Chemistry of Substituted Quinolinones VII. Utility in Syntheses and Reactions of 3-[4-(Chromen-3-ylmethylene)pyrazolin-3-yl]quinolin-2(1*H*)-ones with Some Bidentate Nucleophiles

M. ABASS* and A. HASSAN

Department of Chemistry, Faculty of Education, Ain Shams University, Roxy, Cairo 11711, Egypt
e-mail: mohamedabass@hotmail.com

Received 10 June 2002
Accepted for publication 27 January 2003

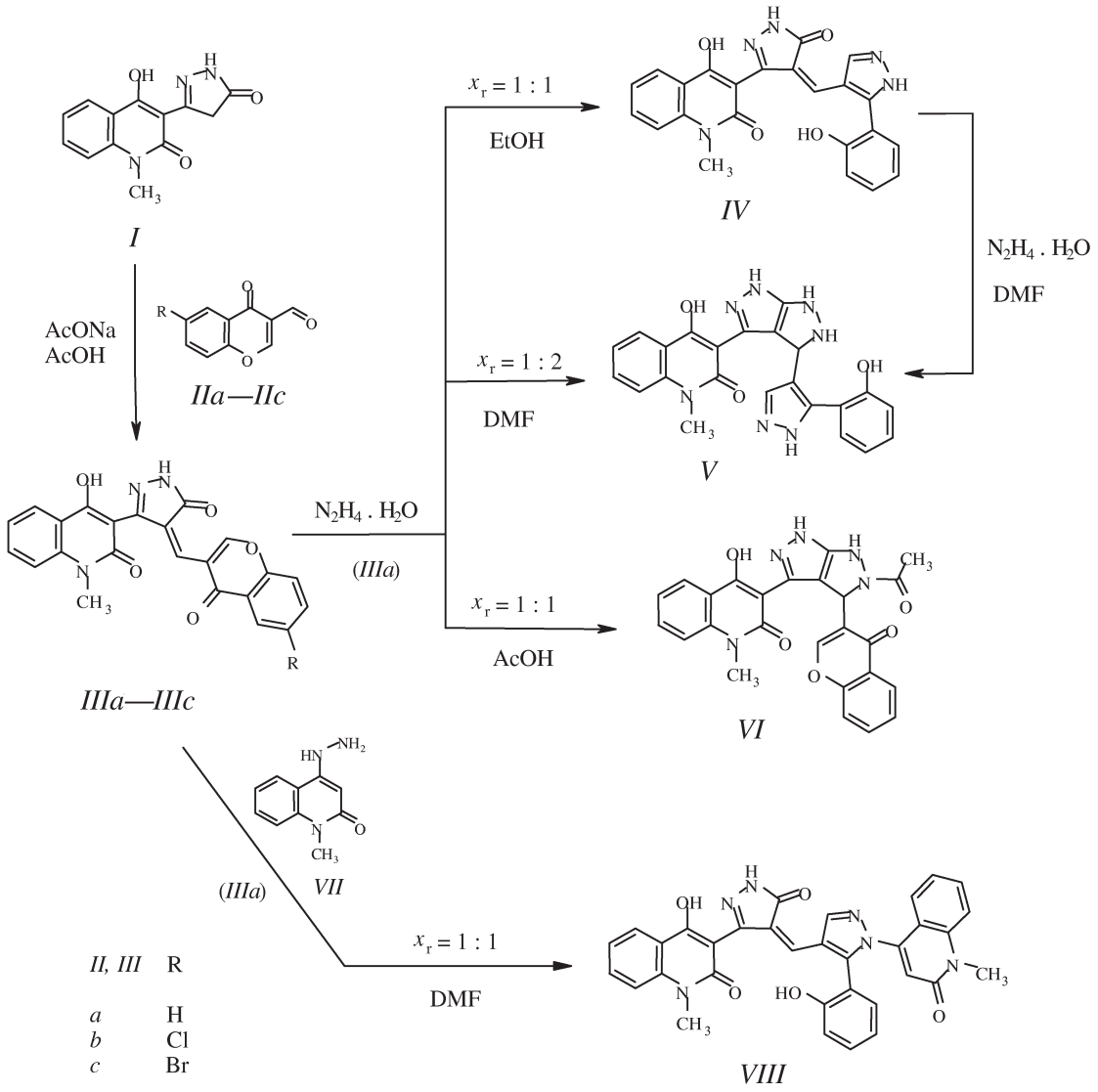
Dedicated to the memory of the late Professor Abdelazim A. Sayed

Condensation of 3-formylchromenes with pyrazolinylquinolinone afforded the chromenylmethylenepyrazolinones. The reactivity of these products towards different bidentate heteroatom nucleophiles, *viz.* hydrazine, quinolinylhydrazine, hydroxylamine, ketene-*S*,*S*-acetal, sulfanylacetic acid, cyanthioacetamide, thiourea, guanidine, thiobarbituric acid, 2-aminothiophenol, and 4-aminotriazole-3-thiol, was investigated at different mole ratios and reaction conditions. Versatile novel heteropolycyclic systems were obtained as substituents at the 3-pyrazolinylquinolinone moiety derived from nucleophilic ring opening of chromene.

3-Formylchromenes are excellent precursors for synthesis of versatile heterocycles because of similarity of their chemical behaviour to α,β-unsaturated ketones [1]. In general, chromenes are known as useful building blocks in organic synthesis. Derivatives of chromenes are considered possible synthons in formation of novel aza- and diazaheterocycles upon nucleophilic γ-pyrone ring opening [2]. Besides the reported biological activity of chromenylmethylenepyrazolinones [3], the facile conversion of γ-pyrone in chromenes into pyrazole ring or its related heterocycles attracted our attention to get novel pyrazolylpyrazolinones and their related systems of expected biological activities starting from certain chromenylmethylenepyrazolinones. Pyrazoles themselves deserve special interest due to their well-known significant analgesic activity [4, 5]. Also there are considerable antiviral [6], anti-inflammatory, neoplasm-inhibitory, and analgesic [7] activities connected with 2-quinolinones. All of this led us to try utilization of chromenylpyrazolylquinolinones to obtain novel heterocyclic systems, which combine pyrazolinone and quinolinone in one molecular frame including other heterocyclic substituents.

Earlier *Polyokov et al.* reported on the condensation of 3-formylchromene with pyrazolin-5-ones at its active methylene centre (position 4) [8]. Under similar conditions, the condensation of 4-hydroxy-1-methyl-3-(5-oxo-2-pyrazolin-3-yl)quinolin-2(1*H*)-one (*I*) [9] with 6-substituted 3-formylchromenes *IIa*—*IIc* (R = H, Cl, Br) [1, 2, 10] was carried out, in the presence of fused sodium acetate in glacial acetic acid, to give 3-{5-oxo-4-[(4-oxo-4*H*-chromen-3-yl)methylene]pyrazolin-3-yl}quinolinones *IIIa*—*IIIc* (Scheme 1). When compound *IIIa* was subjected to react with hydrazine hydrate, at the mole ratio $x_r = 1{:}1$ in boiling ethanol, it furnished a product of pyrone ring opening and pyrazole ring closure [11]. The structure of the product was characterized as 3-{4-[(pyrazol-4-yl)methylene]pyrazolin-3-yl}quinolinone (*IV*). Compound *IV* gave deep violet coloration with $FeCl_3$ and its ^{1}H NMR spectrum revealed the presence of a singlet methylene signal at $\delta = 6.46$ and the disappearance of the peak specific for C-2 proton of chromene ring which had been seen in the spectrum of the parent *IIIa* at $\delta = 8.18$. Treating compound *IIIa* with a slight excess of hydrazine hydrate in boiling DMF did not improve the yield of *IV* but instead, a mixture of this product and the product of addition-condensation reaction with two molecules of hydrazine was obtained. The latter reaction was repeated between *IIIa* and hydrazine hydrate at the mole ratio $x_r = 1{:}3$ to give only (pyrazolylpyrazolino[3,4-*c*]pyrazolyl)quinolinone (*V*). Furthermore, compound *V* was obtained by treating compound *IV* with an excess amount of hydrazine hydrate in boiling DMF. ^{1}H NMR and IR spectra of

