Synthesis and Cyclization Reactions with Quinolinyl Keto Esters II. Synthesis of Novel 3-Diazolylquinolinones and their Enzymic Activity

M. M. ISMAIL* and H. M. MOHAMED

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

Received 11 September 2003

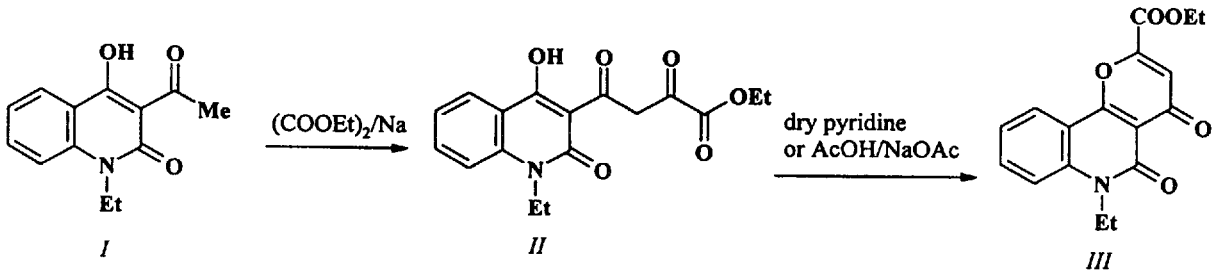
Ethyl 4-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2,4-dioxobutyrate, ethyl 5-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)pyrazole-3-carboxylate and their acid hydrazide derivatives have been prepared and reacted with hydrazines, *o*-phenylenediamine, triethyl orthoformate, carbon disulfide, and thiosemicarbazides in order to obtain some new 3-substituted quinolin-2-ones as: pyrazolines, isoxazolines, imidazoles, pyrazolotriazines, thiadiazoles, and triazoles. All the newly prepared compounds revealed the potent effect on increasing reactivity of cellobiase. The structure of the new compounds was established upon their elemental analyses, IR, ^{1}H NMR, and mass fragmentation spectra.

In connection with the previous studies on the chemistry of substituted quinolin-2-ones [1—6], this work deals with the synthesis of new quinolinones substituted at position 3 with pyrazolyl, isoxazolyl, triazinyl, and thiadiazolyl moieties. This arose from the recent notable biological applications of quinolinones [1, 7—10], pyrazoles [11, 12], isoxazoles [13, 14], triazines [15, 16], and thiadiazoles [17—20]. This encouraged us to prepare new heterocycles containing quinolinone skeleton loaded with the latter substrates with the aim to improve biological activity of quinoline-α,γ-diketo esters.

Due to the considerable chemical reactivity of quinoline-α,γ-diketo esters, ethyl 4-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2,4-dioxobutyrate (*II*) was synthesized (Scheme 1) and used as starting material to obtain some new 3-heterocyclylquinolinone derivatives. The structure of α,γ-diketo ester *II* was inferred on the basis of its spectral and analytical data. IR spectrum of *II* revealed the presence of carbonyl ester at its characteristic wavenumber 1775 cm^{-1}, in addition to the vibrational bands at $\tilde{\nu}$/cm^{-1} = 1660, 1650, and 1635 (C=O$_\alpha$, C=O$_\gamma$, and C=O$_{\text{quinolinone}}$, respectively). ^{1}H NMR spectrum of compound *II* showed signals at δ = 1.42 (t) and 4.44 (q) specific for OCH_2CH_3 group, at δ = 3.93 specific for $COCH_2CO$ (see Table 2). The mass fragmentation pattern of the ester *II* revealed molecular ion peak at m/z (I_r/%) = 331 (1.62) and the base peak at m/z = 258 stands for $[C_{14}H_{12}NO_4]^+$ (Chart 1). A strong chemical evidence for the proposed structure of diketo ester *II* was obtained when it was treated with glacial acetic acid in the presence of freshly fused sodium acetate or dry pyridine, cyclization reaction took place to afford ethyl 6-ethyl-4,5-dioxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-2-carboxylate (*III*). IR spectrum of compound *III* revealed the presence of specific bands due to γ-pyrone. At the same time the characteristic bands of α-keto ester and phenolic OH groups are absent.

For the purpose of obtaining various 3-substituted quinolinones *II* was subjected to react with some *N*-nucleophiles as hydrazine, phenylhydrazine, and hydroxylamine at different ratio and conditions. Thus, when *II* reacted with hydrazine hydrate at the mole ratio 1:1 in boiling ethanol, ethyl 5-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-pyrazole-3-carboxylate (*IV*) was formed (Scheme 2). On the other hand, using excess of amount of hydrazine under fusion condition resulted in the acid hydrazide *V*, which was also obtained by the hydrazinolysis of *IV* using excess of hydrazine. Elemental analyses and spectral data of compounds *IV* and *V* are in good accordance with the suggested formula. IR spectrum of *IV* showed the disappearance of the vibrational bands specific for α and γ carbonyl groups and the presence of absorption bands specific for the ester group at position 3 of the pyrazole. On the other hand, IR spectrum of *V* revealed bands at $\tilde{\nu}$/cm^{-1} = 3420, 3300 specific for NH_2 group and its ^{1}H NMR spectrum showed signal at δ = 3.4 specific for NH_2 group of the acid hydrazide.

*The author to whom the correspondence should be addressed.



