Synthesis and Enzymic Effect of Some Novel 1,2-Dihydro-3-(triazin-5/6-yl)benzo[*h*]quinolin-2-one Derivatives

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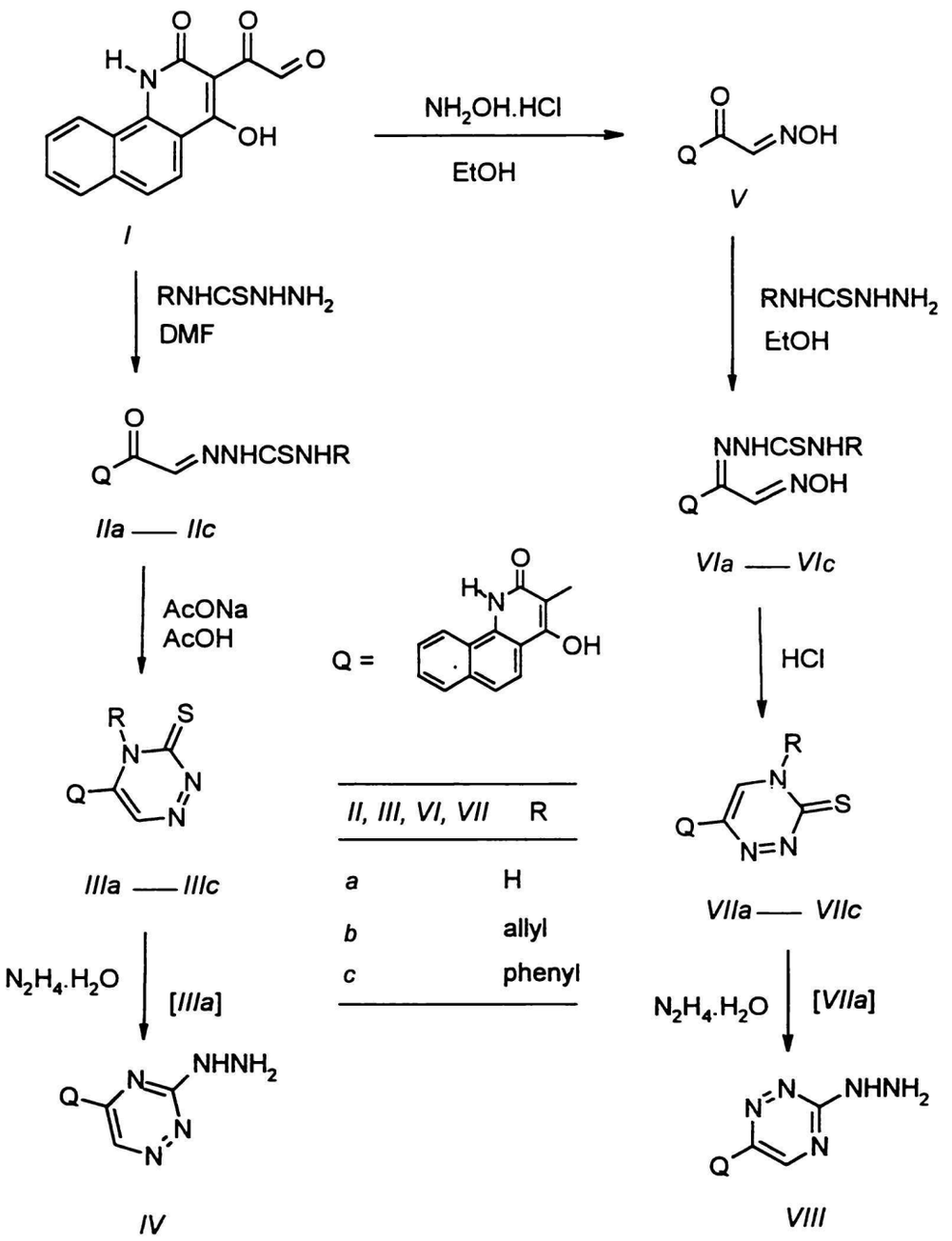
Some 3-(triazin-5/6-yl)quinolinones were obtained starting with benzoquinolylglyoxal. Hydrazinolysis of these triazines furnished hydrazinotriazines. The latter compounds were cyclized to give some triazolo/tetrazolotriazinylquinolin-2-ones. Reaction of hydrazinotriazines with formylquinoline and quinolinyl β-keto ester gave the corresponding hydrazones, which were consequently cyclized to pyrazole derivatives. All the newly prepared compounds revealed potent effect on increasing reactivity of cellobiase.

In continuation of the current research work on quinolinones bearing multiazaheterocycles as substituents at the position 3 [1—3], we report herein on the synthesis of 1,2,4-triazine as a substituent at the position 3 of benzo[*h*]quinolinone, hoping to get new category of compounds of expected biological activity. This expectation is built on what is well known about biological activity of both quinoline [4, 5] and triazine [6, 7] derivatives.

1,2-Dicarbonyl compounds are good precursors for obtaining of 1,2,4-triazines bearing different moieties at positions 5 and 6 [2, 8—10]. Therefore (1,2-dihydro-4-hydroxy-2-oxobenzo[*h*]quinolin-3-yl)glyoxal (*I*) [11] was prepared and condensed with thiosemicarbazide and/or 4-allyl/phenylthiosemicarbazide to give the mono(thiosemicarbazones) *IIa—IIc* (Scheme 1, Tables 1 and 2). In order to ascertain the structure of these α-ketothiosemicarbazones, as there are two possibilities since condensation might take place at either ketonic or aldehydic carbonyl of the glyoxal substrate, cyclization of derivatives *IIa—IIc* was carried out in the presence of anhydrous sodium acetate in glacial acetic acid to give 3-(triazin-5-yl)benzoquinolinones *IIIa—IIIc*. Hydrazinolysis of *IIIa* afforded its corresponding hydrazinotriazine derivative *IV*. To check the assumption that condensation herein took place first at the more active aldehydic carbonyl group and that the cyclization was accomplished by an addition-elimination occurring on the ketonic carbonyl group, we planned to obtain the isomeric derivatives of triazinylquinolines *IIIa—IIIc*. So we carried out condensation of compound *I* with an equimolar amount of hydroxylammonium chloride in ethanol which furnished its (benzoquinolin-3-yl)glyoxaldoxime *V*. This monoxime *V* was subjected to react with the same thiosemicarbazides (R = H, allyl, phenyl) in ethanol to give the isonitrosoacetyl thiosemicarbazones *VIa—VIc*. Cyclization of *VIa—VIc* in acidic medium furnished the isomeric derivatives of compound *III*, which were characterized as 3-(triazin-6-yl)benzoquinolinones *VIIa—VIIc*. Hydrazinolysis of compound *VIIa* gave the hydrazinotriazine *VIII*. Comparison of spectral data of both compounds *IV* and *VIII* clarified that they are of different isomeric structures and hence their precursors *IIa—IIc* and *VIa—VIc* bear thiosemicarbazono group at different carbons of glyoxal side chain. These results are in accordance with the reported ones in literature [1, 12, 13].

