QUINAZOLINONE DERIVATIVES OF BIOLOGICAL INTEREST V. NOVEL 4(3*H*)-QUINAZOLINONES WITH SEDATIVE-HYPNOTIC, ANTICONVULSANT AND ANTIINFLAMMATORY ACTIVITIES*

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2-Methyl-4(3*H*)-quinazolinones carrying alkyl, cykloalkyl, aralkyl or aryl substituents at N-3 of the quinazolinone ring exhibit analgetic, antipyretic and antiinflammatory activities comparable to those of aspirin and phenylbutazone[1-4]. In our previous work[5-8], various 4(3*H*)-quinazolinone derivatives were prepared. The present communication is a continuation of our efforts in this field.

EXPERIMENTAL

The melting points were determined on Electrothermal melting point apparatus and are uncorrected. IR spectra (KBr disks) were recorded on Pye Unicam SP 1000 infrared spectrophotometer. ^{1}H NMR spectra ($CDCl_3$ unless otherwise stated) were run on EM-390 (90 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were performed on Shimadzu QP 1000 EX spectrometer. Elemental microanalyses were done with Perkin–Elmer, 240 C Elemental analyzer at Department of Chemistry, Faculty of Science, University of Assiut.

Synthesis of Compounds *IIIa*, *IIIb*

To a mechanically stirred suspension of N-chloroacetylanthranilic acid *I* (refs[9,10]) (0.02 mol) and ethyl *p-aminobenzoate IIa* (0.02 mol) in dry toluene (120 ml), phosphorus trichloride (2 ml in 20 ml dry toluene) was added dropwise over a period of 30 min. The reaction mixture was then refluxed in an oil bath at 120 – 130 °C for 3 h. The solvent was distilled in vacuo and the cold residue was poured onto a solution of sodium bicarbonate (5%, 50 ml). The precipitated solid was filtered, washed with water, dried and crystallized from benzene–ethanol (2 : 1) to afford *IIIa* (76% yield), m.p. 216 – 217 °C (as reported ref.[5]).

Compound *IIIb* was obtained by the same procedure using methyl *p*-aminosalicylate *IIb* and xylene as a solvent instead of toluene. Crystallization from benzene–ethanol afforded *IIIb* (74% yield), m.p.

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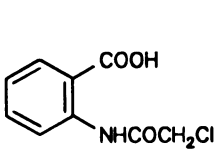
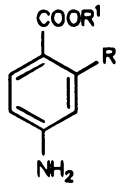
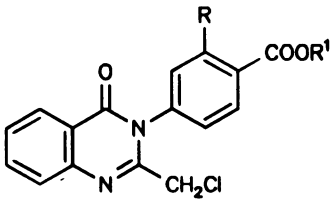


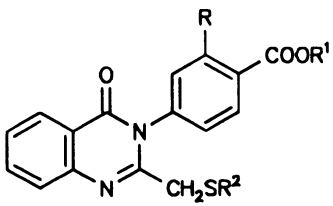
I



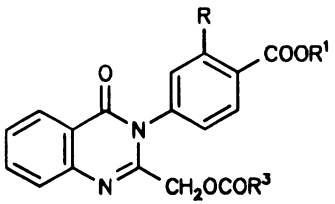
IIa, b



IIIa, b



IV – IX



X, XI

In formulae *II*, *III* : *a*, R = H; $R^1 = C_2H_5$

b, R = OH; $R^1 = C_2H_5$

	R	R^1	R^2		R	R^1	R^3
IVa	H	C_2H_5	C_6H_5	*Xa*	H	C_2H_5	CH_3
IVb	OH	CH_3	C_6H_5	*Xb*	OH	CH_3	CH_3
Va	H	C_2H_5	$CH_2C_6H_5$	*XIa*	H	C_2H_5	C_2H_5
Vb	OH	CH_3	$CH_2C_6H_5$	*XIb*	OH	CH_3	C_2H_5
VIa	H	C_2H_5	CH_2COOH				
VIb	OH	CH_3	CH_2COOH				
VIIa	H	C_2H_5	CH_2CH_2COOH				
VIIb	OH	CH_3	CH_2CH_2COOH				
VIIIa	H	C_2H_5	$CH(CH_3)COOH$				
VIIIb	OH	CH_3	$CH(CH_3)COOH$				
IXa	H	C_2H_5	CH_2CH_2OH				