Scheme 1

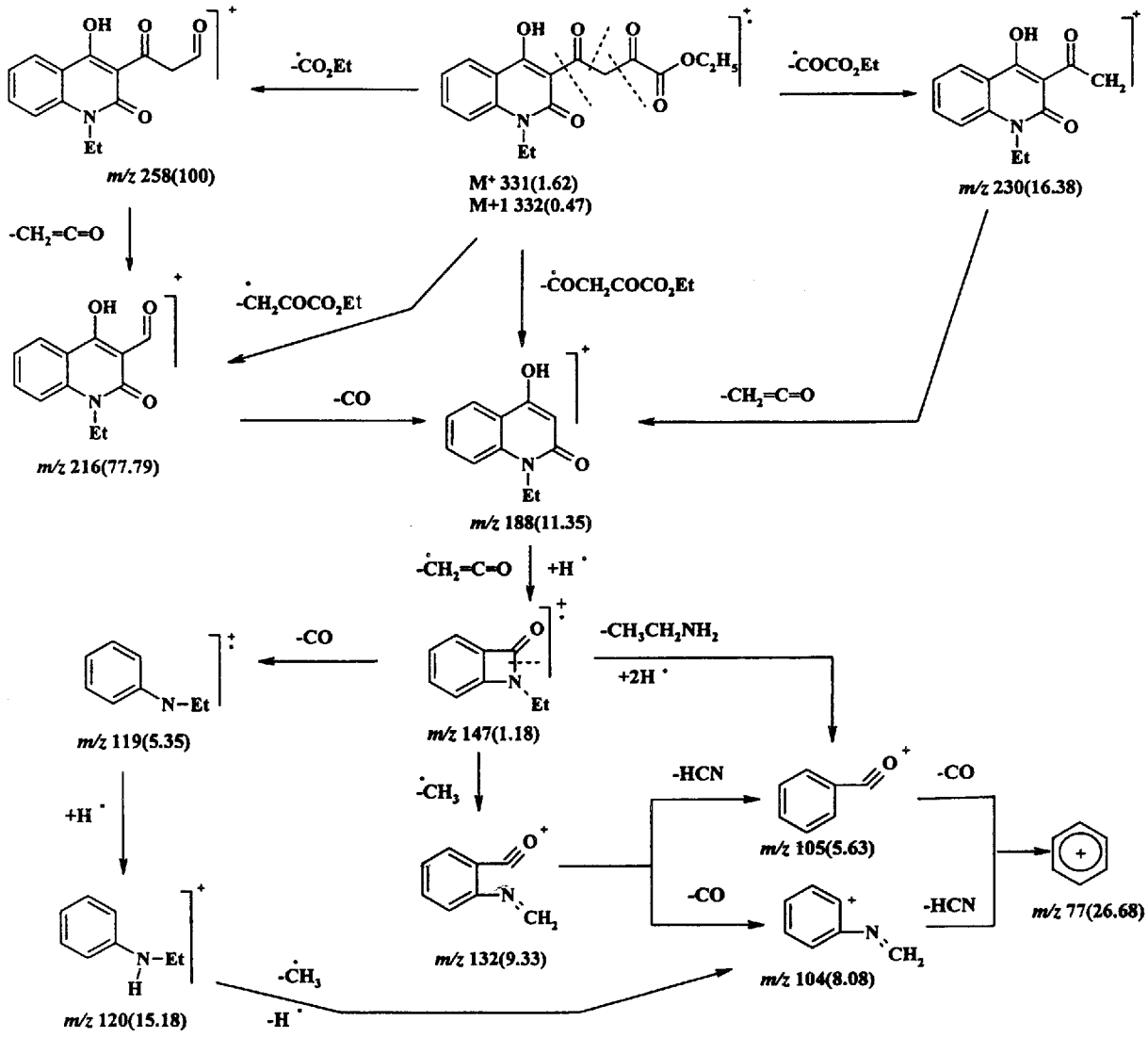
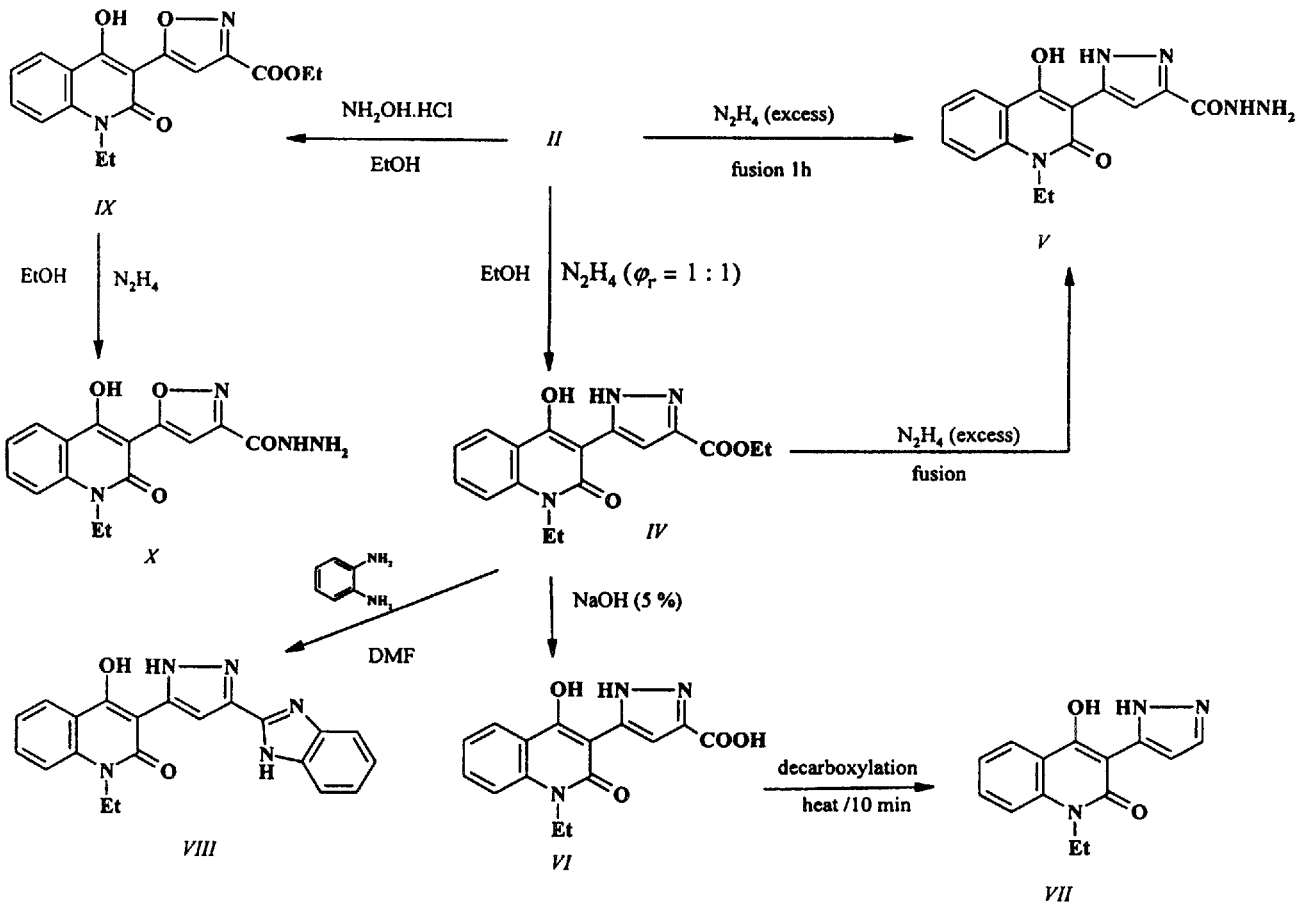


Chart 1. Mass fragmentation pattern of compound *II*.

Hydrolysis of the ester *IV*, using aqueous solution of sodium hydroxide furnished the carboxylic acid derivative *VI*, which gave positive acidity test. When compound *VI* was heated above its melting point in the absence of solvent a decomposition product was obtained, which was characterized by its analytical and spectral data and it was deduced to be 1-ethyl-4-hydroxy-3-(1*H*-pyrazol-5-yl)quinolin-2(1*H*)-one (*VII*).

Additional support for the structure of *IV* was achieved by its reaction with *o*-phenylenediamine, where benzoimidazole derivative *VIII* was obtained.

In continuation to the study devoted to investigation of the chemical reactivity of quionolinone deriva-



Scheme 2

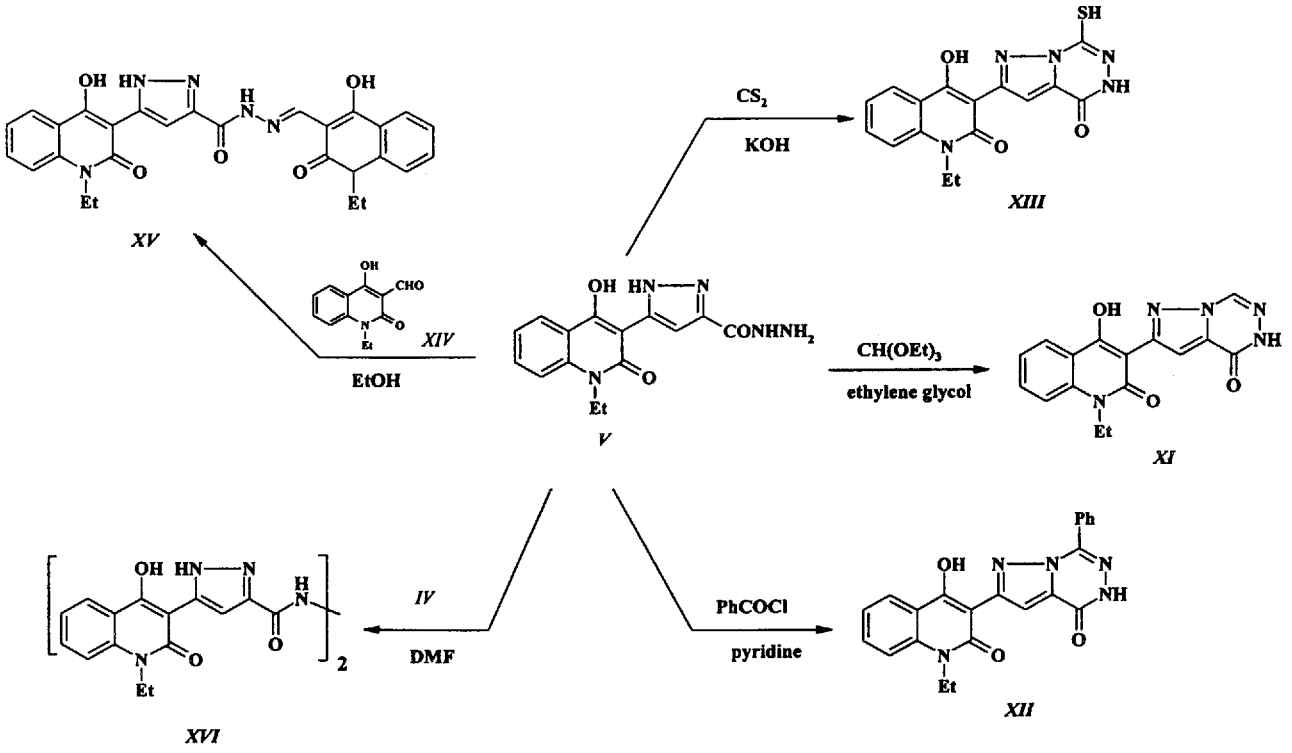
tives the keto ester *II* was subjected to react with hydroxylammonium chloride in boiling ethanol giving isoxazole derivative *IX*. The hydrazinolysis of the latter product, using the excess amount of hydrazine hydrate, led to the formation of acid hydrazide *X*. The structures of both compounds *IX* and *X* met satisfactory elemental analyses and spectral data.