The preparation of azolotriazines *IX—XII* and *XIII—XV* was accomplished by selective cyclization reactions of the corresponding hydrazinotriazines *IV* and *VIII* (Scheme 2). Thus, when either hydrazinotriazines *IV* or *VIII* were treated with carbon disulfide in the presence of ethanolic potassium hydroxide, 4-hydroxy-3-(3-thioxo-2,3-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7/6-yl)-1,2-dihydrobenzo[*h*]quinolin-2-ones *IX* resp. *XIII* were obtained. The oxo isomers *X* and *XIV* of the latter triazolotriazines were obtained when compounds *IV* or *VIII* were heated under fusion conditions with diethyl carbonate. Similarly, heating hydrazinotriazines *IV* and/or *VIII* with triethyl orthoformate furnished their corresponding 3-(triazolotriazin-7/6-yl)quinolinones *XI* and/or *XV*. Tetrazolotriazines *XII* and *XVI* were also obtained by treating both compounds *IV* and *VIII* with nitrous acid at 0—5 °C. IR spectra of both compounds *XII* and *XVI* did not reveal any indication for their tautomeric azidotriazine forms.

Through our long experience on reactivity of 3-acyl-4-hydroxy-2-quinolinones towards hydrazines [14, 15], we thought that reaction of both hydrazino-



Scheme 1

triazines *IV* and *VIII* with 3-formyl-4-hydroxy-1-methyl-1,2-dihydroquinolin-2-one (*XVII*) [16] and 3-(ethoxycarbonylacetyl)-4-hydroxy-1-methyl-1,2-dihydroquinolin-2-one (*XX*) [17] might afford some interesting heterocyclic compounds including triazine and two different quinolinone moieties in addition to pyrazole ring either as fused to quinoline or isolated. To get these targeted systems, the hydrazines *IV* and *VIII* were reacted with the aldehyde *XVII* in ethanol to give their corresponding hydrazones *XVIII* and *XXIII* (Schemes 3 and 4). Cyclization of the latter hydrazones furnished the desired benzoquinolinyltriazinylpyrazoloquinolines *XIX* and *XXIV*. This cyclization was carried out using glacial acetic acid in the presence of fused sodium acetate. On the other hand, reaction of the β-keto ester *XX* with both hydrazines *IV* and *VIII* led to the formation of β-hydrazono esters *XXI* or *XXV*, which underwent smooth cyclization in glacial acetic acid to give the aimed isolated heterocyclic systems *XXII* and *XXVI*.

The effect of most of the newly prepared compounds on the activity of cellobiase, an enzyme produced by the thermotolerant fungus *Absidia corymbifera*, was studied [18]. The results showed that most