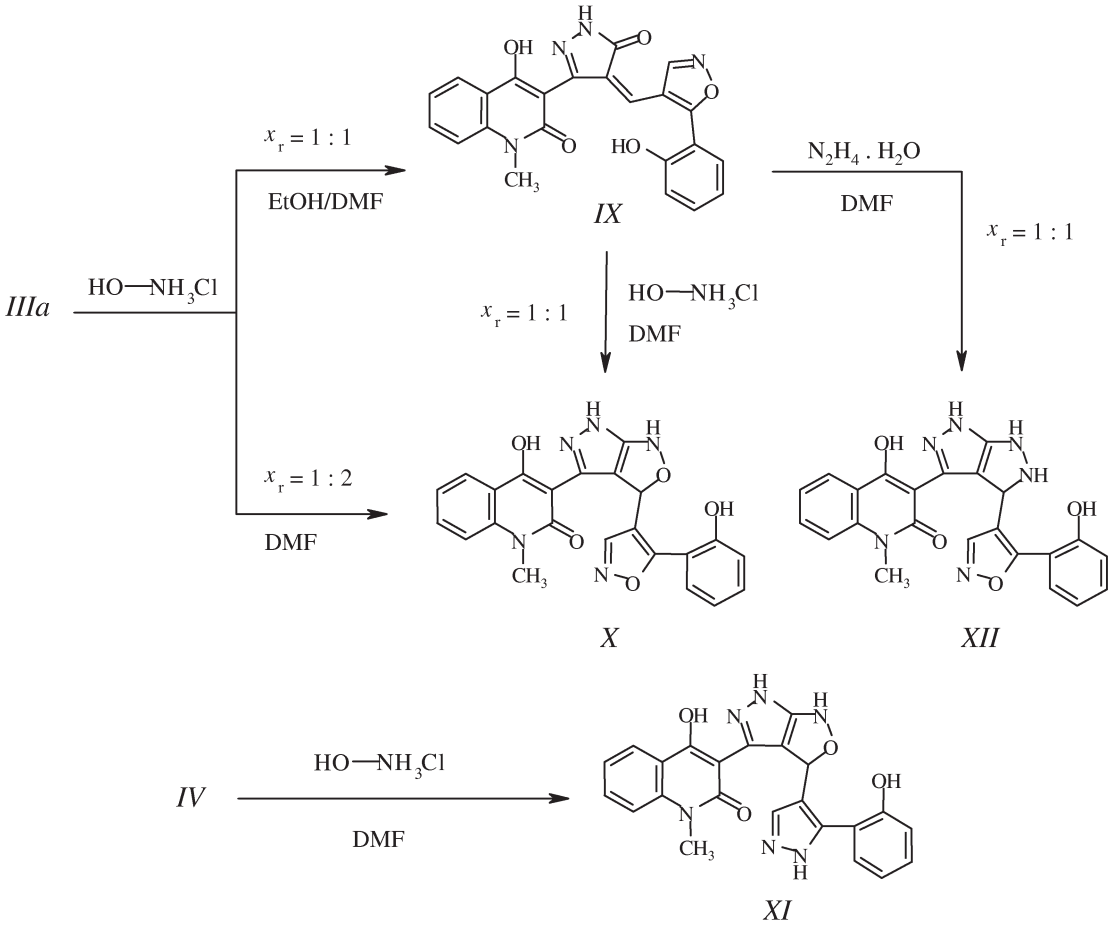
*The author to whom the correspondence should be addressed.



Scheme 1

derivatives *IV* and*V* showed that both γ-pyrone ring and pyrazoline exocyclic enone system are involved in the course of reaction with excess reagent while the reaction with exactly equimolar amount of reagent effected only the γ-pyrone ring system. This indicated that γ-pyrone ring opening took place prior to the attack at the exocyclic enone system when the reaction was carried out in neutral media such as ethanol or DMF. This prompted us to investigate this reaction in acidic medium, therefore we repeated the reaction with hydrazine hydrate in boiling glacial acetic acid at the mole ratio $x_r = 1{:}1$. Surprisingly, the product revealed features completely different from both *IV* and *V*; primary chemical tests identified that γ-pyrone was still not attacked. ^{1}H NMR spectrum of the product showed both characteristic chemical shifts due to the C-2 proton of chromene at $\delta = 8.19$ and a new signal at $\delta = 2.34$ attributed to acetyl methyl protons. At the same time, the chemical shift of the methine proton disappeared. The IR spectrum is concurrent with these results which suggest that in glacial acetic acid the exocyclic enone system is much more activated towards nucleophilic attack and pyrazolinopyrazole formed is acetylated at the most reactive N—H site to give 3-[5-acetyl(chromenyl)pyrazolino[3,4-*c*]pyrazolyl]quinolinone (*VI*). Results obtained show resemblance to the findings reported by *Shanker et al.* [12]. Likewise reaction of *IIIa* with hydrazine, its reaction with 4-hydrazino-1-methylquinolin-2(1*H*)-one (*VII*) [13] in boiling DMF afforded 3-{4-[(quinolinyl)-pyrazolylmethylene]pyrazolinyl}quinolinone (*VIII*).

When the reaction of *IIIa* with bidentate heteroatom nucleophiles was extended to hydroxylammonium chloride mutually with hydrazine hydrate, three interesting 3-(diazolyldiazolinopyrazolyl)quinolinone derivatives were obtained. Reaction of *IIIa* with hydroxylammonium chloride at the mole ratio $x_r = 1{:}1$ in ethanol and DMF as a mixed solvent [14] gave 3-