For the purpose of obtaining various pyrazolotriazines attached directly to quinolinone at position 3, the acid hydrazide *V* reacted with some selected reagents. Thus, *V* was treated with triethyl orthoformate in ethylene glycol to give the pyrazolotriazine derivative *XI* (Scheme 3). When the acid hydrazide *V* was allowed to react with benzoyl chloride in dry pyridine, cyclocondensation product *XII* was obtained. The IR and ^{1}H NMR spectra of compounds *XI* and *XII* showed the inclusion of both amino groups due to the acid hydrazide along with N—H group due to the pyrazole ring system in the cyclization process.

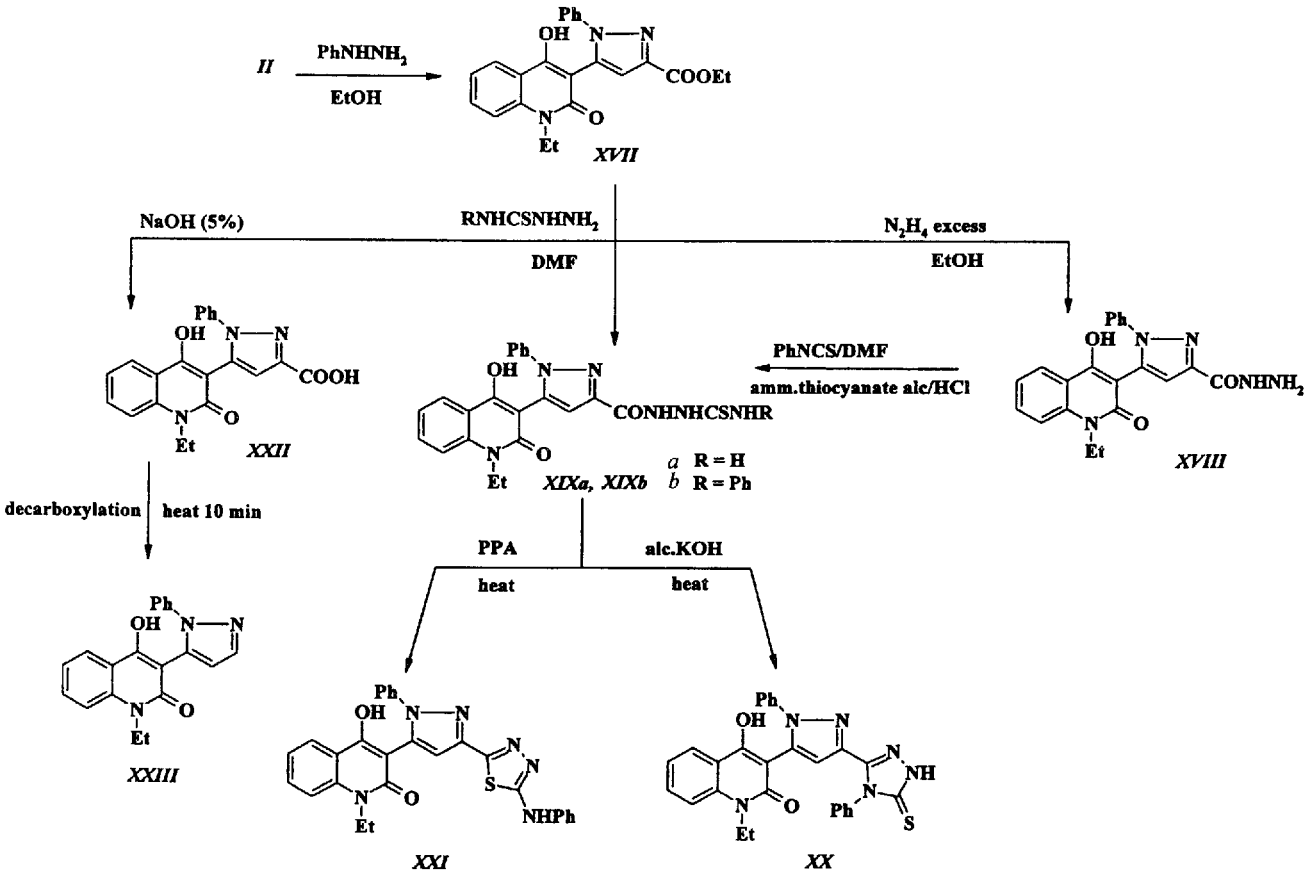
For obtaining other derivative of quinolinone bearing pyrazolotriazine moiety, the reaction of the acid hydrazide *V* with carbon disulfide was investigated. Thus, reacting *V* with carbon disulfide in the presence of alcoholic potassium hydroxide furnished the desired pyrazolotriazine derivative *XIII*, the IR spectrum of which revealed the presence of absorption band at $\tilde{\nu}/\mathrm{cm}^{-1} = 2660$ specific for SH group.

Treatment of the acid hydrazide *V* with equimolar amount of 1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxaldehyde (*XIV*) in boiling ethanol afforded the corresponding hydrazone *XV*, while the reaction of the compound *V* with the ester *IV* led to the formation of the interesting bis(quinolinylpyrazole)-hydrazide *XVI*. IR spectra of the hydrazone *XV* and the hydrazide *XVI* were characterized by the absence of the vibrational bands specific for the NH_2 group. Also elemental microanalyses of these compounds fortified their proposed formulas.

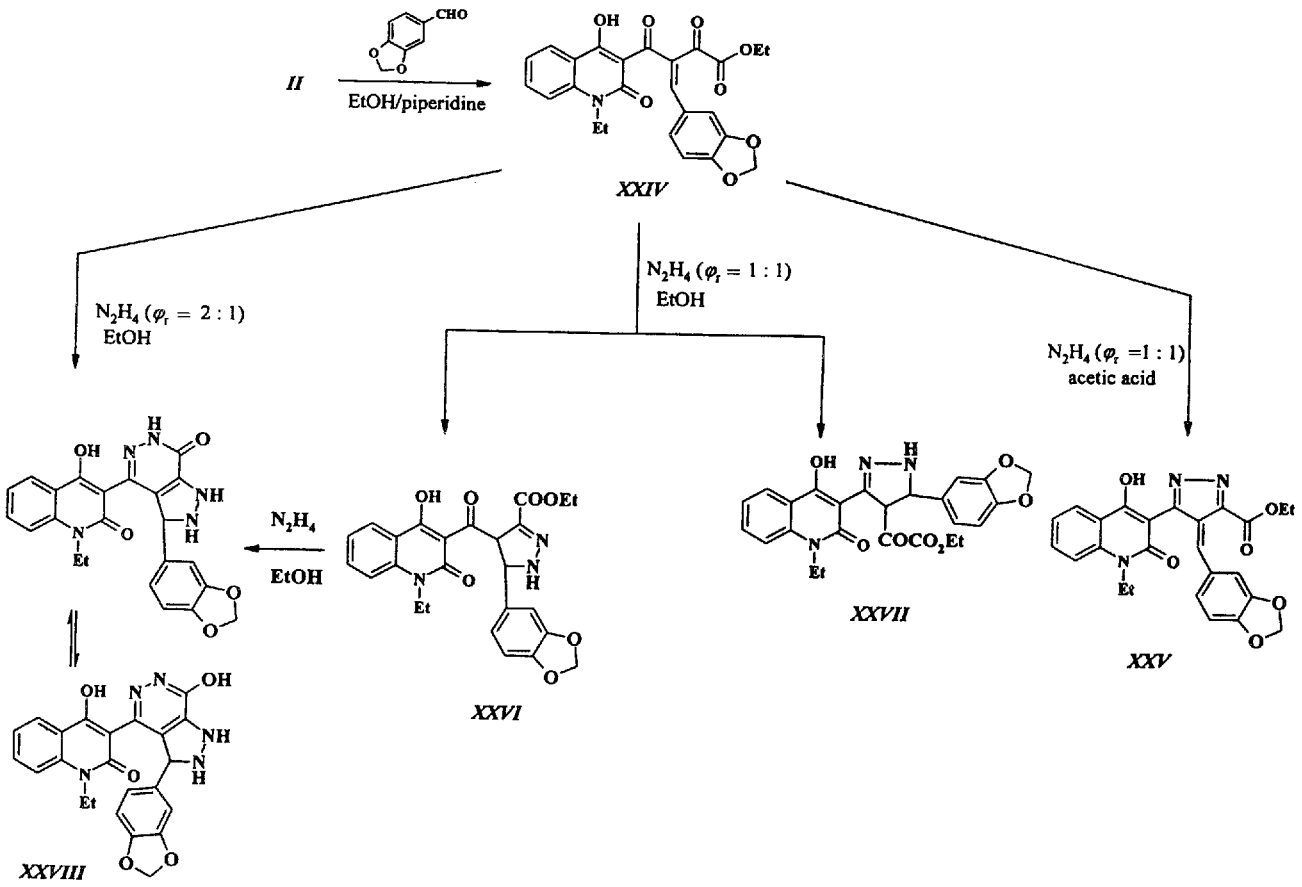
Condensation cyclization reaction between *II* and phenylhydrazine performed in ethanol produced ethyl 5-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-1*H*-pyrazole-3-carboxylate (*XVII*) (Scheme 4), which is considered as good precursor for the synthesis of the target compounds. Thus, the reaction of *XVII* with excess of hydrazine hydrate gave the corresponding acid hydrazide *XVIII*, while the condensation reaction between the ester *XVII* and 4-substituted thiosemicarbazides afforded the corresponding pyrazole-3-carbonyl thiosemicarbazides *XIXa*, *XIXb*. The same products were obtained when the acid hydrazide *XVIII* was subjected to react with ammo-