Table 1. Analytical Data of the New Compounds

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield %	M.p./°C Solvent
IIa	$C_{16}H_{12}N_4O_3S$	56.46	3.55	16.46	92	>300
	340.36	56.20	3.50	16.10		DMF
IIb	$C_{19}H_{16}N_4O_3S$	59.99	4.24	14.73	93	>300
	380.43	59.80	4.20	14.80		DMF
IIc	$C_{22}H_{16}N_4O_3S$	63.45	3.87	13.45	90	>300
	416.46	63.30	3.90	13.30		DMF
IIIa	$C_{16}H_{10}N_4O_2S$	59.62	3.13	17.38	64	250
	322.35	59.60	3.00	17.10		AcOH
IIIb	$C_{19}H_{14}N_4O_2S$	62.97	3.89	15.46	58	190
	362.41	62.70	3.80	15.50		AcOH
IIIc	$C_{22}H_{14}N_4O_2S$	66.32	3.54	14.06	55	220
	398.45	66.40	3.40	13.80		AcOH
IV	$C_{16}H_{12}N_6O_2$	60.00	3.78	26.24	66	300
	320.32	59.80	3.80	26.30		Dioxane
V	$C_{15}H_{10}N_2O_4$	63.83	3.57	9.93	89	>300
	282.26	63.80	3.50	10.00		Pyridine
VIa	$C_{16}H_{13}N_5O_3S$	54.08	3.69	19.71	85	240
	355.38	53.80	3.50	19.60		DMF
VIb	$C_{19}H_{17}N_5O_3S$	57.71	4.33	17.71	80	180
	395.44	57.40	4.30	17.50		DMF
VIc	$C_{22}H_{17}N_5O_3S$	61.24	3.97	16.23	91	>300
	431.48	61.00	3.80	16.10		DMF
VIIa	$C_{16}H_{10}N_4O_2S$	59.62	3.13	17.38	51	>300
	322.35	59.40	3.00	17.20		BuOH
VIIb	$C_{19}H_{14}N_4O_2S$	62.97	3.89	15.46	47	270
	362.41	62.70	3.90	15.30		BuOH
VIIc	$C_{22}H_{14}N_4O_2S$	66.32	3.54	14.06	49	>300
	398.45	66.10	3.40	14.10		DMF
VIII	$C_{16}H_{12}N_6O_2$	60.00	3.78	26.24	57	>300
	320.32	59.80	3.70	26.10		DMSO
IX	$C_{17}H_{10}N_6O_2S$	56.35	2.78	23.19	72	220
	362.37	56.30	2.70	23.00		AcOH
X	$C_{17}H_{10}N_6O_3$	58.96	2.91	24.27	63	290
	346.31	58.80	2.80	24.10		DMF
XI	$C_{17}H_{10}N_6O_2$	61.82	3.05	25.44	65	>300
	330.31	61.70	3.00	25.20		AcOH
XII	$C_{16}H_9N_7O_2$	58.01	2.74	29.60	83	300
	331.30	58.20	2.60	29.50		EtOH
XIII	$C_{17}H_{10}N_6O_2S$	56.35	2.78	23.19	59	260
	362.37	56.40	2.70	23.10		BuOH
XIV	$C_{17}H_{10}N_6O_3$	58.96	2.91	24.27	47	>300
	346.31	58.70	2.90	24.00		Dioxane
XV	$C_{17}H_{10}N_6O_2$	61.82	3.05	25.44	60	>300
	330.31	61.60	2.90	25.10		AcOH
XVI	$C_{16}H_9N_7O_2$	58.01	2.74	29.60	86	299 (*d*)
	331.30	57.80	2.70	29.50		Acetone
XVIII	$C_{27}H_{19}N_7O_4$	64.16	3.79	19.40	93	>300
	505.50	63.90	3.80	19.30		DMSO
XIX	$C_{27}H_{17}N_7O_3$	66.53	3.52	20.11	56	250
	487.48	66.40	3.50	19.80		DMSO
XXI	$C_{31}H_{25}N_7O_6$	62.94	4.26	16.57	83	200
	591.59	62.70	4.10	16.20		BuOH
XXII	$C_{29}H_{19}N_7O_5$	63.85	3.51	17.97	67	> 300
	545.52	63.70	3.40	17.80		DMF
XXIII	$C_{27}H_{19}N_7O_4$	64.16	3.79	19.40	88	>300
	505.50	64.00	3.80	19.30		DMSO
XXIV	$C_{27}H_{17}N_7O_3$	66.53	3.52	20.11	58	285
	487.48	66.30	3.60	19.90		DMF
XXV	$C_{31}H_{25}N_7O_6$	62.94	4.26	16.57	85	230
	591.59	62.60	4.10	16.50		BuOH
XXVI	$C_{29}H_{19}N_7O_5$	63.85	3.51	17.97	73	>300
	545.52	63.80	3.40	17.70		DMF