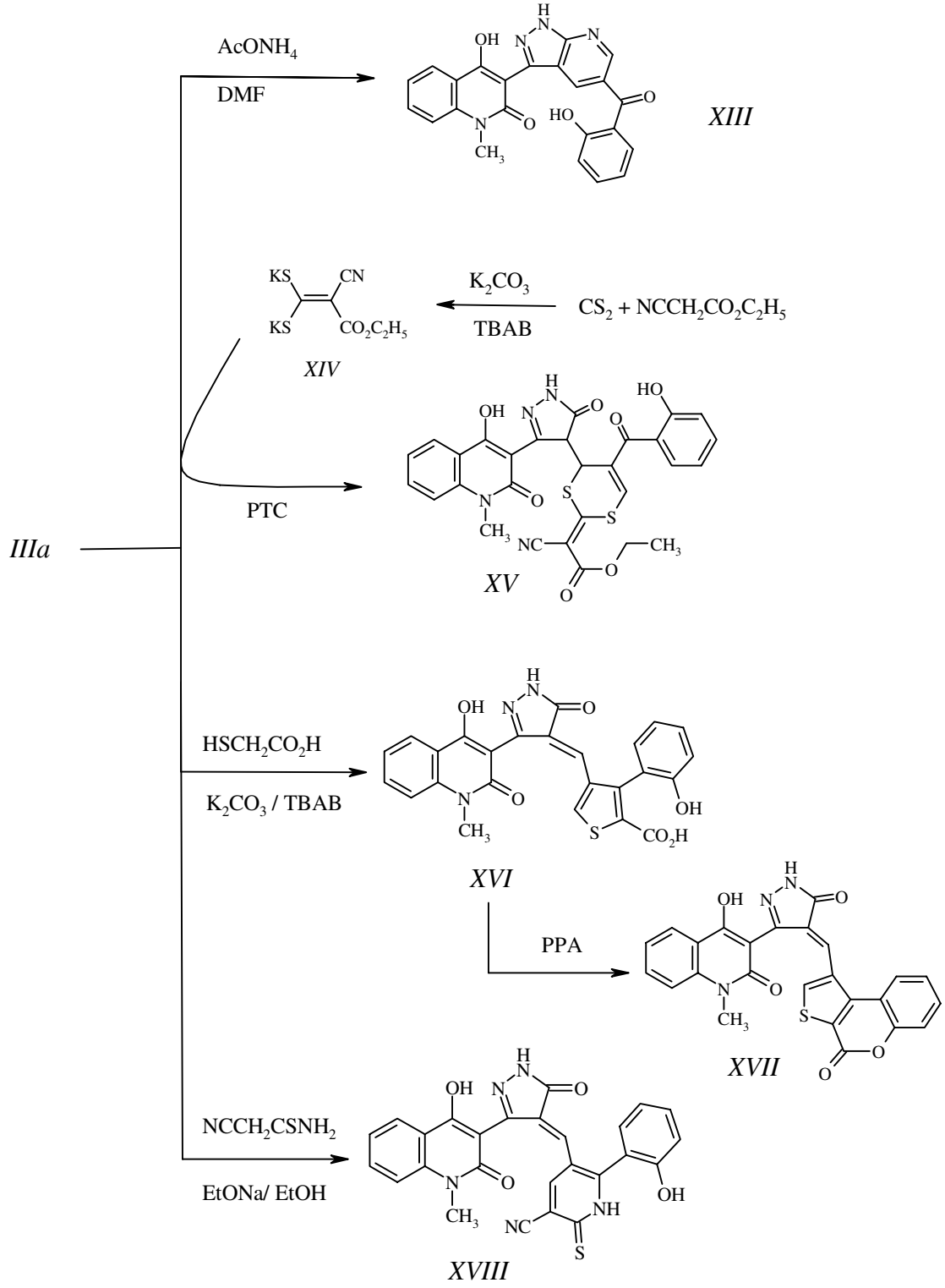


Scheme 2

[(isoxazol-4-ylmethylene)pyrazolinyl]quinolin-2(1*H*)-one (*IX*) (Scheme 2). Structure assignment of the compound *IX* was achieved from its spectral results in which ^{1}H NMR spectrum presented the characteristic chemical shift at δ = 6.91 due to the methine proton along with three broad peaks at δ = 11.40, 13.05, and 14.65 due to one N—H and two O—H protons. The IR spectrum and elemental microanalysis fortified the proposed structure. Furthermore, carrying out the reaction of *IIIa* with a double molarity of hydroxylammonium chloride in boiling DMF yielded (isoxazolylpyrazolo[3,4-*c*]isoxazolinyl)quinolinone (*X*), in which both γ-pyrone and pyrazoline exocyclic enone moieties were attacked by the two molecules of hydroxylamine and cyclized. Treating compound *IX* with the excess of hydroxylammonium chloride furnished a cyclization product identical in all aspects with compound *X*. From this observation it can be concluded again that the reactivity of γ-pyrone ring system is higher, comparing with exocyclic enone system, towards nucleophilic reagents. Hydroxylammonium chloride underwent a similar isoxazoline-ring formation when it reacted with compound *IV* in boiling DMF. In this case the product was characterized as (pyrazolylpyrazolo[3,4-*c*]isoxazolinyl)quinolinone (*XI*). Another isomer of both compounds *X* and *XI*, (isoxazolylpyrazolino[4,3-*d*]pyrazolyl)quinolinone (*XII*), was obtained from treatment of compound *IX* with hydrazine hydrate at the mole ratio x_r = 1:1 in boiling DMF. The structures of compounds *X*—*XII* were inferred from accumulation of their spectral and analytical data.

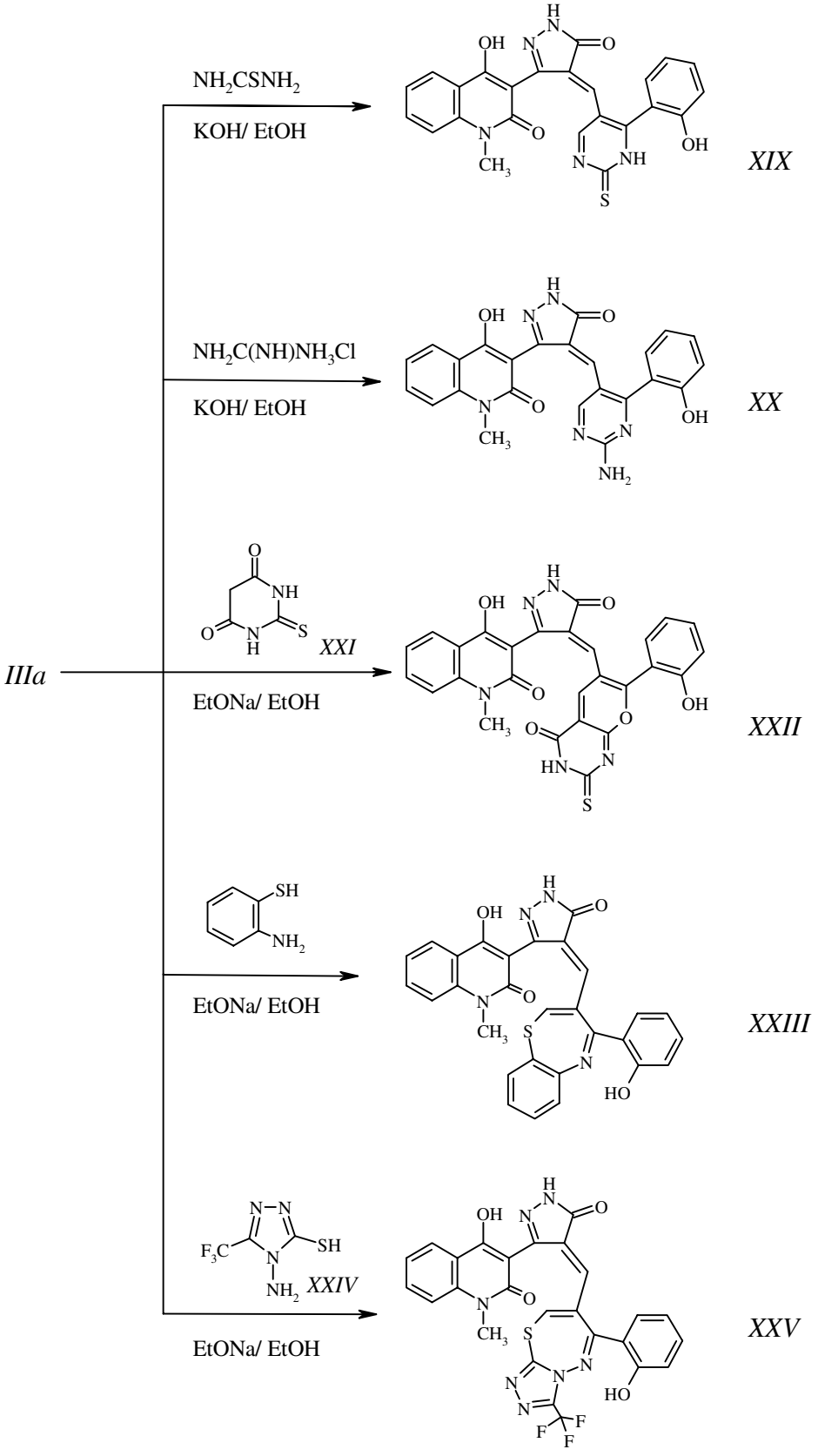
The action of ammonia on β-(chromen-3-yl)-α,β-unsaturated ketones was cited in the literature describing conversion of such systems into 3-(2-hydroxybenzoyl)pyridines [15, 16]. The resemblance of the key compound *IIIa* with the above-cited systems encouraged us to investigate its reaction with ammonium acetate in boiling DMF. As expected we got 3-(pyrazolo[3,4-*b*]pyridinyl)quinolinone (*XIII*) (Scheme 3) which showed IR spectrum bands at $\tilde{\nu}$ = 1661 cm^{-1} and 1687 cm^{-1} specific to carbonyl absorption vibrations of α-quinolinone and aromatic ketones, respectively. The ^{1}H NMR spectrum of *XIII* revealed three downfield signals at δ = 11.27, 12.72, and 14.49 due to one N—H and two O—H protons and also a very distinctive singlet at δ = 8.56 due to C-2 proton of pyridine.