Scheme 3



Scheme 4



Scheme 5

nium thiocyanate in boiling ethanol in the presence of hydrochloric acid and phenyl isothiocyanate in DMF, respectively.

When compound *XIXb* was treated with alcoholic potassium hydroxide, cyclization reaction took place. In this reaction carbonylthiosemicarbazide side chain underwent intramolecular-condensation cyclization and gave 1-ethyl-4-hydroxy-3-[1-phenyl-3-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-1*H*-pyrazol-5-yl]quinolin-2(1*H*)-one (*XX*). ^{1}H NMR spectrum of *XX* revealed the presence of skeletal N—H at $\delta = 10.6$, fortifying the proposed cyclization to the triazole system. On the other hand, treatment of *XIXb* with polyphosphoric acid (PPA) furnished 1-ethyl-4-hydroxy-3-[1-phenyl-3-(5-phenylamino-1,3,4-thiadiazol-2-yl)-1*H*-pyrazol-5-yl]quinolin-2(1*H*)-one (*XXI*). Such cyclization reaction found support in the spectral data which proved the elimination of a molecule of water besides the presence of a signal of N—H at the H-aromatic zone due to phenylamino group.

The reactivity of the ester group of the pyrazole derivative *XVII* towards basic hydrolysis was also studied. Thus, hydrolysis of the ester *XVII* led to the carboxylic acid derivative *XXII*, which gave positive acidity test. When the latter acid was subjected to decarboxylation reaction, it gave 1-ethyl-4-hydroxy-3-(1-phenylpyrazol-5-yl)quinolin-2(1*H*)-one (*XXIII*). The found C, H, and N elemental analyses of compound *XXIII* are in good accordance with calculated values, IR spectrum showed the disappearance of the carboxylic group characteristic bands.

Comparative study of the reactivity of α,β-unsaturated carbonyl group against keto ester group, when present in one molecular frame, has been carried out, thus ethyl 4-(1,3-benzodioxolan-5-yl)-3-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)-2-oxobut-3-enoate (*XXIV*) was synthesized by the action of piperonal on *II* in the presence of piperidine as a catalyst (Scheme 5). ^{1}H NMR spectrum of the butenoic acid ester *XXIV* showed distinctive chemical shifts at $\delta = 5.59$ (s) due to OCH_2O and $\delta = 6.62$ (s) due to an olefinic CH which revealed that condensation of piperonal took place at the active β-methylene of the diketo ester.

On treatment of compound *XXIV* with hydrazine at the mole ratio 1:1 in glacial acetic acid, condensation reaction took place to give ethyl 4-(1,3-benzodioxolan-5-ylmethylene)-5-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-pyrazole-3-carboxylate (*XXV*). IR spectrum of compound *XXV* showed the disappearance of the vibrational bands specific for α- and γ-carbonyl groups and the presence of absorp-

Table 1. Effect of New Compounds on the Activity of Cellobiase*

Compound	ρ(Glucose) / μg cm^{-3}	Compound	ρ(Glucose) / μg cm^{-3}
II	2.70	*XVI*	1.87
III	1.95	*XVII*	1.73
IV	1.75	*XVIII*	1.89
V	1.83	*XIXa*	2.00
VI	2.10	*XIXb*	1.97
VII	1.39	*XX*	2.35
VIII	1.70	*XXI*	2.23
IX	1.77	*XXII*	2.15
X	1.80	*XXIII*	1.44
XI	2.10	*XXIV*	3.23
XII	2.00	*XXV*	2.95
XIII	2.30	*XXVI*	2.89
XIV	1.60	*XXVIII*	1.99
XV	1.99	Control**	0.28

* Blank test using bidistilled water produced $\rho = 0.592$ μg cm^{-3}.
**Using DMF (0.1 cm^3) without sample.

tion bands due to the ester group at postion 3 of the pyrazole. ^{1}H NMR spectrum of the ester *XXV* gave much more information about the structure of this compound, showing peaks at $\delta = 1.25$ (t) and 4.34 (q) specific for OCH_2CH_3 indicating that ester group does not participate in the cyclocondensation.

Surprisingly, on repeating the latter reaction at the same ratio but in ethanol instead of acetic acid the corresponding ethyl 5-(1,3-benzodioxolan-5-yl)-4-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)-4, 5-dihydro-1*H*-pyrazole-3-carboxylate (*XXVI*) was obtained and neither *XXV* nor *XXVII* were formed. The IR spectrum of the product revealed the presence of C=O and COOEt characterized by vibrational absorption at $\tilde{\nu}/\text{cm}^{-1} = 1678$ for keto C=O and $\tilde{\nu}/\text{cm}^{-1} = 1734$ for $C{=}O_{ester}$ indicating that the ester group was still present and not involved in the cyclization process.

Besides the analytical and spectral evidences for the structure of *XXVI* a good support for this chemical structure was achieved by the reaction of *XXVI* with another mole of hydrazine hydrate in ethanol to give 3-[3-(1,3-benzodioxolan-5-yl)-7-oxo-3,3a,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl]-1-ethyl-4-hydroxyquinolin-2-(1*H*)-one (*XXVIII*). The evident formation of the latter product indicated that compound *XXVI* must contain a free carbonyl group and an ethoxycarbonyl group, which are involved in the cyclization reaction to form the fused pyrazolopyridazine system. On the other hand, compound *XXIV* was subjected to condense with hydrazine hydrate at the mole ratio 1:2 in ethanol. The product formed was found to be identical in every respect with the product that was obtained by the action of N_2H_4 on compound *XXVI*. The formation of *XXVIII* by these two pathways is considered as good support for the formulas of both *XXVI* and *XXVIII*.

The effect of the newly prepared compounds on the activity of cellobiase, an enzyme produced by the thermotolerant fungus *Absidia corymbifera*, was studied [21]. The results showed (see Table 1) that most of the tested compounds enhanced the effect of the enzyme in the production of glucose ($\rho_{glucose} = 1.39$—3.23 μg cm^{-3}). The data obtained proved that compound *XXIV* is the most active one (3.23 μg cm^{-3}) and this may be due to the presence of α,γ-diketo ester and α,β-unsaturated system in one molecular frame, this was supported by the amount of glucose produced by the effect of α,γ-diketo ester derivative *II* (2.70 μg cm^{-3}). On the other hand, these results also showed that the relatively high values (2.10—2.35 μg cm^{-3}) may be due to the presence of pyrazolotriazines, substituted pyrazoles or triazoles and thiadiazoles bearing quinolinone.

EXPERIMENTAL

Melting points are uncorrected and measured in open capillary tubes using a Gallenkamp electric melting point apparatus. IR spectra were recorded on Perkin—Elmer 598 and FT-IR 1650 spectrophotometers, using samples in KBr disks. ^{1}H NMR spectra were taken on an EM-NMR spectrometer (300 MHz) using DMSO-d_6 or $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were obtained on an HP MS-5988 by direct inlet ($E = 70$ eV). Elemental microanalyses were performed at the Cairo University, Microanalytical Centre. Compounds *I* and *XIV* were prepared according to the methods cited in literature [22]. Analytical and spectral data are listed in Tables 2 and 3.