Table 2. Spectral Data of the New Compounds

Compound	IR, $\tilde{\nu}$/cm^{-1}	^{1}H NMR, δ
IIa	1020, 1150, 1370 ν(NHC=S), 1590—1615 ν(C=N), 1645 ν(C=O$_{quinolone}$), 1665 ν(C=O), ≈2500 ν(H-bonded OH), 3180 ν(NH), 3280, 3390 ν(NH$_2$)	7.09—8.07 (m, 7H, H$_{arom}$ + CH=N), 9.26 (b, 2H, NH$_2$), 10.20 (b, 1H, CSN—H), 11.85 (b, 1H, N—H$_{quinolone}$), 12.88 (b, 1H, O—H)
IIb	1027, 1120, 1240 ν(NHC=S), 1585—1610 ν(C=N), 1645 ν(C=O$_{quinolone}$), 1670 ν(C=O), ≈2500 ν(H-bonded OH), 2980 ν(C—H$_{aliph}$), 3170, 3210 ν(N—H)	
IIc	1025, 1120, 1240 ν(NHC=S), 1590—1615 ν(C=N), 1640 ν(C=O$_{quinolone}$), 1665 ν(C=O), ≈2500 ν(H-bonded OH), 3165, 3205 ν(N—H)	7.21—8.15 (m, 12H, H$_{arom}$ + CH=N), 10.10 (b, 1H, CSN—H), 10.25 (b, 1H, PhNHCS), 11.90 (b, 1H, N—H$_{quinolone}$), 12.65 (b, 1H, O—H)
IIIa	1027, 1120, 1245 ν(NHC=S), 1312, 1393, 1450, 1490, 1571, 1585—1615 ν(C=N), 1645 ν(C=O$_{quinolone}$), 2860—3167 ν(N—H, O—H)	7.11—8.10 (m, 7H, H$_{arom}$ + 6-H$_{triazine}$), 10.90 (b, 1H, CSN—H), 11.03 (b, 1H, CON—H), 12.80 (b, 1H, O—H)
IIIb	1020, 1125, 1270 ν(NHC=S), 1590, 1610 ν(C=N), 1647 ν(C=O$_{quinolone}$), 2800—2995 ν(C—H$_{aliph}$), 3170, 3190 ν(N—H)	
IIIc	1022, 1120, 1370 ν(NHC=S), 1585—1610 ν(C=N), 1646 ν(C=O$_{quinolone}$), 3170—3195 ν(N—H)	7.22—8.15 (m, 12H, H$_{arom}$ + 6-H$_{triazine}$), 11.60 (b, 1H, CON—H), 12.73 (b, 1H, O—H)
IV	1590—1605 ν(C=N), 1650 ν(C=O), ≈2560 ν(H-bonded OH), 3170—3400 ν(N—H, NH$_2$)	6.42 (s, 2H, NH$_2$), 7.25—8.20 (m, 7H, H$_{arom}$ + 6-H$_{triazine}$), 8.45 (b, 1H, N—H$_{hydrazine}$), 11.79 (b, 1H, CON—H), 12.85 (b, 1H, O—H)
V	1585—1615 ν(C=N), 1650 ν(C=O$_{quinolone}$), 1670 ν(C=O$_{acetyl}$), ≈2560 ν(H-bonded OH), 3190 ν(N—H)	7.10—8.12 (m, 7H, H$_{arom}$ + CH=N), 11.25 (b, 1H, CON—H), 12.80 (b, 1H, O—H$_{quinolinol}$), 13.42 (b, 1H, O—H$_{oxime}$)
VIa	1020, 1130, 1250 ν(NHC=S), 1585—1615 ν(C=N), 1655 ν(C=O), ≈2500 (H-bonded OH), 3180—3395 ν(N—H, NH$_2$)	7.20—8.05 (m, 7H, H$_{arom}$ + CH=N), 9.20 (b, 2H, NH$_2$), 10.30 (b, 1H, CSN—H), 11.25 (b, 1H, CON—H), 12.75 (b, 1H, O—H$_{quinolinol}$), 13.35 (b, 1H, O—H$_{oxime}$)
VIb	1026, 1120, 1230 ν(NHC=S), 1580—1610 ν(C=N), 1660 ν(C=O), ≈2500 ν(H-bonded OH), 2900—2985 ν(C—H$_{aliph}$), 3170—3195 ν(N—H)	
VIc	1020, 1120, 1240 ν(NHC=S), 1585—1610 ν(C=N), 1657 ν(C=O), ≈2500 ν(H-bonded OH), 3165—3190 ν(N—H)	7.25—8.15 (m, 12H, H$_{arom}$ + CH=N), 10.15 (b, 1H, CSN—H), 10.40 (b, 1H, PhNHCS), 11.55 (b, 1H, CON—H), 12.70 (b, 1H, O—H$_{quinolinol}$), 13.30 (b, 1H, O—H$_{oxime}$)
VIIa	1020, 1122, 1245 ν(NHC=S), 1590—1605 ν(C=N), 1645 ν(C=O), ≈2500 ν(H-bonded OH), 3175, 3195 ν(N—H)	7.08—8.10 (m, 7H, H$_{arom}$ + 5-H$_{triazine}$), 10.20 (b, 1H, CSN—H), 11.30 (b, 1H, CON—H), 12.87 (b, 1H, O—H)
VIIb	1025, 1120, 1240 ν(NHC=S), 1595-1615 ν(C=N), 1645 ν(C=O), ≈2500 ν(H-bonded OH), 2860—2990 ν(C—H$_{aliph}$), 3180 ν(N—H)	4.69 (d, 2H, N—CH$_2$), 5.47 (d, 2H, CH=C*H*$_2$), 5.86 (m, 1H, C*H*=CH$_2$), 7.20—8.05 (m, 7H, H$_{arom}$ + 5-H$_{triazine}$), 10.80 (b, 1H, CON—H), 12.27 (b, 1H, O—H)
VIIc	1023, 1125, 1250 ν(NHC=S), 1590—1610 ν(C=N), 1650 ν(C=O), 3175 ν(N—H)	
VIII	1595—1610 ν(C=N), 1655 ν(C=O) ≈2500 ν(H-bonded OH), 3170—3220, 3390 ν(N—H, NH$_2$)	6.80 (s, 2H, NH$_2$), 7.20—8.15 (m, 7H, H$_{arom}$ + 5-H$_{triazine}$), 8.54 (b, 1H, N—H$_{hydrazine}$), 11.75 (b, 1H, CON—H), 12.73 (b, 1H, O—H)
IX	1020, 1130, 1270 ν(NHC=S), 1580—1610 ν(C=N), 1650 ν(C=O) ≈2500 (H-bonded OH), 3175—3240 ν(N—H)	7.09—8.29 (m, 7H, H$_{arom}$ + 6-H$_{triazine}$), 9.19 (b, 1H, N—H$_{triazole}$), 10.89 (b, 1H, CON—H), 12.70 (b, 1H, O—H)
X	1585—1605 ν(C=N), 1645 ν(C=O$_{quinolone}$), 1655 ν(C=O$_{triazolone}$), ≈2500 ν(H-bonded OH), 3165—3210 ν(N—H)	7.12—8.18 (m, 7H, H$_{arom}$ + 6-H$_{triazine}$), 9.83 (b, 1H, N—H$_{triazole}$), 10.85 (b, 1H, CON—H), 12.63 (b, 1H, O—H)
XI	1585—1615 ν(C=N), 1645 ν(C=O$_{quinolone}$), ≈2500 ν(H-bonded OH), 3185 ν(N—H)	7.26—8.07 (m, 7H, H$_{arom}$ + 6-H$_{triazine}$), 8.83 (s, 1H, H$_{triazole}$), 10.95 (b, 1H, CON—H), 12.80 (b, 1H, O—H)
XII	1000—1100 ν(tetrazole ring vib.), 1595—1615 ν(C=N), 1650 ν(C=O), ≈2500 ν(H-bonded OH), 3180 ν(N—H)	7.07—7.95 (m, 6H, H$_{arom}$), 8.33 (s, 1H, H$_{triazine}$), 11.22 (b, 1H, CON—H), 12.85 (b, 1H, O—H)
XIII	1020, 1130, 1245 ν(NHC=S), 1590—1605 ν(C=N), 1655 ν(C=O), ≈2500 ν(H-bonded OH), 3175 ν(N—H)	7.26—7.90 (m, 7H, H$_{arom}$ + 5-H$_{triazine}$), 9.32 (b, 1H, CSN—H), 10.85 (b, 1H, CON—H), 12.70 (b, 1H, O—H)

Table 2. (Continued)