The addition of ketene-*S*,*S*-acetal derivative *XIV* to compound *IIIa* was carried out by *in situ* reaction of ethyl cyanoacetate and carbon disulfide under phase



Scheme 3

transfer catalysis (PTC) conditions (K_2CO_3/dioxane/ tetrabutylammonium bromide (TBAB)) [17, 18]. The ^{1}H NMR spectrum of the product showed the presence of an ethyl ester set of protons as a triplet at $\delta = 1.2$ and a quartet at $\delta = 4.18$ and its IR spectrum represented an absorption band at $\tilde{\nu} = 2222$ cm^{-1} due to a nitrile group. These spectral evidences besides the chemical and analytical data highlight that the product is ethyl cyano[(quinolinylpyrazolinyl)dithiinylidene]acetate (*XV*). Using similar PTC conditions (K_2CO_3/dioxane /TBAB) compound *IIIa* was reacted with sulfanylacetic acid to give thiophene-2-carboxylic acid (*XVI*). The latter reaction may proceed *via* nucleophilic γ-



Scheme 4

pyrone ring opening followed by thiophene ring closure, which is effected by intramolecular condensation of benzoyl (C═O) with *S*-acetic acid (CH_2) [19]. The dehydration of compound *XVI* was tried for the

purpose of intramolecular cyclization to obtain a new thieno-α-benzopyrone derivative. We considered this cyclization as a good chemical confirmation for the structure of *XVI*. The intended compound thieno[2,3-*c*]chromene (*XVII*) was obtained by the action of polyphosphoric acid (PPA). The reaction of cyanothioacetamide with compound *IIIa* in the presence of sodium ethoxide gave the pyridine-3-carbonitrile (*XVIII*) [20].

The pyrimidinethione *XIX* was obtained when compound *IIIa* was treated with thiourea in the presence of sodium ethoxide (Scheme 4). Similar chromene—pyrimidine transformation was achieved in the course of reaction of guanidinium chloride with compound *IIIa*, giving the aminopyrimidine *XX*. Thiobarbituric acid (*XXI*) is considered one of the best cyclic *C*-nucleophiles, which are useful precursors for polyaza-fused heterocycles, hence its reaction with our key compound *IIIa* was carried out in the presence of sodium ethoxide [21]. This reaction resulted in the pyrano[2,3-*d*]pyrimidinone (*XXII*). The ferric chloride test for the product *XXII* showed the existence of phenolic O—H indicating the γ-pyrone ring fission. Elemental analysis as well as spectral data fortified the structure suggestion of compound *XXII*.

Finally, the reaction of compound *IIIa* with 1,4-*S*,*N*-nucleophiles led to the formation of interesting thiazepine derivatives [22], thus the reaction of *IIIa* with an equimolar amount of 2-aminothiophenol in the presence of sodium ethoxide furnished [1,5]benzothiazepine (*XXIII*). In the same manner, reaction of *IIIa* with 4-amino-5-(trifluoromethyl)-4*H*-[1,2,4]triazole-3-thiol (*XXIV*) [23] gave triazolo[3,4-*b*][1,5,6]thiadiazepine (*XXV*). It is obvious that γ-pyrone ring is initially attacked and opened by the S—H group of the aminothiol [24], subsequently the NH_2 group underwent intramolecular condensation reaction to effect cyclization to the seven-membered ring systems *XXIII* and *XXV* (Scheme 4).

EXPERIMENTAL

Melting points were obtained on a digital Gallenkamp MFB-595, in open capillary tubes. IR spectra ($\tilde{\nu}$/cm^{-1}) were taken in KBr pellets on a Perkin—Elmer FT-IR 1650 spectrophotometer. ^{1}H NMR spectra (δ) were recorded on a Varian Gemini 200 instrument (200 MHz). TMS was used as the internal standard and DMSO-d_6 as the solvent. Elemental analyses were performed on a Perkin—Elmer CHN-2400 analyzer at the Cairo University Microanalytical Centre. Analytical and spectral data are reported in Tables 1 and 2, respectively.

4-Hydroxy-1-methyl-3-{5-oxo-4-[(4-oxo-4*H*-chromen-3-yl)methylene]-2-pyrazolin-3-yl}-quinolin-2(1*H*)-one (*IIIa*)

A mixture of pyrazolinone *I* [9] (25.7 g; 100 mmol), aldehyde *IIa* (17.4 g; 100 mmol), and freshly fused sodium acetate (8.2 g; 100 mmol) in glacial acetic acid (200 cm^3) was heated under reflux for 2 h. The crystalline precipitate that formed was collected by suction, washed with ethanol and recrystallized to give 32.2 g (78 %) of *IIIa*.

3-{4-[(6-Chloro/bromo-4-oxo-4*H*-chromen-3-yl)methylene]-5-oxo-2-pyrazolin-3-yl}-4-hydroxy-1-methylquinolin-2(1*H*)-ones (*IIIb*) and (*IIIc*)

From compound *I* in 10 times lesser amount with aldehyde *IIb* (2.09 g) or *IIc* (2.53 g) according to the method described for *IIIa*, the chromenes *IIIb* (3.72 g, 83 %) and *IIIc* (3.94 g, 80 %) were obtained.

4-Hydroxy-3-{4-[5-(2-hydroxyphenyl)-1*H*-pyrazol-4-ylmethylene]-5-oxo-2-pyrazolin-3-yl}-1-methylquinolin-2(1*H*)-one (*IV*)

The compound *IIIa* (2.07 g; 5 mmol) was treated with hydrazine hydrate (0.25 cm^3, w = 100 %, 5 mmol) in ethanol (25 cm^3) and the reaction mixture was heated under reflux for 1 h. The solid that separated after cooling to room temperature was collected by suction and crystallized to give 1.41 g (66 %) of compound *IV*.

4-Hydroxy-3-{4-[5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl]-3-pyrazolino[3,4-*c*]pyrazol-3-yl}-1-methylquinolin-2(1*H*)-one (*V*)

Method A. To a solution of compound *IIIa* (2.07 g; 5 mmol) in DMF (25 cm^3) hydrazine hydrate (0.75 cm^3, w = 100 %, 15 mmol) was added and the clear solution so obtained was heated under reflux for 2 h. The crystalline product that formed on cooling was collected by filtration and recrystallized to yield 1.3 g (59 %) of compound *V*.

Method B. From compound *IV* (0.43 g; 1 mmol), hydrazine hydrate (0.1 cm^3, w = 100 %, 2 mmol), and DMF (5 cm^3), according to the above method *A*, 0.39 g (89 %) of the same product was obtained.

3-[5-Acetyl-4-(4-oxo-4*H*-chromen-3-yl)-pyrazolino[3,4-*c*]pyrazol-3-yl]-4-hydroxy-1-methylquinolin-2(1*H*)-one (*VI*)

A mixture of compound *IIIa* (1.04 g; 2.5 mmol) and hydrazine hydrate (0.13 cm^3, w = 100 %, 2.5 mmol) in glacial acetic acid (10 cm^3) was heated under reflux for 4 h. The solvent was evaporated in vacuum and the solid residue was triturated with ethanol (5 cm^3), filtered off and crystallized to furnish 0.67 g (57 %) of *N*-acetylpyrazoline *VI*.