Ethyl 4-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2,4-dioxobutyrate (*II*)

Table 2. Analytical Data of the New Compounds

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield %	M.p. °C	Solvent
II	$C_{17}H_{17}NO_6$	61.63	5.13	4.23	89	114—115	EtOH
	331	61.10	5.10	4.20			
III	$C_{17}H_{15}NO_5$	65.17	4.79	4.47	84[a]	190—191	EtOH
	313	64.90	5.30	4.60	62[b]		DMF
IV	$C_{17}H_{17}N_3O_4$	62.38	5.19	12.84	89	180—182	EtOH
	327	62.90	5.20	13.00			
V	$C_{15}H_{15}N_5O_3$	57.51	4.79	22.36	49[a]	> 300	DMF
	313	57.40	5.50	22.40	54[b]		
VI	$C_{15}H_{13}N_3O_4$	60.20	4.35	14.04	82	> 300	EtOH/
	299	60.30	4.20	14.10			DMF
VII	$C_{14}H_{13}N_3O_2$	65.88	5.09	16.47	44	260—262	EtOH
	255	65.20	5.20	16.60			
VIII	$C_{21}H_{17}N_5O_2$	67.92	4.58	18.86	52	205—207	DMF/
	371	68.50	4.20	18.70			H_2O
IX	$C_{17}H_{16}N_2O_5$	62.19	4.87	8.53	88	170—171	MeOH
	328	61.50	5.30	8.50			
X	$C_{15}H_{14}N_4O_4$	57.32	4.46	17.83	42	238—239	DMF
	314	57.30	4.60	17.90			
XI	$C_{16}H_{13}N_5O_3$	59.44	4.02	21.67	59	180—182	EtOH/
	323	58.60	4.00	21.70			H_2O
XII	$C_{22}H_{13}N_5O_3$	66.16	4.26	17.54	53	195—196	Benzene
	399	66.60	4.70	17.30			
XIII	$C_{15}H_{13}N_5O_3S$	52.47	3.79	20.40	49	230—232	MeOH
	343	54.30	3.50	20.40			
XV	$C_{27}H_{24}N_6O_5$	63.28	4.68	16.40	70	160—161	EtOH
	512	63.30	4.50	16.40			
XVI	$C_{30}H_{26}N_8O_6$	60.60	4.37	18.85	62	190—191	EtOH
	594	60.60	5.00	19.00			
XVII	$C_{23}H_{21}N_3O_4$	68.48	5.21	10.42	85	205—207	EtOH
	403	68.90	4.70	10.50			
XVIII	$C_{21}H_{19}N_5O_3$	64.78	4.88	17.99	49	250—253	EtOH/
	389	64.90	4.80	17.80			DMF
XIXa	$C_{22}H_{20}N_6O_3S$	58.93	4.46	18.75	60[a]	220—222	EtOH
	448	59.40	4.80	18.80	73[b]		
XIXb	$C_{28}H_{24}N_6O_3S$	64.12	4.58	16.03	62[a]	190—191	EtOH
	524	64.30	4.60	16.10	81[c]		
XX	$C_{28}H_{22}N_6O_2S$	66.40	4.34	16.60	38	242—243	Benzene
	506	66.70	4.20	16.50			
XXI	$C_{28}H_{22}N_6O_2S$	66.53	4.30	16.63	40	280—282	Benzene
	505	66.50	4.10	16.70			
XXII	$C_{21}H_{17}N_3O_4$	67.20	4.53	11.20	76	255—256	MeOH
	375	66.80	4.00	11.30			
XXIII	$C_{20}H_{17}N_3O_2$	72.50	5.31	12.68	39	200—201	EtOH
	331	71.70	4.70	12.70			
XXIV	$C_{25}H_{21}NO_8$	64.79	4.53	3.02	92	210—212	Benzene
	463	63.70	4.50	2.90			
XXV	$C_{25}H_{21}N_3O_6$	65.36	4.57	9.15	82	160—161	EtOH/
	459	66.60	4.70	9.10			DMF
XXVI	$C_{25}H_{23}N_3O_7$	62.89	4.80	8.80	80	181—182	EtOH
	477	63.30	4.50	9.00			
XXVIII	$C_{23}H_{19}N_5O_5$	62.02	4.27	15.73	73[a]	> 300	DMF/
	445	62.70	4.00	15.80	56[b]		H_2O

A mixture of *I* (0.03 mol), finely dusted sodium metal (0.15 mol), and dry diethyl oxalate (0.68 mol) was refluxed for 4 h. The reaction mixture was kept at room temperature overnight, then poured into dilute

acetic acid. The precipitate that formed was filtered off, washed with water and crystallized.

Ethyl 6-Ethyl-4,5-dioxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-2-carboxylate (*III*)

Method A. To a solution of compound *II* (0.01 mol) in acetic acid (10 cm^3), 2 g of fused sodium acetate were added. The reaction mixture was heated for 6 h and poured into ice-cold water. The product so deposited was collected and crystallized.

Method B. Compound *II* (0.01 mol) in dry pyridine (25 cm^3) was refluxed for 10 h and then diluted with ice-cold water containing hydrochloric acid, the resulting precipitate that formed was collected by filtration and crystallized.

Ethyl 5-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-pyrazole-3-carboxylate (*IV*)

A mixture of compound *II* (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (10 cm^3) was refluxed for 4 h. The reaction mixture was left to cool at room temperature and the precipitate that formed was filtered off and crystallized.

5-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-pyrazole-3-carbohydrazide (*V*)

A mixture of compound *IV* or *II* (0.01 mol) and hydrazine hydrate (0.09 mol) was heated under fusion condition for 1 h, then it was treated with ethanol (20 cm^3) and refluxed for another 4 h. The product so formed during the course of the reaction was collected by filtration and crystallized.

5-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-pyrazole-3-carboxylic Acid (*VI*)

A solution of compound *IV* (0.01 mol) in sodium hydroxide (25 cm^3, 5 %) was heated under reflux on a water bath for 2 h. The clear solution was filtered off from any insoluble materials and neutralized with hydrochloric acid, the solid product that formed was filtered off and crystallized.

1-Ethyl-4-hydroxy-3-(1*H*-pyrazol-5-yl)-quinolin-2(1*H*)-one (*VII*)

The acid *VI* (1 g) was heated until it melted and the temperature of the melt was kept constant above the melting point of the acid by 10 °C for 10 min, then the molten mass after cooling was treated with ethanol (20 cm^3) and the solid product that formed was collected and crystallized.

3-[3-(1*H*-Benzoimidazol-2-yl)-1*H*-pyrazol-5-yl]-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (*VIII*)

To a solution of compound *IV* (0.01 mol) in DMF (30 cm^3), *o*-phenylenediamine (0.01 mol) was added and the reaction mixture was refluxed for 5 h, afterwards the mixture was poured into ice-cold water. The precipitate so formed was filtered off and crystallized.

Ethyl 5-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)isoxazole-3-carboxylate (*IX*)

Compound *II* was treated with hydroxylamine utilizing the same procedure as described for compound *IV*, and worked up as cited therein.

5-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)isoxazole-3-carbohydrazide (*X*)

Treatment of compound *IX* with hydrazine hydrate, using the same method as for preparation of compound *V*, yielded the acid hydrazide *X*.

2-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)pyrazolo[1,5-*d*][1,2,4]triazin-4(5*H*)-one (*XI*)

A mixture of compound *V* (0.01 mol) and triethyl orthoformate (0.015 mol) was heated at the boiling point of the mixture for 2 h, using a short air condenser. The mass of the reaction was allowed to cool and treated with diethyl ether (20 cm^3). The solid that formed was filtered off and crystallized.

2-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-7-phenylpyrazolo[1,5-*d*][1,2,4]-triazin-4(5*H*)-one (*XII*)

A mixture of compound *V* (0.01 mol) and benzoyl chloride (0.01 mol) in dry pyridine was refluxed for 6 h, the product so formed during the course of the reaction was filtered off, washed with dilute hydrochloric acid and crystallized.

2-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-7-sulfanylpyrazolo[1,5-*d*][1,2,4]-triazin-4(5*H*)-one (*XIII*)

A mixture of *V* (0.01 mol), carbon disulfide (0.02 mol), and potassium hydroxide (5 cm^3, 10 %) in ethanol (30 cm^3) was refluxed on a water bath for 4 h, then it was poured into ice-cold water, acidified with dilute hydrochloric acid and the solid so separated was collected and crystallized.