Compound	IR, $\tilde{\nu}$/cm^{-1}	^{1}H NMR, δ
XIV	1890—1610 ν(C=N), 1647 ν(C=O$_{quinolinone}$), 1660 ν(C=O$_{triazolidinone}$), ≈2500 ν(H-bonded OH), 3170—3220 ν(N—H)	7.08—8.10 (m, 7H, H$_{arom}$ + 5-H$_{triazine}$), 10.20 (b, 1H, N—H$_{triazole}$), 11.30 (b, 1H, N—H$_{quinolone}$), 12.63 (b, 1H, O—H)
XV	1580—1610 ν(C=N), 1645 ν(C=O), ≈2500 ν(H-bonded OH), 3175 ν(N—H)	7.09—8.12 (m, 7H, H$_{arom}$ + 5-H$_{triazine}$), 8.49 (s, 1H, H$_{triazole}$), 10.80 (b, 1H, CON—H), 12.80 (b, 1H, O—H)
XVI	1000—1100 ν(tetrazolo ring vib.), 1590—1610 ν(C=N), 1655 ν(C=O), ≈2500 ν(H-bonded OH), 3175 ν(N—H)	7.07—8.05 (m, 6H, H$_{arom}$), 8.33 (s, 1H, H$_{triazine}$), 10.95 (b, 1H, CON—H), 12.72 (b, 1H, O—H)
XVIII	1585—1615 ν(C=N), 1645, 1655 ν(C=O), ≈2500 ν(H-bonded OH), 2800—2990 ν(C—H$_{aliph}$), 3160—3230 ν(N—H)	3.67 (s, 3H, N—CH$_3$), 7.05—8.15 (m, 1H, H$_{arom}$ + 6-H$_{triazine}$), 8.54 (s, 1H, CH=N), 9.30 (b, 1H, N—H$_{hydrazone}$), 11.20 (b, 1H, CON—H), 11.82 (b, 1H, O—H), 12.41 (b, 1H, O—H)
XIX	1585—1610 ν(C=N), 1640, 1655 ν(C=O), ≈2500 ν(H-bonded OH), 2840—2995 ν(C—H$_{aliph}$), 3210 ν(N—H)	3.65 (s, 3H, N—CH$_3$), 7.10—8.15 (m, 11H, H$_{arom}$ + H$_{pyrazole}$), 8.38 (s, 1H, 6-H$_{triazine}$), 10.83 (b, 1H, CON—H), 12.48 (b, 1H, O—H)
XXI	1120 ν(C—O—C), 1580—1615 ν(C=N), 1645, 1660 ν(C=O$_{quinolone}$), 1735 ν(C=O$_{ester}$), ≈2500 ν(br H-bonded OH), 2860—2995 ν(C—H$_{aliph}$), 3185—3210 ν(N—H)	1.44 (t, 3H, OCH$_2$—C*H*$_3$), 2.95 (s, 2H, C*H*$_2$CO$_2$Et), 3.68 (s, 3H, N—CH$_3$), 4.40 (q, 2H, OC*H*$_2$—CH$_3$), 7.20—8.15 (m, 10H, H$_{arom}$), 8.30 (s, 1H, 6-H$_{triazine}$), 8.95 (b, 1H, N—H$_{hydrazone}$), 10.84 (b, 1H, CON—H), 11.89 (b, 1H, O—H), 12.45 (b, 1H, O—H)
XXII	1585—1610 ν(C=N), 1647—1655 ν(C=O$_{quinolone}$), 1660 ν(C=O$_{pyrazolone}$), ≈2600 ν(H-bonded OH), 2880—2995 ν(C—H$_{aliph}$), 3190 ν(N—H)	3.20 (s, 2H, CH$_{2pyrazolone}$), 3.65 (s, 3H, N—CH$_3$), 7.05—8.13 (m, 10H, H$_{arom}$), 8.45 (s, 1H, 6-H$_{triazine}$), 10.80 (b, 1H, CON—H), 11.85 (b, 1H, O—H), 12.50 (b, 1H, O—H)
XXIII	1590—1615 ν(C=N), 1645, 1655 ν(C=O), ≈2500 ν(H-bonded OH), 2900—2990 ν(C—H$_{aliph}$), 3175—3210 ν(br N—H)	3.68 (s, 3H, N—CH$_3$), 7.05—8.20 (m, 11H, H$_{arom}$ + 5-H$_{triazine}$), 8.40 (s, 1H, CH=N), 9.40 (b, 1H, N—H$_{hydrazone}$), 11.18 (b, 1H, CON—H), 11.85 (b, 1H, O—H), 12.65 (b, 1H, O—H)
XXIV	1590—1605 ν(C=N), 1645, 1655 ν(C=O), ≈2560 ν(H-bonded OH), 2900—2995 ν(C—H$_{aliph}$), 3195 ν(N—H)	3.60 (s, 3H, CH$_3$), 7.08—8.18 (m, 11H, H$_{arom}$ + H$_{pyrazole}$), 8.41 (s, 1H, 6-H$_{triazine}$), 10.90 (b, 1H, CON—H), 12.45 (b, 1H, O—H)
XXV	1120 ν(C—O—C), 1585—1610 ν(C=N), 1645, 1655 ν(C=O$_{quinolone}$), 1730 ν(C=O$_{ester}$), ≈2600 ν(H-bonded OH), 2890—2990 ν(C—H$_{aliph}$), 3170—3200 ν(N—H)	1.35 (t, 3H, OCH$_2$—C*H*$_3$), 2.90 (s, 2H, C*H*$_2$CO$_2$Et), 3.60 (s, 3H, N—CH$_3$), 4.42 (q, 2H, OC*H*$_2$—CH$_3$), 7.15—8.16 (m, 10H, H$_{arom}$), 8.34 (s, 1H, 5-H$_{triazine}$), 8.85 (b, 1H, N—H$_{hydrazone}$), 10.80 (b, 1H, CON—H), 11.75 (b, 1H, O—H), 12.62 (b, 1H, O—H)
XXVI	1585—1610 ν(C=N), 1645, 1660 ν(C=O), ≈2550 ν(H-bonded OH), 2880—2900 ν(C—H$_{aliph}$), 3195 ν(N—H)	3.24 (s, 2H, CH$_{2pyrazolone}$), 3.68 (s, 3H, N—CH$_3$), 7.15—8.10 (m, 10H, H$_{arom}$), 8.38 (s, 1H, 5-H$_{triazine}$), 11.20 (b, 1H, CON—H), 11.65 (b, 1H, O—H), 12.48 (b, 1H, O—H)