Table 1. Characterization of the Synthesized Compounds

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield %	M.p. ℃	Solvent
IIIa	$C_{23}H_{15}N_3O_5$	66.83	3.66	10.16	78	215—216	AcOH
	413.39	66.60	3.50	10.20			
IIIb	$C_{23}H_{14}ClN_3O_5$	61.69	3.15	9.38	83	263—265	AcOH
	447.84	61.50	3.00	9.30			
IIIc	$C_{23}H_{14}BrN_3O_5$	56.12	2.87	8.54	80	255—256	AcOH
	492.29	56.00	2.70	8.50			
IV	$C_{23}H_{17}N_5O_4$	64.63	4.01	16.39	66	275—276	Dioxane
	427.42	64.40	3.90	16.30			
V	$C_{23}H_{19}N_7O_3$	62.58	4.34	22.21	59[a]	258—260	EtOH
	441.45	62.30	4.30	22.30	89[b]		
VI	$C_{25}H_{19}N_5O_5$	63.96	4.08	14.92	57	252—253	EtOH
	469.46	63.80	4.00	15.10			
VIII	$C_{33}H_{24}N_6O_5$	67.80	4.14	14.38	73	> 300	DMF
	584.60	67.70	4.20	14.10			
IX	$C_{23}H_{16}N_4O_5$	64.48	3.76	13.08	84	271—272	DMF
	428.41	64.40	3.50	12.90			
X	$C_{23}H_{17}N_5O_5$	62.30	3.86	15.79	71[a]	> 300	DMF
	443.42	62.20	3.80	15.60	85[b]		
XI	$C_{23}H_{18}N_6O_4$	62.44	4.10	18.99	62	> 300	DMF
	442.44	62.20	4.20	19.10			
XII	$C_{23}H_{18}N_6O_4$	62.44	4.10	18.99	64	261—262	DMF
	442.44	62.30	4.30	18.90			
XIII	$C_{23}H_{16}N_4O_4$	66.99	3.91	13.59	80	248—249	Acetone
	412.41	66.80	3.80	13.50			
XV	$C_{29}H_{22}N_4O_7S_2$	57.80	3.68	9.30	77	199—201	Dioxane
	602.65	57.80	3.50	9.20			
XVI	$C_{25}H_{17}N_3O_6S$	61.60	3.52	8.62	53	189—190	Dioxane
	487.49	61.60	3.50	8.50			
XVII	$C_{25}H_{15}N_3O_5S$	63.96	3.22	8.95	52	175—176	Dioxane
	469.48	63.80	3.10	8.70			
XVIII	$C_{26}H_{17}N_5O_4S$	63.02	3.46	14.13	73	214—215	EtOH
	495.52	63.10	3.50	14.20			
XIX	$C_{24}H_{17}N_5O_4S$	61.14	3.62	14.85	85	196—198	MeOH
	471.50	61.00	3.50	14.70			
XX	$C_{24}H_{18}N_6O_4$	63.43	3.99	18.49	79	204—205	EtOH
	454.45	63.30	3.80	18.30			
XXII	$C_{27}H_{17}N_5O_6S$	60.11	3.18	12.98	68	243—245	DMF
	539.53	60.10	3.00	12.70			
XXIII	$C_{29}H_{20}N_4O_4S$	66.91	3.87	10.76	51	190—191	EtOH
	520.57	66.70	3.80	10.60			
XXV	$C_{26}H_{16}F_3N_7O_4S$	53.89	2.78	16.92	65	243—246	EtOH
	579.52	53.80	2.80	16.80			

a) and *b*) Methods *A* and *B*, respectively.

4-Hydroxy-3-{4-[5-(2-hydroxyphenyl)-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-1*H*-pyrazol-4-ylmethylene]-5-oxo-2-pyrazolin-3-yl}-1-methylquinolin-2(1*H*)-one (*VIII*)

A mixture of compound *IIIa* (1.04 g; 2.5 mmol) and 4-hydrazinoquinolone *VII* [13] (0.47 g; 2.5 mmol) in DMF (20 cm^3) was heated under reflux for 4 h. Then the mixture was left to cool and the crystalline material so formed was filtered off and recrystallized to give 1.08 g (73 %) of compound *VIII*.

4-Hydroxy-3-{4-[5-(2-hydroxyphenyl)isoxazol-4-ylmethylene]-5-oxo-2-pyrazolin-3-yl}-1-methylquinolin-2(1*H*)-one (*IX*)

A mixture of compound *IIIa* (2.07 g; 5 mmol) and hydroxylammonium chloride (0.35 g; 5 mmol) in a mixed solvent of ethanol (10 cm^3) and DMF (5 cm^3) was heated under reflux for 3 h. Then the mixture was left to cool and the crystalline material so obtained was filtered off and recrystallized to give 1.8 g (84 %) of isoxazole *IX*.