1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxaldehyde[5-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-pyrazole-3-carbohydrazone] (*XV*)

Equimolar amounts of *V* and *XIV* (0.01 mol) in

Table 3. IR and ^{1}H NMR Data of the New Compounds

Compound	IR, $\tilde{\nu}$/cm^{-1}	^{1}H NMR, δ
II	1635, 1650 and 1660 ν(C=O$_{\text{quinolone}}$, γC=O and αC=O), 1745 ν(C=O$_{\text{ester}}$), ≈ 2550 ν(H-bonded OH), 2975 ν(C—H$_{\text{aliph}}$)	1.28 (t, 3H, NCH$_2$CH$_3$), 1.42 (t, 3H, OCH$_2$CH$_3$), 3.93 (s, 2H, CO—CH$_2$—CO), 4.35 (q, 2H, NCH$_2$CH$_3$), 4.44 (q, 2H, OCH$_2$CH$_3$), 7.25—8.30 (m, 4H, H$_{\text{arom}}$), 13.50 (bs, 1H, O—H)
III	1051 ν(C—O—C), 1610 ν(C=C), 1636 ν(C=O$_{\text{quinolinone}}$), 1680 ν(C=O$_{\text{pyrone}}$), 1726 ν(C=O$_{\text{ester}}$), 2934—2977 ν(C—H$_{\text{aliph}}$)	
IV	1629 ν(C=O$_{\text{quinolinone}}$), 1729 ν(C=O$_{\text{ester}}$), 2779 ν(H-bonded OH), 2925—2972 ν(C—H$_{\text{aliph}}$), 3167 ν(N—H)	1.20 (t, 3H, NCH$_2$CH$_3$), 1.40 (t, 3H, OCH$_2$CH$_3$), 4.21 (q, 2H, NCH$_2$CH$_3$), 4.42 (q, 2H, OCH$_2$CH$_3$), 6.90—8.1 (m, 6H, H$_{\text{arom}}$, C-4—H$_{\text{pyrazoline}}$, N—H$_{\text{pyrazoline}}$), 12.5 (bs, 1H, O—H)
V	1640 ν(C=O$_{\text{quinolinone}}$), 1680 ν(C=O$_{\text{acid hydrazide}}$), ≈ 2500 ν(H-bonded OH), 3163 ν(N—H), 3420, 3300 ν(NH$_2$)	1.24 (t, 3H, NCH$_2$CH$_3$), 3.4 (bs, 2H, NH$_2$), 4.35 (q, 2H, NCH$_2$CH$_3$), 7.30–8.12 (m, 6H, H$_{\text{arom}}$ + C-4—H$_{\text{pyrazoline}}$ + N—H$_{\text{pyrazoline}}$), 10.00 (bs, 1H, N—H$_{\text{hydrazide}}$), 13.60 (bs, 1H, O—H)
VI	1634 ν(C=O$_{\text{quinolinone}}$), 1729 ν(C=O$_{\text{carboxylic}}$), ≈ 2500 ν(H-bonded OH and O—H$_{\text{carboxylic}}$), 2931—2976 ν(C—H$_{\text{aliph}}$), 3168 ν(N—H)	1.26 (t, 3H, NCH$_2$CH$_3$), 4.38 (q, 2H, NCH$_2$CH$_3$), 7.25—8.3 (m, 5H, H$_{\text{arom}}$, H$_{\text{olefin}}$), 9.6 (s, 1H, N—H$_{\text{pyrazoline}}$), 13.45 (bs, 1H, O—H$_{\text{quinolinone}}$), 15.9 (bs, 1H, O—H$_{\text{carboxylic}}$)
VII	1595—1610 ν(C=N), 1640 ν(C=O$_{\text{quinolinone}}$), ≈2500 ν(H-bonded OH), 2975 ν(C—H$_{\text{aliph}}$), 3175 ν(N—H)	1.24 (t, 3H, NCH$_2$CH$_3$), 4.30 (q, 2H, NCH$_2$CH$_3$), 7.20—8.2 (m, 6H, H$_{\text{arom}}$, 2H$_{\text{pyrazole}}$), 9.7 (s, 1H, N—H$_{\text{pyrazole}}$), 13.50 (b, 1H, O—H$_{\text{quinolinone}}$)
VIII	1587—1605 ν(C=N), 1622 ν(C=O$_{\text{quinolinone}}$), 2571 ν(H-bonded OH), 3125—3253 ν(N—H)	
IX	1044 ν(C—O—C), 1653 ν(C=O$_{\text{quinolinone}}$), 1730 ν(C=O$_{\text{ester}}$), ≈ 2660 ν(H-bonded OH), 2932—2977 ν(C—H$_{\text{aliph}}$)	
X	1640 ν(C=O$_{\text{quinolinone}}$), 1714 ν(C=O$_{\text{acid hydrazide}}$), 2601 ν(H-bonded OH), 3203 ν(N—H), 3283, 3322 ν(NH$_2$)	
XI	1580—1598 ν(C=N), 1626 ν(C=O$_{\text{quinolinone}}$), 1680 ν(C=O$_{\text{triazinone}}$), ≈2500 ν(H-bonded OH), 3170 ν(N—H)	1.23 (t, 3H, NCH$_2$CH$_3$), 4.34 (q, 2H, NCH$_2$CH$_3$), 7.25—8.11 (m, 6H, H$_{\text{arom}}$, C—H$_{\text{pyrazole}}$, C—H$_{\text{triazine}}$), 9.92 (bs, 1H, N—H$_{\text{triazine}}$), 13.62 (bs, 1H, O—H)
XII	1595—1613 ν(C=N), 1641 ν(C=O$_{\text{quinolinone}}$), 1675 ν(C=O$_{\text{triazinone}}$), ≈2600 ν(H-bonded OH), 3195 ν(N—H)	1.26 (t, 3H, NCH$_2$CH$_3$), 4.35 (q, 2H, NCH$_2$CH$_3$), 7.20—8.3 (m, 10H, H$_{\text{arom}}$ + CH$_{\text{pyrazole}}$), 9.90 (bs, 1H, NH$_{\text{triazine}}$), 13.55 (bs, 1H, O—H)
XIII	1590—1610 ν(C=N), 1641 ν(C=O$_{\text{quinolinone}}$), 1675 ν(C=O$_{\text{triazinone}}$), 2660 ν(S—H), 3165—3195 ν(N—H)	1.24 (t, 3H, NCH$_2$CH$_3$), 1.95 (bs, H, S—H), 4.34 (q, 2H, NCH$_2$CH$_3$), 7.15—8.25 (m, 5H, H$_{\text{arom}}$ + C—H$_{\text{pyrazole}}$), 10.3 (bs, 1H, N—H$_{\text{triazine}}$), 13.30 (bs, 1H, O—H)
XV	1580 ν(C=N), 1623 ν(C=O$_{\text{quinolinone}}$), 1680 ν(HNC=O), 2500 ν(H-bonded OH), 3190, 3173 ν(N—H)	
XVI	1580 ν(C=N), 1631 ν(C=O$_{\text{quinolinone}}$), 1674 ν(HNC=O), 2658 ν(H-bonded OH), 3182—3250 ν (N—H)	
XVII	1575—1600 ν(C=N), 1630 ν(C=O$_{\text{quinolinone}}$), 1726 ν(C=O$_{\text{ester}}$), ≈ 2500 ν(H-bonded OH), 2926—2976 ν(C—H$_{\text{aliph}}$)	1.24 (t, 3H, NCH$_2$CH$_3$), 1.36 (t, 3H, OCH$_2$CH$_3$), 4.19 (q, 2H, NCH$_2$CH$_3$), 4.39 (q, 2H, OCH$_2$CH$_3$), 6.92 (s, 1H, C—H$_{\text{pyrazole}}$), 7.25—8.07 (m, 9H, H$_{\text{arom}}$)
XVIII	1626 ν(C=O$_{\text{quinolinone}}$), 1676 ν(C=O$_{\text{acid hydrazide}}$), ≈ 2500 ν(H-bonded OH), 2926—2979 ν(C—H$_{\text{aliph}}$), 3260—3313, 3170 ν(NH$_2$, N—H)	1.29 (t, 3H, NCH$_2$CH$_3$), 3.28 (bs, 2H, NH$_2$), 4.41 (q, 2H, NCH$_2$CH$_3$), 7.32—8.13 (m, 10H, H$_{\text{arom}}$ + C—H$_{\text{pyrazole}}$), 10.2 (bs, 1H, N—H), 12.95 (bs, 1H, O—H)
XIXa	1165, 1221, 1278, 1369 ν(NHC=S), 1588 ν(C=N), 1643 ν(C=O$_{\text{quinolinone}}$), 1717 ν(HNC=O), 2532 ν(H-bonded OH), 2648 ν(S—H), 2951—2977 ν(C—H$_{\text{aliph}}$), 3178, 3263, 3368 ν(NH$_2$, N—H)	1.28 (t, 3H, NCH$_2$CH$_3$), 4.39 (q, 2H, NCH$_2$CH$_3$), 7.17—8.14 (m, 12H, H$_{\text{arom}}$ + C—H$_{\text{pyrazole}}$ + NH$_2$C=S), 9.4 (bs, 1H, NHC=S), 10.80 (bs, 1H, NHC=O), 12.65 (bs, 1H, O—H)