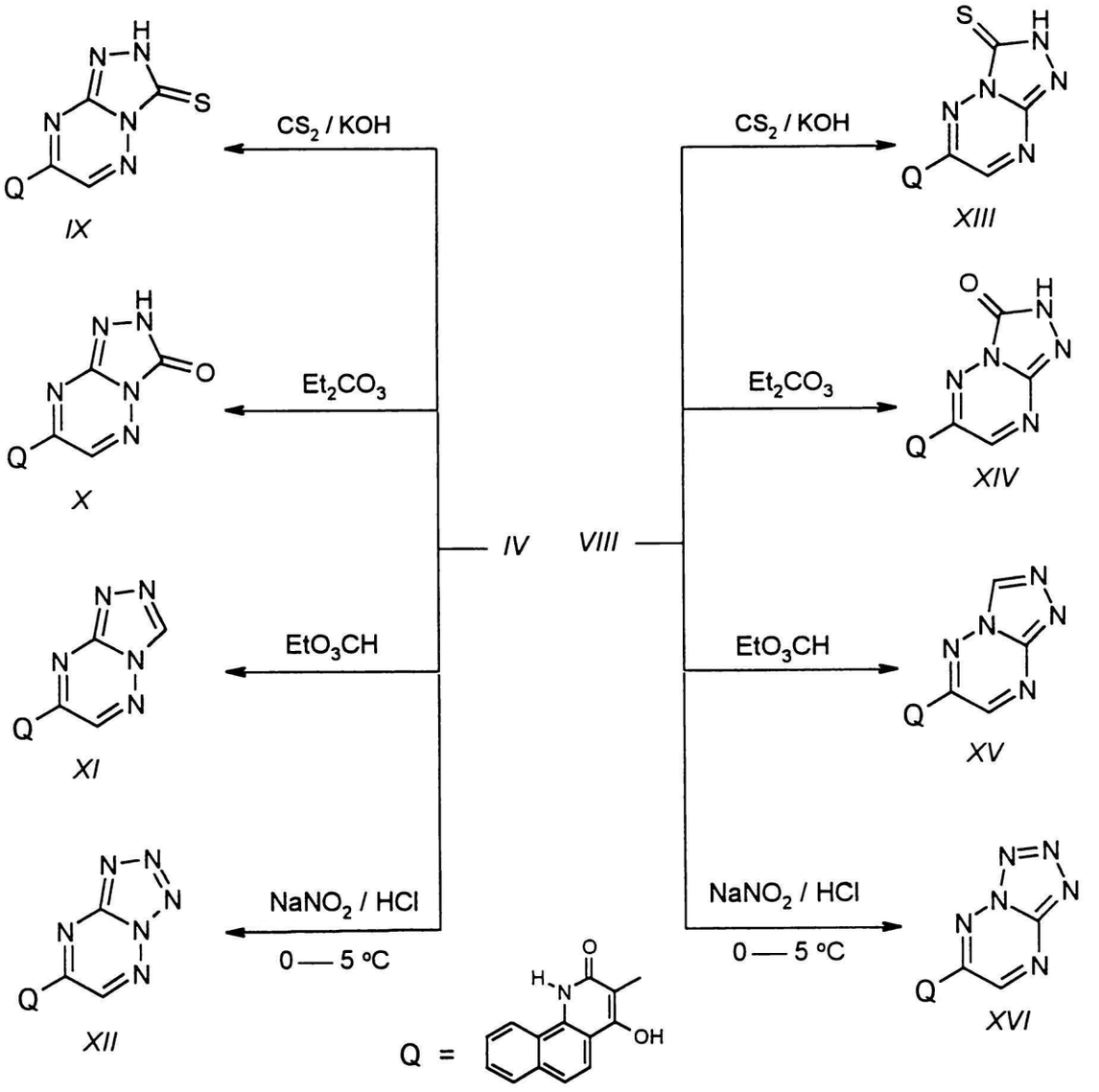
of the tested compounds enhanced the effect of the enzyme in the production of glucose (1.22—1.97 μg cm^{-3}). Surprisingly the starting compound *I* revealed much higher activity (2.03 μg cm^{-3}). These results also showed that *N*-unsubstituted triazines *IIIa* and *VIIa* have lesser promotional effect on cellobiase than their substituted derivatives *IIIb*, *IIIc* and *VIIb*, *VIIc* (Table 3).

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes on Gallenkemp MFB-595 apparatus. IR spectra were taken on a Perkin—Elmer FTIR 1650 spectrophotometer, using samples in KBr disks. ^{1}H NMR spectra were measured on Jeol FX-90 spectrometer at 90 MHz, using DMSO-d_6 as solvent and TMS as internal standard. Elemental analyses were performed on a Perkin—Elmer CHN-2400 analyzer. The synthesis of compound *I* was previously described [11, 13]. Analytical and spectral data are listed in Tables 1 and 2.

2-(4-Hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)-2-oxoacetaldehyde Thiosemicarbazones *IIa—IIc*

A mixture of compound *I* (0.1 mol) and the proper thiosemicarbazide (0.1 mol) in DMF (100 cm^3) was heated under reflux for 3 h. The reaction mixture was then left to cool and the crystalline product so formed was collected by filtration and recrystallized.



Scheme 2

4-Hydroxy-3-(3-thioxo-3,4-dihydro[1,2,4]triazin-5-yl)-1,2-dihydrobenzo[*h*]quinolin-2-ones *IIIa*—*IIIc*

A mixture of the appropriate thiosemicarbazone *IIa*—*IIc* (0.05 mol), anhydrous sodium acetate (0.1 mol), and glacial acetic acid (100 cm^3) was heated under reflux for 4 h. The mixture was poured into crushed ice and the resulting canary yellow deposit that formed was filtered off and crystallized.

4-Hydroxy-3-(3-hydrazino[1,2,4]triazin-5-yl)-1,2-dihydrobenzo[*h*]quinolin-2-one (*IV*)