Table 2. ^{1}H NMR and IR Spectral Data of the Synthesized Compounds

Compound	IR, $\tilde{\nu}$/cm^{-1}	^{1}H NMR, δ
IIIa	1647 ν(C═O$_{\text{quinolone}}$), 1652 ν(C═O$_{\text{chromene}}$), 1662 ν(C═O$_{\text{pyrazolone}}$), 2825—3234 ν(NH, OH)	3.64 (s, 3H, NCH$_3$), 6.96 (s, 1H, H$_{\text{olefin}}$), 7.25—8.10 (m, 8H, H$_{\text{arom}}$), 8.18 (s, 1H, C-2—H$_{\text{chromene}}$), 11.28 (b, 1H, NH$_{\text{pyrazolone}}$), 12.83 (b, 1H, OH)
IIIb	1642 ν(C═O$_{\text{quinolone}}$), 1650 ν(C═O$_{\text{chromene}}$), 1663 ν(C═O$_{\text{pyrazolone}}$), 2855—3230 ν(NH, OH)	
IIIc	1643 ν(C═O$_{\text{quinolone}}$), 1648 ν(C═O$_{\text{chromene}}$), 1660 ν(C═O$_{\text{pyrazolone}}$), 2603—3320 ν(NH, OH)	
IV	1629 ν(C═O$_{\text{quinolone}}$), 1682 ν(C═O$_{\text{pyrazolone}}$), 2710—3250 ν(NH, OH)	3.65 (s, 3H, NCH$_3$), 6.46 (s, 1H, H$_{\text{olefin}}$), 7.26—8.07 (m, 10H, H$_{\text{arom}}$ + NH$_{\text{pyrazole}}$), 11.28 (b, 1H, NH$_{\text{pyrazolone}}$), 12.73 (b, 1H, OH$_{\text{quinolinol}}$), 14.42 (b, 1H, OH$_{\text{phenol}}$)
V	1610 ν(C═N), 1628 ν(C═O$_{\text{quinolone}}$), 2630—3261 ν(NH, OH)	3.65 (s, 3H, NCH$_3$), 4.88 (s, 1H, H$_{\text{pyrazoline}}$), 6.94 (b, 1H, NH$_{\text{pyrazoline}}$), 7.20—8.18 (m, 10H, H$_{\text{arom}}$ + NH$_{\text{pyrazoline}}$), 8.95 (b, 1H, NH$_{\text{pyrazole}}$), 11.24 (b, 1H, NH$_{\text{pyrazole}}$), 12.78 (b, 1H, OH$_{\text{quinolinol}}$), 14.36 (b, 1H, OH$_{\text{phenol}}$)
VI	1645 ν(C═O$_{\text{quinolone}}$), 1661 ν(C═O$_{\text{chromene}}$), 1700 ν(C═O$_{\text{acetyl}}$), 2630—3261 ν(NH, OH)	2.34 (s, 3H, COCH$_3$), 3.68 (s, 3H, NCH$_3$), 4.93 (s, 1H, H$_{\text{pyrazoline}}$), 7.17—8.09 (m, 9H, H$_{\text{arom}}$ + NH$_{\text{pyrazoline}}$), 8.19 (s, 1H, C-2—H$_{\text{chromene}}$), 11.19 (b, 1H, NH$_{\text{pyrazole}}$), 12.68 (b, 1H, OH$_{\text{quinolinol}}$)
VIII	1634—1643 ν(C═O$_{\text{quinolone}}$), 1669 ν(C═O$_{\text{pyrazolone}}$), 2678—3219 ν(NH, OH)	3.60 (s, 3H, NCH$_3$), 3.68 (s, 3H, NCH$_3$), 6.12 (s, 1H, C-3—H$_{\text{quinoline}}$), 6.78 (s, 1H, H$_{\text{olefin}}$), 7.35—8.24 (m, 13H, H$_{\text{arom}}$), 11.17 (b, 1H, NH$_{\text{pyrazolone}}$), 12.42 (b, 1H, OH$_{\text{quinolinol}}$), 14.38 (b, 1H, OH$_{\text{phenol}}$)
IX	1630 ν(C═O$_{\text{quinolone}}$), 1663 ν(C═O$_{\text{pyrazolone}}$), 2620—3284 ν(NH, OH)	3.74 (s, 3H, NCH$_3$), 6.91 (s, 1H, H$_{\text{olefin}}$), 7.23—8.14 (m, 9H, H$_{\text{arom}}$ + H$_{\text{isoxazole}}$), 11.40 (b, 1H, NH$_{\text{pyrazolone}}$), 13.05 (b, 1H, OH$_{\text{quinolinol}}$), 14.65 (b, 1H, OH$_{\text{phenol}}$)
X	1605 ν(C═N), 1631 ν(C═O$_{\text{quinolone}}$), 2857—3228 ν(NH, OH)	3.65 (s, 3H, NCH$_3$), 4.95 (s, 1H, H$_{\text{isoxazoline}}$), 7.01 (b, 1H, NH$_{\text{isoxazoline}}$), 7.19—8.10 (m, 9H, H$_{\text{arom}}$ + H$_{\text{isoxazole}}$), 11.24 (b, 1H, NH$_{\text{pyrazole}}$), 12.52 (b, 1H, OH$_{\text{quinolinol}}$), 14.44 (b, 1H, OH$_{\text{phenol}}$)
XI	1612 ν(C═N), 1671 ν(C═O$_{\text{quinolone}}$), 2613—3240 ν(NH, OH)	3.66 (s, 3H, NCH$_3$), 4.75 (s, 1H, H$_{\text{isoxazoline}}$), 7.21 (b, 1H, NH$_{\text{isoxazoline}}$), 7.31—8.08 (m, 10H, H$_{\text{arom}}$ + H$_{\text{pyrazole}}$), 11.19 (b, 1H, NH$_{\text{pyrazole}}$), 12.73 (b, 1H, OH$_{\text{quinolinol}}$), 14.46 (b, 1H, OH$_{\text{phenol}}$)
XII	1617 ν(C═N), 1666 ν(C═O$_{\text{quinolone}}$), 2621—3226 ν(NH, OH)	3.67 (s, 3H, NCH$_3$), 4.87 (s, 1H, H$_{\text{pyrazoline}}$), 7.38—8.24 (m, 10H, H$_{\text{arom}}$ + NH$_{\text{pyrazoline}}$), 8.95 (b, 1H, NH$_{\text{pyrazoline}}$), 11.20 (b, 1H, NH$_{\text{pyrazole}}$), 12.46 (b, 1H, OH$_{\text{quinolinol}}$), 14.45 (b, 1H, OH$_{\text{phenol}}$)
XIII	1618 ν(C═N), 1661 ν(C═O$_{\text{quinolone}}$), 1687 ν(C═O$_{\text{ketone}}$), 2620—3228 ν(NH, OH)	3.65 (s, 3H, NCH$_3$), 7.29—8.08 (m, 9H, H$_{\text{arom}}$ + C-4—H$_{\text{pyridine}}$), 8.56 (s, 1H, C-2—H$_{\text{pyridine}}$), 11.27 (b, 1H, NH$_{\text{pyrazole}}$), 12.72 (b, 1H, OH$_{\text{quinolinol}}$), 14.49 (b, 1H, OH$_{\text{phenol}}$)
XV	1605 ν(C═N), 1629—1660 ν(C═O$_{\text{quinolone}}$ and C═O$_{\text{pyrazolone}}$), 1690 ν(C═O$_{\text{ketone}}$), 1730 ν(C═O$_{\text{ester}}$), 2222 ν(C≡ N), 2835—3265 ν(NH, OH)	1.20 (t, 3H, CO$_2$CH$_2$*CH*$_3$), 3.41 (d, 1H, C-4—H$_{\text{pyrazoline}}$), 3.68 (s, 3H, NCH$_3$), 3.92 (d, 1H, C-6—H$_{\text{dithiine}}$), 4.18 (q, 2H, CO$_2$*CH*$_2$CH$_3$), 6.79 (s, 1H, C-4—H$_{\text{dithiine}}$), 7.18—8.16 (m, 8H, H$_{\text{arom}}$), 11.13 (b, 1H, NH$_{\text{pyrazolone}}$), 12.44 (b, 1H, OH$_{\text{quinolinol}}$), 14.37 (b, 1H, OH$_{\text{phenol}}$)
XVI	1605 ν(C═N), 1637—1641 ν(C═O$_{\text{quinolone}}$ and C═O$_{\text{pyrazolone}}$), 1703 ν(C═O$_{\text{carboxylic}}$), 2821—3557 ν(NH, OH)	3.67 (s, 3H, NCH$_3$), 6.84 (s, 1H, H$_{\text{olefin}}$), 7.20—8.25 (m, 9H, H$_{\text{arom}}$ + H$_{\text{thiophene}}$), 10.77 (b, 1H, NH$_{\text{pyrazoline}}$), 12.44 (b, 1H, OH$_{\text{quinolinol}}$), 14.31 (b, 1H, OH$_{\text{phenol}}$), 15.52 (b, 1H, OH$_{\text{carboxylic}}$)
XVII	1617 ν(C═N), 1634 ν(C═O$_{\text{quinolone}}$), 1661 ν(C═O$_{\text{pyrazolone}}$), 1684 ν(C═O$_{\text{pyrone}}$), 2625—3250 ν(NH, OH)	3.64 (s, 3H, NCH$_3$), 6.83 (s, 1H, H$_{\text{olefin}}$), 7.23—8.26 (m, 9H, H$_{\text{arom}}$+ C-2—H$_{\text{thiophene}}$), 11.18 (b, 1H, NH$_{\text{pyrazolone}}$), 12.46 (b, 1H, OH$_{\text{quinolinol}}$)
XVIII	1600 ν(C═N), 1629 ν(C═O$_{\text{quinolone}}$), 1683 ν(C═O$_{\text{pyrazolone}}$), 2230 ν(C≡N), 2856—3240 ν(NH, OH)	3.66 (s, 3H, NCH$_3$), 6.80 (s, 1H, H$_{\text{olefin}}$), 7.38—8.15 (m, 9H, H$_{\text{arom}}$+ C-3—H$_{\text{pyridine}}$), 10.40 (b, 1H, NH$_{\text{pyridine}}$), 11.26 (b, 1H, NH$_{\text{pyrazolone}}$), 12.45 (b, 1H, OH$_{\text{quinolinol}}$), 14.33 (b, 1H, OH$_{\text{phenol}}$)

