{pyrazoline}$), 1613—1615 ν(C=N), 1647—1655 ν(C=O_{lactam}), 2520—3100 (br, H-bonded OH, NH). ^{1}H NMR spectrum, δ: 3.68 (s, 3H, NCH_3), 3.80 (s, 3H, NCH_3), 4.15 (dd, 1H, H-$3_{pyrazoline}$), 6.32 (d, 1H, bridged CH), 6.50 (bs, 1H, NH), 7.15—8.11 (m, 8H, H_{arom}), 10.95 (bs, 1H, OH).

5-(1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinylmethylene)-1-phenyl(or allyl)-2-thioxoperhydropyrimidine-4,6-diones (*VIa*, *VIb*)

To the aldehyde *II* (0.01 mol) 1-phenyl(or allyl)-2-thiobarbituric acid (0.01 mol), anhydrous sodium acetate (0.015 mol), and glacial acetic acid (30 cm^3) were added and the mixture was refluxed for 6 h and then poured into ice-cold water. The resulting solid was filtered and crystallized. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$ (*VIa*): 1155, 1200, 1385 ν(N—C=S), 1615 ν(C=$C_{exocyclic}$), 1650 ν(C=$O_{quinolone}$), 1665 ν(C=O at C-4), 1695 ν(C=O at C-6), 2560, 2800, 3120 ν(H-bonded OH, SH, NH). ^{1}H NMR spectrum, δ (*VIa*): 3.72 (s, 3H, NCH_3), 6.68—8.15 (m, 10H, H_{arom} and methine), 10.93 (bs, 1H, NH), 11.10 (bs, 1H, OH).

3-(1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinyl)-7-phenyl-6-thioxo-2-pyrazolino-[3,4-*d*]perhydropyrimidin-4-one (*VII*) and 5-(1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinylmethylene)-2-hydrazono-1-phenylperhydropyrimidine-4,6-dione (*VIII*)

To a suspension of the compound *VIa* (0.01 mol) in absolute ethanol (50 cm^3) hydrazine hydrate (0.012 mol; w = 98 %) was added and the mixture was refluxed for 4 h, then cooled and the yellowish white precipitate so formed was filtered and crystallized affording the product *VII*. Concentration of the above filtrate to one half of its initial volume and cooling in an ice-cold water bath for *ca.* 1 h afforded the hydrazino derivative *VIII* as yellow crystals. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$ (*VII*): 1150, 1240, 1375 ν(N—C=S), 1550, 1570 ν(def NH), 1650 ν(C=$O_{quinolone}$), 1663 ν(C=$O_{pyrimidone}$), 2500—3120 ν(H-bonded OH, SH, NH). ^{1}H NMR spectrum, δ(*VII*): 3.70 (s, 3H, NCH_3), 4.20 (dd, 1H, $H_{pyrazoline}$), 6.45 (d, 1H, bridged CH), 6.55 (bs, 1H, $NH_{pyrazoline}$), 7.22—8.18 (m, 9H, H_{arom}), 11.05—11.10 (b, 2H, OH and NH). IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$ (*VIII*): 1570, 1590 ν(def NH), 1620 ν(C=N), 1655 ν(C=$O_{quinolone}$), 1663, 1687 ν(C=$O_{pyrimidone}$), 3120—3300 ν(NH, NH_2).

3-(1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinyl)-6-hydrazono-7-phenyl-2-pyrazolino[3,4-*d*]perhydropyrimidin-4-one (*IX*)

To a solution of the compound *VIa* (0.01 mol) in DMF (50 cm^3) hydrazine hydrate (0.03 mol; w = 98 %) was added and the reaction mixture was heated under reflux for 6 h. On cooling to the room temperature, pale yellow crystals were separated which on filtration and recrystallization afforded the product *IX*. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1550, 1570 ν(def NH), 1610—1620 ν(C=N), 1650 ν(C=$O_{quinolone}$), 1665 (C=$O_{pyrimidone}$), 3180 ν(NH), 3280, 3300 ν(NH_2). ^{1}H NMR spectrum, δ: 3.71 (s, 3H, NCH_3), 4.25 (dd, 1H, $H_{pyrazoline}$), 5.56 (s, 2H, NH_2), 6.46 (d, 1H, bridged CH), 6.53 (bs, 1H, $NH_{pyrazoline}$), 7.20—8.15 (m, 9H, H_{arom}), 10.80—11.00 (b, 2H, OH and NH).

5-(1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinylmethylene)-2-methylthio-1-phenyl-1,4,5,6-tetrahydropyrimidine-4,6-dione (*X*)

The pyrimidine *VI* (0.005 mol) was dissolved in a solution of sodium hydroxide (0.01 mol) in water (25 cm^3) and then dimethyl sulfate (0.005 mol) was added gradually to the resulting solution. The reaction mixture was stirred for 2 h and left to stand overnight. The precipitate so obtained was filtered off, washed with water and recrystallized to give *X*. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1570, 1590 ν(C=C_{arom}), 1600—1610 ν(C=$C_{exocyclic}$), 1620 ν(C=N), 1655 ν(C=$O_{quinolone}$), 1680 ν(C=$O_{pyrimidone}$ at C-4), 1700 ν(C=$O_{pyrimidone}$ at C-6), 2620 ν(H-bonded OH). ^{1}H NMR spectrum, δ: 2.55 (s, 3H, SCH_3), 3.67 (s, 3H, NCH_3), 6.90—8.05 (m, 10H, H_{arom} and methine), 10.82 (s, 1H, OH).