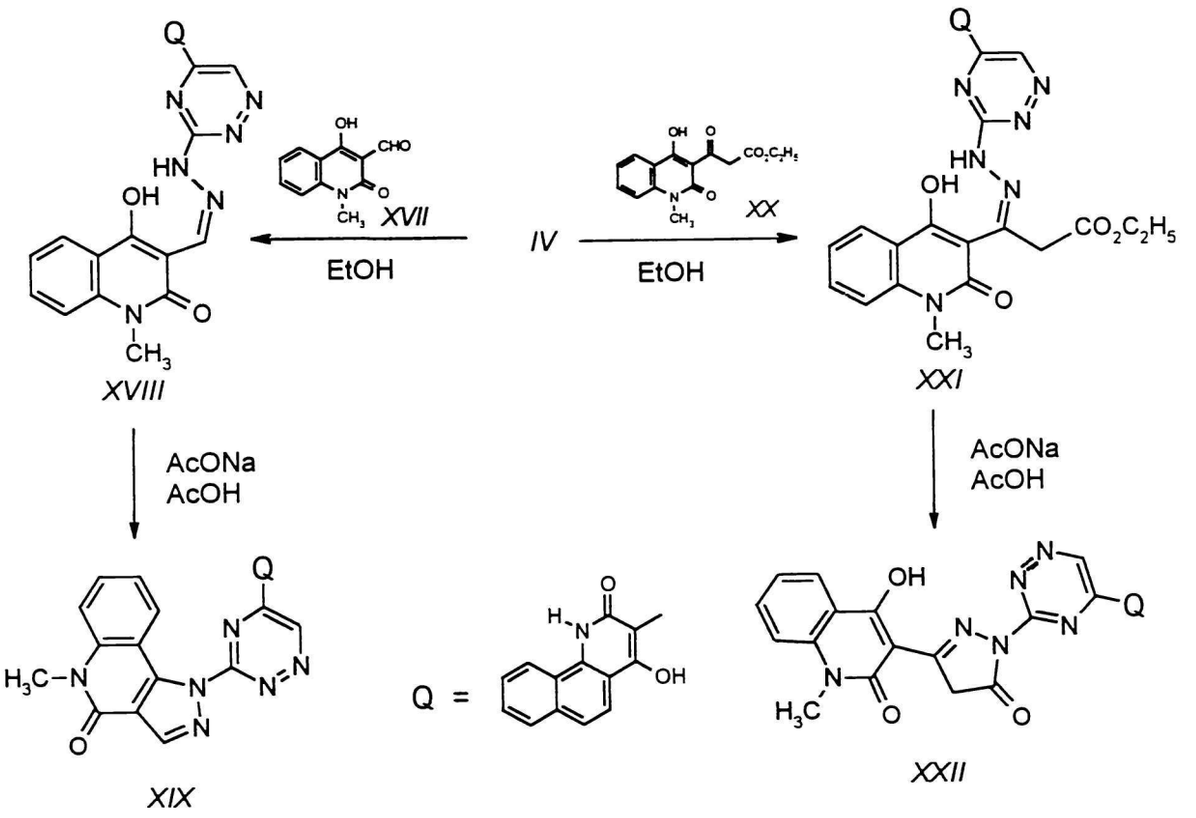
To a solution of compound *IIIa* (0.025 mol) in DMF (100 cm^3) hydrazine hydrate (0.05 mol) was added and the mixture was refluxed for 2 h. Then the mixture was left to cool and the separated material was filtered off and recrystallized.

4-Hydroxy-3-(isonitrosoacetyl)-1,2-dihydrobenzo[*h*]quinolin-2-one (*V*)

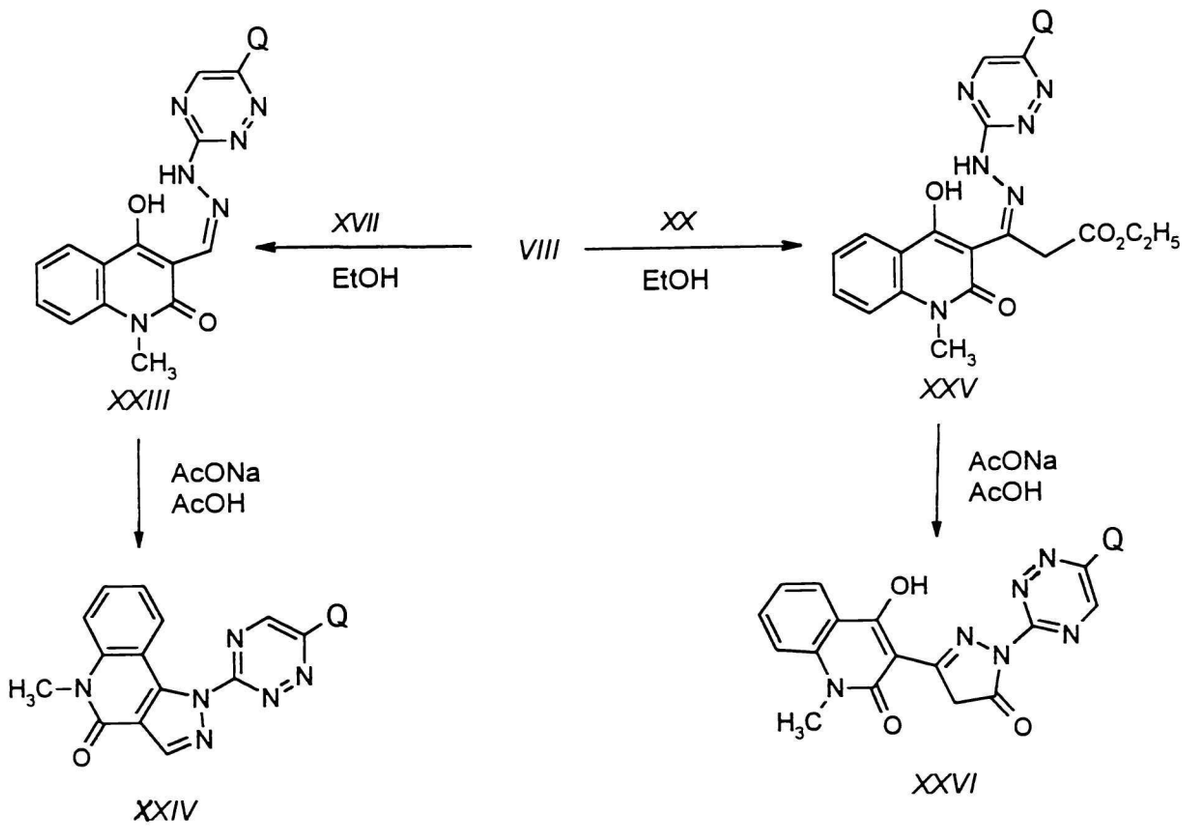
Equimolar amounts (0.05 mol) of compound *I* and hydroxylammonium chloride in absolute ethanol (50 cm^3) were heated under reflux for 3 h. The yellow deposits which formed on hot were filtered off and recrystallized.