Table 3 (Continued)

Compound	IR, $\tilde{\nu}$/cm^{-1}	^{1}H NMR, δ
XIXb	1168, 1229, 1247 ν(NHC=S), 1609 ν(C=N), 1633 ν(C=O$_{quinolinone}$), 1695 ν(HNC=O), ≈ 2500 ν(H-bonded OH), 2668 ν(S—H), 2925—2990 ν(C—H$_{aliph}$), 3276, 3381 ν(N—H)	1.26 (t, 3H, NCH$_2$CH$_3$), 4.37 (q, 2H, NCH$_2$CH$_3$), 7.15–8.20 (m, 16H, H$_{arom}$ + C—H$_{pyrazole}$ + CSN—H), 9.4 (bs, 1H, CSN—H), 10.85 (bs, 1H, CON—H), 13.30 (bs, 1H, O—H)
XX	1198, 1258, 1396 ν(NHC=S), 1590—1610 ν(C=N), 1630 ν(C=O$_{quinolinone}$), ≈ 2500 ν(H-bonded OH), 3193 ν(NH)	1.21 (t, 3H, NCH$_2$CH$_3$), 4.34 (q, 2H, NCH$_2$CH$_3$), 7.20—8.10 (m, 15H, H$_{arom}$ + C—H$_{pyrazole}$), 10.6 (bs, 1H, CSN—H), 12.6 (bs, 1H, O—H)
XXI	1018, 1206 ν(C—S—C), 1627 ν(C=O$_{quinolinone}$), 2926—2977 ν(C—H$_{aliph}$), 3240 ν(N—H)	1.26 (t, 3H, NCH$_2$CH$_3$), 4.37 (q, 2H, NCH$_2$CH$_3$), 7.32–8.00 (m, 14H, H$_{arom}$), 8.65 (s, 1H, C—H$_{pyrazole}$), 12.7 (bs, 1H, N—H$_{thiadiazole}$), 13.25 (bs, 1H, O—H)
XXII	1640 ν(C=O$_{quinolinone}$), 1730 ν(C=O$_{carboxylic\ group}$), 2600 ν(H-bonded OH, the carboxylic O—H)	1.22 (t, 3H, NCH$_2$CH$_3$), 4.34 (q, 2H, NCH$_2$CH$_3$), 7.1—8.2 (m, 10H, H$_{arom}$ + C—H$_{pyrazole}$), 13.40 (bs, 1H, O—H$_{enolic}$), 15.5 (bs, 1H, O—H$_{acid}$)
XXIII	1610 ν(C=N), 1635 ν(C=O$_{quinolinone}$), ≈2555 ν(H-bonded OH), 2930—2995 ν(C—H$_{aliph}$)	1.26 (t, 3H, NCH$_2$CH$_3$), 4.33 (q, 2H, NCH$_2$CH$_3$), 7.2—8.3 (m, 11H, H$_{arom}$ + 2 × C—H$_{pyrazole}$), 13.30 (bs, 1H, O—H)
XXIV	1033, 1093 ν(C—O—C), 1608 ν(C=C), 1635 ν(C=O$_{quinolinone}$), 1667 ν(C=O$_{\gamma\text{-keto}}$), 1690 ν(C=O$_{\alpha\text{-keto}}$), 1716 ν(C=O$_{ester}$), ≈ 2607 ν(H-bonded OH), 2977 ν(C—H$_{aliph}$)	1.24 (t, 3H, NCH$_2$CH$_3$), 1.28 (t, 3H, OCH$_2$CH$_3$), 4.28 (q, 2H, NCH$_2$CH$_3$), 4.31 (q, 2H, OCH$_2$CH$_3$), 5.96 (s, 2H, OCH$_2$O), 6.62 (s, 1H, H$_{olefin}$), 6.84—8.02 (m, 7H, H$_{arom}$), 13.25 (bs, 1H, OH)
XXV	1040 ν(C—O—C), 1590—1610 ν(C=C, C=N), 1628 ν(C=O$_{quinolinone}$), 1735 ν(C=O$_{ester}$), ≈ 2571 ν(H-bonded OH), 2928—2975 ν(C—H$_{aliph}$)	1.20 (t, 3H, NCH$_2$CH$_3$), 1.25 (t, 3H, OCH$_2$CH$_3$), 4.17 (q, 2H, NCH$_2$CH$_3$), 4.34 (q, 2H, OCH$_2$CH$_3$), 5.96 (s, 2H, OCH$_2$O), 6.68—7.92 (m, 8H, H$_{arom}$ + CH$_{olefin}$), 13.20 (bs, 1H, OH)
XXVI	1036, 1077, 1213 ν(C—O—C), 1580—1610 ν(C=N, C=C), 1635 ν(C=O$_{quinolinone}$), 1678 ν(C=O$_{ketonic}$), 1734 ν(C=O$_{ester}$), ≈ 2500 ν(H-bonded OH), 2913—2982 ν(C—H$_{aliph}$), 3190—3249 ν(N—H)	1.22 (t, 3H, NCH$_2$CH$_3$), 1.36 (t, 3H, OCH$_2$CH$_3$), 3.39 (d, 1H, C-5—H$_{pyrazoline}$), 4.32 (q, 2H, NCH$_2$CH$_3$), 4.39 (q, 2H, OCH$_2$CH$_3$), 5.94 (s, 2H, OCH$_2$O), 6.53 (d, H, C-4—H$_{pyrazoline}$), 6.76–8.11 (m, 7H, H$_{arom}$), 10.20 (bs, 1H, N—H), 12.95 (bs, 1H, O—H)
XXVIII	1590—1612 ν(C=N, C=C), 1644 ν(C=O$_{quinolinone}$), ≈ 2500 ν(H-bonded OH), 2904—2969 ν(C—H$_{aliph}$), 3163—3253 ν(N—H)	1.23 (t, 3H, NCH$_2$CH$_3$), 3.65 (d, 1H, C-3—H$_{pyrazoline}$), 4.33 (q, 2H, NCH$_2$CH$_3$), 5.95 (s, 2H, OCH$_2$O), 6.67—8.06 (m, 7H, H$_{arom}$), 9.72 (bs, 1H, N—H$_{pyrazoline}$), 9.97 (bs, 1H, N—H$_{pyrazoline}$), 13.70 (bs, 1H, O—H), 13.95 (bs, 1H, O—H)

absolute ethanol (25 cm^3) were refluxed for 4 h, the product so formed during the course of the reaction was filtered off and crystallized.

N,*N*′-Bis[5-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2*H*-pyrazole-3-carbohydrazide] (*XVI*)

A mixture of compound *V* (0.01 mol) and the ester *IV* (0.01 mol) in DMF (10 cm^3) was heated under reflux for 2 h. Then, the reaction mixture was poured into cold water and the precipitate that formed was filtered off and crystallized.

Ethyl 5-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-1*H*-pyrazole-3-carboxylate (*XVII*)

Similarly, using the same method as described for preparation of compound *IV*, treatment of compound *II* with phenylhydrazine afforded compound *XVII*.

5-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (*XVIII*)

Using the same procedure as described for compounds *V* and *X*, treatment of *XVII* with hydrazine hydrate gave compound *XVIII*.

1-[5-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-1*H*-pyrazol-3-carbonyl]thiosemicarbazide (*XIXa*) and -4-phenylthiosemicarbazide (*XIXb*)

Method A. To a solution of compound *XVII* (0.01 mol) in DMF (10 cm^3) thiosemicarbazide or phenylthiosemicarbazide (0.01 mol) was added and the re-

action mixture was refluxed for 6 h. The mixture was then cooled and poured into crushed ice and the precipitate that formed was filtered off and crystallized.