Table 2. (Continued)

Compound	IR, $\tilde{\nu}$/cm^{-1}	^{1}H NMR, δ
XIX	1161, 1220, 1327 ν(N—C═S), 1631 ν(C═O$_{quinolone}$), 1662 ν(C═O$_{pyrazolone}$), 2858—3223 ν(NH, OH)	3.67 (s, 3H, NCH$_3$), 6.78 (s, 1H, H$_{olefin}$), 7.18—8.27 (m, 8H, H$_{arom}$), 8.62 (s, 1H, C-4—H$_{pyrimidine}$), 10.93 (b, 1H, NH$_{pyrimidine}$), 11.38 (b, 1H, NH$_{pyrazolone}$), 12.83 (b, 1H, OH$_{quinolinol}$), 14.63 (b, 1H, OH$_{phenol}$)
XX	1605, 1618 ν(C═N), 1629 ν(C═O$_{quinolone}$), 1661 ν(C═O$_{pyrazolone}$), 2825—3186 ν(NH, OH), 3347, 3403 ν(NH$_2$)	3.68 (s, 3H, NCH$_3$), 6.45 (b, 2H, NH$_2$), 6.81 (s, 1H, H$_{olefin}$), 7.38—8.22 (m, 8H, H$_{arom}$), 8.83 (s, 1H, C-4—H$_{pyrimidine}$), 10.91 (b, 1H, NH$_{pyrazoline}$), 12.32 (b, 1H, OH$_{quinolinol}$), 13.86 (b, 1H, OH$_{phenol}$)
XXII	1160, 1213, 1328 ν(N—C═S), 1622 ν(C═N), 1631 ν(C═O$_{quinolone}$), 1655 ν(C═O$_{pyrazolone}$), 1683 ν(C═O$_{pyrimidone}$), 2650—3204 ν(NH, OH)	3.70 (s, 3H, NCH$_3$), 6.60 (s, 1H, H$_{olefin}$), 7.18—8.23 (m, 8H, H$_{arom}$), 8.35 (s, 1H, C-4—H$_{pyran}$), 10.06 (b, 1H, NH$_{pyrimidone}$), 10.80 (b, 1H, NH$_{pyrazolone}$), 12.32 (b, 1H, OH$_{quinolinol}$), 13.86 (b, 1H, OH$_{phenol}$)
XXIII	1616 ν(C═N), 1632 ν(C═O$_{quinolone}$), 1664 ν(C═O$_{pyrazolone}$), 2750—3250 ν(NH, OH)	3.65 (s, 3H, NCH$_3$), 6.62 (s, 1H, H$_{olefin}$), 7.39—8.32 (m, 13H, H$_{arom}$ + C-2—H$_{thiazepine}$), 11.20 (b, 1H, NH$_{pyrazolone}$), 12.45 (b, 1H, OH$_{quinolinol}$), 14.30 (b, 1H, OH$_{phenol}$)
XXV	1116, 1160 ν(CF$_3$), 1610 ν(C═N), 1630 ν(C═O$_{quinolone}$), 1663 ν(C═O$_{pyrazolone}$), 2718—3263 ν(NH, OH)	3.66 (s, 3H, NCH$_3$), 6.66 (b, 1H, H$_{olefin}$), 7.39—8.29 (m, 9H, H$_{arom}$ + C-2—H$_{thiadiazepine}$), 11.48 (b, 1H, NH$_{pyrazolone}$), 12.79 (b, 1H, OH$_{quinolinol}$), 14.53 (b, 1H, OH$_{phenol}$)

4-Hydroxy-3-{3-[5-(2-hydroxyphenyl)isoxazol-4-yl]-6*H*-pyrazolo[3,4-*c*]isoxazolin-4-yl}-1-methylquinolin-2(1*H*)-one (*X*)

Method A. From compound *IIIa* (2.07 g; 5 mmol) and hydroxylammonium chloride (0.7 g; 10 mmol) in DMF (15 cm^3) according to the procedure described for isoxazole *IX*, compound *X* (1.57 g, 71 %) was obtained.

Method B. From compound *IX* (0.54 g; 1.25 mmol) and hydroxylammonium chloride (0.17 g; 2 mmol) in DMF (5 cm^3) according to the method described above compound *X* (0.47 g, 85 %) was obtained.

4-Hydroxy-3-{3-[5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl]-6*H*-pyrazolo[3,4-*c*]-isoxazolin-4-yl}-1-methylquinolin-2(1*H*)-one (*XI*)

Using the same procedure as described for compound *IX*, compound *XI* (1.37 g, 62 %) was obtained from treating pyrazole *IV* (2.14 g; 5 mmol) with hydroxylammonium chloride (0.35 g; 5 mmol) in DMF (15 cm^3).

4-Hydroxy-3-{3-[5-(2-hydroxyphenyl)isoxazol-4-yl]-1*H*-pyrazolino[4,3-*d*]pyrazol-3-yl}-1-methylquinolin-2(1*H*)-one (*XII*)

From compound *XI* (0.86 g; 2 mmol) and hydrazine hydrate (0.1 cm^3, $w = 100$ %, 2 mmol) in DMF (5 cm^3) according to the method *A* described for *V*, compound *XII* (0.57 g, 64 %) was afforded.

4-Hydroxy-3-[5-(2-hydroxybenzoyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-1-methylquinolin-2(1*H*)-one (*XIII*)

A mixture of compound *IIIa* (2.07 g; 5 mmol) and ammonium acetate (0.39 g; 5 mmol) in DMF (20 cm^3) was heated under reflux for 3 h. Then the reaction mixture was left to cool and poured onto crushed ice. The yellow precipitate so obtained was filtered off and crystallized to give 1.65 g (80 %) of *XIII*.

Ethyl Cyano-{5-(2-hydroxybenzoyl)-4-[3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-2-pyrazolin-4-yl]-4*H*-1,3-dithiin-2-ylidene}acetate (*XV*)

A mixture of ethyl cyanoacetate (1.1 cm^3, 10 mmol), carbon disulfide (0.6 cm^3, 10 mmol), anhydrous potassium carbonate (2.07 g; 15 mmol), and TBAB (1 g) in dioxane (20 cm^3) was stirred at 60 °C for 30 min. Afterwards, compound *IIIa* (2.07 g; 5 mmol), dissolved in dioxane (30 cm^3), was added to the reaction mixture and heated on a boiling water bath for additional 30 min. The reaction mixture was filtered off and the filtrate was subjected to vacuum evaporation and the solid residue so obtained was washed several times with water, dried and crystallized to give 2.32 g (77 %) of dithiine *XV*.

4-[3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-2-pyrazolin-4-ylidenemethyl]-3-(2-hydroxyphenyl)thiophene-2-carboxylic Acid (*XVI*)

A mixture of sulfanylacetic acid (0.8 cm^3, 11 mmol), compound *IIIa* (2.07 g; 5 mmol), anhydrous potassium carbonate (2.76 g; 20 mmol), and TBAB (1 g) in dioxane (20 cm^3) was stirred at 60 °C for 2 h. After that dioxane was evaporated in vacuum and the solid residue so obtained was dissolved in water, filtered off and reprecipitated using dilute acetic acid.

The yellow precipitate was collected by filtration and crystallized to give 1.29 g (53 %) of the acid *XVI*.

4-Hydroxy-1-methyl-3-[5-oxo-4-(4-oxo-4*H*-thieno[2,3-*c*]chromen-1-ylmethylene)-2-pyrazolin-3-yl]quinolin-2(1*H*)-one (*XVII*)

To a stirred freshly prepared PPA (5 g), the carboxylic acid *XVI* (0.97 g; 2 mmol) was added portionwise, after that the mixture was heated at 170 °C for 20 min. The reaction temperature was raised gradually to 220 °C over a period of 30 min, then the reaction mixture was cooled and poured onto icy sodium acetate saturated solution (15 cm^3). The solidified material was collected by suction and crystallized to give 0.49 g (52 %) of thienochromene *XVII*.