4-Hydroxy-3-[1-(4-R-thiosemicarbazono)-2-oximoethyl]-1,2-dihydrobenzo[*h*]quinolin-2-ones *VIa*—*VIc*

A mixture of isonitrosoacetyl derivative *V* (0.02



Scheme 3



Scheme 4

Table 3. Effect of New Compounds on Activity of Cellobiase*

Compound	ρ (Glucose) / μg cm^{-3}	Compound	ρ (Glucose) / μg cm^{-3}
I	2.03	*XI*	1.97
IIIa	1.32	*XII*	1.89
IIIb	1.56	*XIII*	1.54
IIIc	1.52	*XIV*	1.76
IV	1.22	*XV*	1.88
V	1.37	*XVI*	1.83
VIa	1.55	*XVIII*	1.95
VIb	1.86	*XIX*	1.49
VIc	1.74	*XXI*	1.54
VIIa	1.49	*XXII*	1.39
VIIb	1.70	*XXIII*	1.74
VIIc	1.66	*XXIV*	1.52
VIII	1.71	*XXV*	1.63
IX	1.59	*XXVI*	1.46
X	1.78	Control**	0.28

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

mol) and the proper thiosemicarbazide (0.02 mol) in ethanol (25 cm^3) was refluxed for 2—4 h. The solid material that formed was filtered off and recrystallized.

4-Hydroxy-3-(3-thioxo-3,4-dihydro[1,2,4]triazin-6-yl)-1,2-dihydrobenzo[*h*]quinolin-2-ones *VIIa*—*VIIc*

A suspension of the proper derivative *VIa*—*VIc* (0.01 mol) in ethanol (10 cm^3) and hydrochloric acid (25 cm^3, 6 M-HCl) was heated under reflux for 6 h. Then the mixture was neutralized using sodium carbonate till complete precipitation. The solid so formed was filtered off and crystallized.

4-Hydroxy-3-(3-hydrazino[1,2,4]triazin-6-yl)-1,2-dihydrobenzo[*h*]quinolin-2-one (*VIII*)

From triazinylquinoline *VIIa* and hydrazine hydrate, compound *VIII* was obtained using the same method as described for compound *IV*.

4-Hydroxy-3-(3-thioxo-2,3-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7/6-yl)-1,2-dihydrobenzo[*h*]quinolin-2-ones (*IX* and *XIII*)

An ethanolic potassium hydroxide solution (25 cm^3 containing 0.02 mol of KOH) was added to a mixture of hydrazinotriazine *IV* or *VIII* (0.01 mol) and carbon disulfide (10 cm^3). The mixture was then heated under reflux on a boiling water bath for 12 h. After that the excess carbon disulfide was removed in vacuum and the solid residue thus obtained was dissolved in water, filtered off from insoluble materials and acidified using dilute hydrochloric acid till complete precipitation. The obtained deposits were filtered off and crystallized.

4-Hydroxy-3-(3-oxo-2,3-dihydro[1,2,4]triazolo-[4,3-*b*][1,2,4]triazin-7/6-yl)-1,2-dihydrobenzo[*h*]-quinolin-2-ones (*X* and *XIV*)

A mixture of the hydrazinotriazine *IV* or *VIII* (0.01 mol) and diethyl carbonate (0.1 mol) was heated at 110—120 °C using a short air condenser so that the formed ethanol escaped freely for *ca.* 30 min. The pasty solid so obtained was triturated with cold ethanol (20 cm^3), filtered off and recrystallized.

4-Hydroxy-3-([1,2,4]triazolo[4,3-*b*][1,2,4]triazin-7/6-yl)-1,2-dihydrobenzo[*h*]quinolin-2-ones (*XI* and *XV*)

To a suspension of the hydrazinotriazine *IV* or *VIII* (0.01 mol) in ethylene glycol (10 cm^3) triethyl orthoformate (0.015 mol) was added and heated at 110—120 °C in a conical flask for *ca.* 20 min. Then the temperature was raised gradually to ≈ 160—170 °C for *ca.* 20 min. Then the reaction mixture was cooled and triturated with cold methanol (10 cm^3) to give a solid precipitate that was filtered off and crystallized.

4-Hydroxy-3-([1,2,3,4]tetrazolo[1,5-*b*][1,2,4]-triazin-7/6-yl)-1,2-dihydrobenzo[*h*]quinolin-2-ones (*XII* and *XVI*)

To a solution of the hydrazine derivative *IV* or *VIII* (0.01 mol) in hydrochloric acid (10 cm^3, 2 M-HCl) aqueous sodium nitrite solution (10 cm^3, 1 M-$NaNO_2$) was dropwise added with continuous stirring at 0—5 °C. The precipitate that formed was collected by filtration and crystallized.

Hydrazones *XVIII*, *XXI*, *XXIII*, and *XXV*

Equimolar amounts (0.01 mol) of the hydrazines *IV* or *VIII* and the aldehyde *XVII* or the β-keto ester *XX* in ethanol (50 cm^3) were heated under reflux for 1—2 h. The solid product so formed during the course of reaction was collected by suction filtration and crystallized.

Pyrazoloquinolones *XIV* and *XIX* and Pyrazolylquinolones *XXII* and *XXVI*

A mixture of the hydrazone derivative *XVIII*, *XXI*, *XXIII* or *XXV* (0.005 mol) and fused sodium acetate (0.01 mol) in glacial acetic acid (50 cm^3) was heated under reflux for 3—5 h. The yellow-orange crystalline deposits, which formed during the course of reaction, were filtered off while hot and washed with ethanol (25 cm^3). The residue was collected and recrystallized.

Cellobiase Activity Test

The effect of new compounds on the activity of the enzyme cellobiase produced by *Absidia corymbifera* was estimated colorimetrically using the glucose-oxidase method [18]. Samples were tested as solution in DMF (100 μg 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 colorimeter at λ = 505 nm.

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