Hydrazinolysis of Compound *X*

Stirring of *X* (0.002 mol) with hydrazine hydrate (0.0025 mol; w = 98 %) in ethanol (20 cm^3) at room temperature for 4 h and dilution with ice-cold water (20 cm^3) afforded the product *VIII*, identified by its melting point, mixed melting point, and spectral data.

5-(1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinylmethylene)-2-phenyliminothiazolidin-4-one (*XII*)

A mixture of the aldehyde *II* (0.01 mol), the thiazolidine *XI* (0.01 mol), anhydrous sodium acetate (0.01 mol), and glacial acetic acid (25 cm^3) was refluxed for 4 h. The yellow crystals so obtained were filtered, washed with methanol (20 cm^3) and recrystallized affording compound *XII*. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 700 ν(C—S—C), 1180, 1200, 1230 ν(N=C—$S_{iminothiazolidine}$), 1585 ν(C—N), 1600, 1610 ν(C=C), 1620 (C=N), 1645—1650 ν(C=O_{lactam}), 1700 ν(C=$O_{thiazolidinone}$), 2620—3200 ν(br, H-bonded OH and NH). ^{1}H NMR spectrum, δ: 3.70 (s, 3H, CH_3), 6.10 (s, 1H, $H_{methine}$), 7.20—8.03 (m, 9H, H_{arom}), 9.80 (bs, 1H, NH), 10.85 (bs, 1H, OH).

3-(1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinyl)-5-phenylimino-2-pyrazolino-[3,4-*d*]thiazolidine (*XIII*)

To a suspension of *XII* (0.01 mol) in ethanol (25 cm^3) containing glacial acetic acid (0.5 cm^3) hydrazine hydrate (0.01 mol; w = 98 %) was added. The reaction mixture was warmed at 50—60 °C for 2 h and then left to stand overnight. The solid precipitate so formed was filtered and crystallized to give *XIII*. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 690 ν(C—S—C), 1160, 1236 ν(S—C=$N_{iminothiazolidine}$), 1500, 1550 ν(def NH), 1580, 1585, 1605 ν(C—N and C=C_{arom}), 1615, 1630 ν(C=N), 1660 ν(C=O_{lactam}), 2560—3400 ν(br, H-bonded OH, NH). ^{1}H NMR spectrum, δ 3.68 (s, 3H, NCH_3), 4.18 (d, 1H, $H_{pyrazoline}$), 5.92 (d, 1H, bridged CH), 6.34 (bs, 1H, $NH_{pyrazoline}$), 7.11—8.08 (m, 9H, H_{arom}), 9.85 (bs, 1H, $NH_{thiazolidine}$), 10.87 (bs, 1H, OH).

3-Ethoxycarbonylmethyl-5-(1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinylmethylene)-2-phenyliminothiazolidin-4-one (*XIV*)

Ethyl chloroacetate (0.015 mol) was added to a mixture of compound *XII* (0.01 mol), potassium carbonate (0.01 mol), and anhydrous acetone (50 cm^3) and the mixture was refluxed for 10 h. The solvent was then removed and the residue was extracted with chloroform (2 × 20 cm^3). The combined extract was washed with water, dried and the solvent was evaporated leaving pale yellow crystals which on recrystallization gave the ester *XIV* IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 695 ν(C—S—C), 1200 ν(C—O—C_{ester}), 1415 ν(def CH_{aliph}), 1500, 1550 ν(C—N), 1585, 1595 ν(C=C_{arom} and C=$C_{exomethine}$), 1620 ν(C=N), 1650 ν(C=$O_{quinolone}$), 1695 ν(C=$O_{thiazolidine}$), 1750 ν(C=O_{ester}). ^{1}H NMR spectrum, δ: 1.22 (t, 3H, $CH_{3\ ester}$), 3.68 (s, 3H, NCH_3), 4.21 (q, 2H, $CH_{2\ ester}$), 5.71 (s, 2H, NCH_2CO), 6.33 (s, 1H, $H_{methine}$), 7.18—8.10 (m, 9H, H_{arom}), 10.95 (bs, 1H, OH).

8-(1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinylmethylene)-6-phenylimino-2,3,4-trihydrothiazolidino[4,3-*c*]-1,2,4-triazin-3-one (*XV*)

A mixture of the ester *XIV* (0.005 mol), hydrazine hydrate (0.006 mol; w = 98 %), and DMF (20 cm^3) was refluxed for 6 h. The resulting solution was cooled and poured into cold water, and the solid so separated was filtered and crystallized to give compound *XV* IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 690 ν(C—S—C), 1150, 1260, 1350 ν(N=C—S), 1425 ν(def CH_{aliph}), 1500, 1540—1550, 1580 ν(def NH, C—N, C=C_{arom}), 1600 ν(C=$C_{exomethine}$), 1612—1618 ν(C=N), 1640 ν(C=$O_{triazinone}$), 1660 ν(C=$O_{quinolone}$), 2540—3170 ν(br, H-bonded OH, NH).

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