5-[3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-2-pyrazolin-4-ylidenemethyl]-6-(2-hydroxyphenyl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (*XVIII*)

To a mixture of compound *IIIa* (2.07 g; 5 mmol) and cyanothioacetamide (0.5 g; 5 mmol) sodium ethoxide (0.68 g; 10 mmol) was added in ethanol (10 cm^3). Then the reaction mixture was heated under reflux for 4 h, left to cool and poured onto ice-cold water. The solution so formed was filtered off and the pH of the clear filtrate was adjusted to be slightly acidic using dilute hydrochloric acid. The deposited product was crystallized to give 2.17 g (73 %) of nitrile *XVIII*.

4-Hydroxy-3-{4-[6-(2-hydroxyphenyl)-2-thioxo-1,2-dihydropyrimidin-5-ylmethylene]-5-oxo-2-pyrazolin-3-yl}-1-methylquinolin-2(1*H*)-one (*XIX*)

A mixture of compound *IIIa* (2.07 g; 5 mmol), thiourea (0.38 g; 5 mmol), and fine milled potassium hydroxide (0.56 g; 10 mmol) in ethanol (25 cm^3) was heated under reflux for 6 h, then left to cool and diluted with cold water. The solution so formed was filtered off and the pH of the clear filtrate was adjusted to be slightly acidic using dilute hydrochloric acid. The deposited material was crystallized to give 2 g (85 %) of pyrimidinethione *XIX*.

3-{4-[2-Amino-4-(2-hydroxyphenyl)pyrimidin-5-ylmethylene]-5-oxo-2-pyrazolin-3-yl}-4-hydroxy-1-methylquinolin-2(1*H*)-one (*XX*)

A mixture of compound *IIIa* (2.07 g; 5 mmol), guanidinium chloride (0.48 g; 5 mmol), and fine milled potassium hydroxide (0.84 g; 15 mmol) in ethanol (25 cm^3) was heated under reflux for 4 h, then left to cool and diluted with cold water. The solution so formed was filtered off and the pH of the clear filtrate was adjusted to be neutral using dilute hydrochloric acid. The yellow precipitate so formed was crystallized to give 1.8 g (79 %) of aminopyrimidine *XX*.

6-[3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-2-pyrazolin-4-ylidenemethyl]-7-(2-hydroxyphenyl)-2-thioxo-2,3-dihydro-4*H*-pyrano[2,3-*d*]-pyrimidin-4-one (*XXII*)

From compound *IIIa* (2.07 g; 5 mmol), thiobarbituric acid (*XXI*) (0.72 g; 5 mmol), and sodium ethoxide (0.68 g; 10 mmol) in ethanol (25 cm^3), following the procedure described for the nitrile *XVIII*, the pyranopyrimidine *XXII* (1.83 g, 68 %) was obtained.

4-Hydroxy-3-{4-[4-(2-hydroxyphenyl)benzo-[1,5]thiazepin-3-ylmethylene]-5-oxo-2-pyrazolin-3-yl}-1-methylquinolin-2(1*H*)-one (*XXIII*)

A mixture of *IIIa* (2.07 g; 5 mmol) and 2-aminothiophenol (0.55 cm^3, 5 mmol) was treated with sodium ethoxide (0.68 g; 10 mmol) in ethanol (25 cm^3) and then worked up, according to the procedure described for compound *XVIII*, to give benzothiazepine *XXIII* (1.33 g, 51 %).

4-Hydroxy-3-{4-[6-(2-hydroxyphenyl)-3-(trifluoromethyl)[1,2,4]triazolo[3,4-*b*]-[1,5,6]thiadiazepin-7-ylmethylene]-5-oxo-2-pyrazolin-3-yl}-1-methylquinolin-2(1*H*)-one (*XXV*)

A mixture of *IIIa* (2.07 g; 5 mmol) and aminotriazolethiol *XXIV* [23] (0.92 g; 5 mmol) was treated with sodium ethoxide (0.68 g; 10 mmol) in ethanol (25 cm^3) and then worked up, according to the procedure described for compound *XVIII*, to give thiadiazepine *XXV* (1.88 g, 65 %).

REFERENCES

1. Nohara, A., Umetani, T., and Sanno, Y., *Tetrahedron 30*, 3553 (1974).
2. Ghosh, C. K., *J. Heterocycl. Chem. 20*, 1437 (1983).
3. Achaiah, G., Raja Reddy, R., Jayamma, Y., and Reddy, V. M., *Indian J. Pharm. Sci. 53*, 197 (1991).
4. Borne, R. F., in *Principles of Medicinal Chemistry*, p. 550. Williams and Wilkins, Baltimore, 1995.
5. Gursoy, A., Demirayak, S., Capan, G., Erol, K., and Vural, K., *Eur. J. Med. Chem. 32*, 359 (2000).
6. Afonso, A., McCombie, S. W., and Weinstein, J. (Schering Corp.), *U.S.* 5,179,093 (1991); *Chem. Abstr. 118*, 212905*d* (1993).
7. Matsuo, M., Tsuji, K., Nakamura, K., and Spears, G. W. (Fujisawa Pharm. Co.), *PCT Int. Appl. WO* 92 18, 483 (1992); *Chem. Abstr. 118*, 212903*b* (1993).
8. Polyokov, V. K., Babich, Yu. P., Shevtsova, R. G.,

Trusevich, N. B., and Lavrushin, V. F., *Khim. Khim. Tekhnol. 30*, 42 (1987).
9. Abass, M. and Othman, E. S., *Synth. Commun. 31*, 3361 (2001).
10. Nohara, A., Umetani, T., and Sanno, Y., *Tetrahedron Lett. 22*, 1995 (1973).
11. Ghosh, C. K. and Mukhopadhyay, K. K., *J. Indian Chem. Soc. 55*, 386 (1978).
12. Shanker, M. S. S., Reddy, R. B., Chandra Mouli, G. V. P., and Reddy, Y. D., *Asian J. Chem. 4*, 166 (1992).
13. Abass, M., *Synth. Commun. 30*, 2735 (2000).
14. Abdel-Rahman, A. H., Khalil, A. M., El-Desoky, S. I., and Keshk, E. M., *Chem. Pap. 53*, 323 (1999).
15. Ghosh, C. K. and Khan, S., *Synthesis 1983*, 903.
16. Haas, G., Stanton, J. L., Sprecher, A. V., and Paul, W., *J. Heterocycl. Chem. 18*, 607 (1981).
17. Soderback, E., *Acta Chem. Scand. 17*, 362 (1963).
18. El-Shafei, A. K., El-Sayed, A. M., Sultan, A. A., and Abdel-Ghany, H., *Gazz. Chim. Ital. 120*, 197 (1990).
19. Hishmat, O. H., Fawzy, N. M., Farrg, D. S., Abd El All, A. S., and Abdel-Rahman, A. H., *Boll. Chim. Farm. Ann. 138*, 427 (1999).
20. Ibrahim, S. S., El-Shaaer, H. M., and Hassan, A., *Phosphorus, Sulfur Silicon Relat. Elem. 177,* 151 (2002).
21. Jones, W. D. and Albrecht, W. L., *J. Org. Chem. 41*, 706 (1976).
22. Fitton, A. O., Houghton, P. G., and Suschitzky, H., *Synthesis 1979*, 337.
23. Hoggarth, E., *J. Chem. Soc. 1969*, 4811.
24. Reddy, M. S., David Krupadanam, G. L., and Srimannarayana, G., *Indian J. Chem. 290*, 978 (1990).