Method B. To a solution of acid hydrazide *XVIII* (0.01 mol) in hydrochloric acid (10 cm^3, 10 %) and ethanol (20 cm^3) ammonium thiocyanate (0.012 mol) was added and the reaction mixture was heated under reflux for 4 h. The mixture was then poured into ice-cold water containing DMF and the obtained deposits were filtered off and crystallized to produce *XIXa*.

Method C. To a solution of compound *XVIII* (0.01 mol) in DMF (20 cm^3) phenyl isothiocyanate (0.01 mol) was added. The reaction mixture was refluxed for 2 h and then poured into ice-cold water. The precipitate so formed was filtered off and crystallized to give *XIXb*.

1-Ethyl-4-hydroxy-3-[1-phenyl-3-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-1*H*-pyrazol-5-yl]quinolin-2(1*H*)-one (*XX*)

To a solution of compound *XIXb* (0.01 mol) in ethanol (30 cm^3, 95 %) potassium hydroxide (0.015 mol) was added. The reaction mixture was heated under reflux for 4 h. The mixture was filtered and acidified with dilute hydrochloric acid. The precipitate that separated was collected by filtration and crystallized.

1-Ethyl-4-hydroxy-3-[1-phenyl-3-(5-phenylamino-1,3,4-thiadiazol-2-yl)-1*H*-pyrazol-5-yl]-quinolin-2(1*H*)-one (*XXI*)

Compound *XIXb* (0.01 mol) was heated under fusion condition with PPA for 2 h. The mass of the reaction was allowed to cool and it was poured into cold water containing sodium acetate (20 g). The solid that formed was filtered off and crystallized.

5-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1-phenyl-1*H*-pyrazole-3-carboxylic Acid (*XXII*)

Using the same method as described for compound *VI*, treatment of *XVII* with sodium hydroxide (5 %) afforded compound *XXII*.

1-Ethyl-4-hydroxy-3-(1-phenylpyrazol-5-yl)-quinolin-2(1*H*)-one (*XXIII*)

Using the same method for preparation as for compound *VII*, compound *XXII* was subjected to decarboxylation and yielded compound *XXIII*.

Ethyl 4-(1,3-Benzodioxolan-5-yl)-3-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)-2-oxobut-3-enoate (*XXIV*)

A mixture of *II* (0.01 mol), piperonal (0.01 mol), and one drop of piperidine was heated on boiling water bath for 4 h. The reaction mixture was triturated with ethanol and the solid obtained was filtered off, washed with diethyl ether and crystallized.

Ethyl 4-(1,3-Benzodioxolan-5-ylmethylene)-5-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-pyrazole-3-carboxylate (*XXV*)

To a solution of compound *XXIV* (0.01 mol) in glacial acetic acid (20 cm^3), hydrazine hydrate (0.01 mol) was added, the reaction mixture was refluxed for 4 h and poured into ice-cold water, the solid so separated was collected and crystallized.

Ethyl 5-(1,3-Benzodioxolan-5-yl)-4-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate (*XXVI*)

To a solution of compound *XXIV* (0.01 mol) in absolute ethanol, hydrazine hydrate (0.01 mol) was added and the mixture was refluxed for 4 h. The reaction mixture was then cooled and poured into cold water. The formed deposits were filtered off and crystallized.

3-[3-(1,3-Benzodioxolan-5-yl)-7-oxo-3,3a,6,7-tetrahydro-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl]-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (*XXVIII*)

Method A. A mixture of compound *XXIV* (0.01 mol) and hydrazine hydrate (0.02 mol) in absolute ethanol was refluxed for 4 h. The solid so formed was filtered off and crystallized.

Method B. A mixture of equimolar amounts of *XXVI* and hydrazine hydrate (0.01 mol) was treated with absolute ethanol. The reaction mixture was then refluxed for 4 h. The solid so formed was filtered off and crystallized.

Cellobiase Activity Test

The effect of new compounds on the activity of the enzyme cellobiase produced by *Absidia corymbifera* was estimated (Table 1) colorimetrically using the glucose-oxidase method [21]. Samples were tested as solution in DMF (100 $\mu g\ cm^{-3}$), added to an assay mixture consisting of enzyme solution (0.5 cm^3), citrate phosphate buffer (4.5 cm^3, pH = 5.0) containing 1 % cellobiase, then incubated at 40 °C for 30 min and the released glucose was determined on Spekol-11 colorimeter at λ = 505 nm.

Acknowledgements. The author thanks Dr. U. F. Ali, Department of Biological and Geological Sciences, Faculty of Education, Ain Shams University, for evaluation of enzymic activity.

REFERENCES

1. Ismail, M. M., *Chem. Pap. 55*, 242 (2001).
2. Ismail, M. M., Abass, M., and Hassan, M. M., *Phosphorus, Sulfur Silicon Relat. Elem. 167*, 275 (2000).
3. Ismail, M. M., Abass, M., and Hassan, M. M., *Molecules 5*, 1224 (2000).
4. Abass, M. and Ismail, M. M., *Chem. Pap. 54*, 187 (2000).
5. Ismail, M. M., Mohamed, E. A., and Abass, M., *Chem. Pap. 51*, 43 (1997).
6. Ismail, M. M., Abdel-Halim, A. M., and Abass, M., *J. Serb. Chem. Soc. 62*, 977 (1997).
7. Mohamed, E. A., Ismail, M. M., Gabr, Y., and Abass, M., *Chem. Pap. 48*, 285 (1994).
8. Mohamed, E. A., Ismail, M. M., Gabr, Y., Abass, M., and Farrag, H. A., *Indian J. Chem. 34B*, 21 (1995).
9. Nguyen, C. H., Marchand, C., Delage, S., Sun, I. S., Garestier, T., Helene, C., and Bisagni, E., *J. Am. Chem. Soc. 120*, 2501 (1998).
10. Takagaki, H., Yamaguchi, S., Abe, M., Sakai, M., and Misumi, O., *Eur. Pat. Appl.* EP 927, 718 (Cl.CO7D515/38) (1999); *Chem. Abstr. 131*, 73569*a* (1999).
11. Gursoy, A., Demirayak, S., Capan, G., and Erol, K., *Eur. J. Med. Chem. 35*, 359 (2000).
12. Kucukguzel, S. G., Rollas, S., Erdeniz, H., Kiraz, M., Ekinci, A. C., and Vidin, A., *Eur. J. Med. Chem. 35*, 761 (2000).
13. Eddington, N. D., Cox, D. S., Roberts, R. R., Butcher, R. J., Edaflogho, I. O., Stables, J. P., Cooke, N., Goodwin, A. M., Smith, C. A., and Scott, K. R., *Eur. J. Med. Chem. Ther. 37*(8), 635 (2002).
14. Batra, S., Srinivasan, T., Rastogi, S. K., Kundu, B., Batra, A., Bhaduri, A. P., and Dixit, M., *Bioorg. Med. Chem. Lett. 12*(22), 3349 (2002).
15. Abdel-Rahman, R. M., Seada, M., Fawazy, M., and El-Baz, I., *Pharmazie 49*, 729 (1994).
16. Abdel-Rahman, R. M., Morsy, J. M., Hanafy, F., and Amene, H. A., *Pharmazie 54*, 347 (1999).
17. Thomasco, L. M., Gadwood, R. C., and Anderson, D. J., *PCT Int. Appl. WO*, 9902,525 (1997); *Chem. Abstr. 130*, 139334*h* (1999).
18. Shirasako, T., Ishikawa, H., Yasamura, K., Jitsukawa, K., Toyama, S., Tsubouchi, H., Sudo, K., and Tsuji, K., *Eur. Pat. Appl.* EP. 435, 333 (1991); *Chem. Abstr. 115*, 279695*s* (1991).
19. Shevchenko, L. I., Kutsenko, T. A., Lozinskii, M. O., Tatarova, T. A., and Shoroded, T. M., *Fiziol. Akt. Veshchestva 21*, 18 (1989); *Chem. Abstr. 113*, 126046*g* (1990).
20. Tang, P. C., Ramphal, J. Y., and Namatolla, A. S., *PCT Int. Appl. WO*, 9827,092 (1998); *Chem. Abstr. 129*, 95500*g* (1998).
21. Trinder, P., *Ann. Chem. Biochem. 6*, 14 (1969).
22. Tomita, K., *J. Pharm. Soc. Jpn. 71*, 1100 (1951).