TABLE I
Physicochemical data of 2,3-disubstituted-4(3*H*)-quinazolinones

Compound	M. p., °C Yield, %	Formula (M. w.)	Calculated/Found		
			% C	% H	% N
IVa	153 – 154	$C_{24}H_{20}N_2O_3S$	69.22	4.84	6.72
	79	(416.4)	69.19	5.27	6.63
IVb	187 – 188	$C_{23}H_{18}N_2O_4S$	66.02	4.34	6.69
	75	(418.4)	66.34	4.64	6.77
Va	166 – 167	$C_{25}H_{22}N_2O_3S$	69.75	5.15	6.51
	81	(430.4)	70.19	5.46	6.60
Vb	133 – 134	$C_{24}H_{20}N_2O_4S$	66.66	4.66	6.48
	73	(432.4)	66.66	4.58	6.60
VIa	187 – 188	$C_{20}H_{18}N_2O_5S$	60.30	4.56	7.03
	78	(398.4)	59.22	4.53	7.57
VIb	201 – 202	$C_{19}H_{16}N_2O_6S$	57.00	4.03	6.99
	67	(400.3)	57.33	4.35	7.11
VIIa	205 – 206	$C_{21}H_{20}N_2O_5S$	61.16	4.89	6.79
	81	(412.4)	60.88	5.19	6.46
VIIb	198 – 199	$C_{20}H_{18}N_2O_6S$	57.97	4.38	6.78
	69	(414.4)	58.06	4.84	6.58
VIIIa	190 – 191	$C_{21}H_{20}N_2O_5S$	61.16	4.89	6.79
	69	(412.4)	61.38	5.12	6.67
VIIIb	201 – 202	$C_{20}H_{18}N_2O_6S$	57.97	4.38	6.76
	66	(414.4)	58.13	4.12	6.75
IXa	160 – 161	$C_{20}H_{20}N_2O_4S$	62.49	5.25	7.29
	75	(384.4)	61.78	5.54	7.12
Xa	144 – 145	$C_{20}H_{18}N_2O_5$	65.57	4.95	7.64
	82	(366.3)	65.29	5.00	7.67
Xb	148 – 149	$C_{19}H_{16}N_2O_6$	61.96	4.38	7.60
	81	(368.3)	62.12	4.19	7.87
XIa	267 – 268	$C_{21}H_{20}N_2O_5$	66.31	5.30	7.37
	83	(380.4)	66.61	4.95	7.31
XIb	166 – 167	$C_{20}H_{18}N_2O_6$	62.82	4.75	7.32
	83	(382.3)	63.13	4.61	7.35

172 – 173 °C. IR spectrum: 750, 780, 810, 830, 1 040, 1 450, 1 580 (aromatic); 1 600 (C=N); 1 660 (amide C=O); 1 705 (ester C=O); 2 900 (aliph.-H); 3 080 (Ar-H); 3 350, 3 600 (OH). ^{1}H NMR spectrum: 10.80 s, 1 H (Ar-OH, exchangeable with D_2O); 8.22 – 6.80 m, 7 H (H-5, H-6, H-7, H-8, H-3',

TABLE II
^{1}H NMR spectral data of 2,3-disubstituted-4(3*H*)-quinazolinones

Compound	Chemical shifts (δ values)
IVa	8.22 – 7.00 m, 13 H (Ar–H), 4.34 q, 2 H ($COOCH_2CH_3$, J = 7.40); 3.78 s, 2 H ($Ar-CH_2-S$); 1.38 t, 3 H ($COOCH_2CH_3$, J = 7.30)
IVb	10.80 s, 1 H (OH); 8.25 – 6.70 m, 12 H (Ar–H); 3.90 s, 3 H ($COOCH_3$); 3.85 s, 2 H ($Ar-CH_2-S$)
Va	8.25 – 7.00 m, 13 H (Ar–H); 4.35 q, 2 H ($COOCH_2CH_3$, J = 7.35); 3.72 s, 2 H ($Ar-CH_2-S$); 3.25 s, 2 H ($S-CH_2-Ph$); 1.35 t, 3 H ($COOCH_2CH_3$, J = 7.50)
Vb	10.70 s, 1 H (OH, exchangeable with D_2O); 8.20 – 6.65 m, 12 H (Ar–H); 3.90 s, 3 H ($COOCH_3$); 3.72 s, 2 H ($Ar-CH_2-S$); 3.28 s, 2 H ($S-CH_2-Ph$)
VIa	8.60 m, 8 H (Ar–H); 4.55 q, ($COOCH_2CH_3$, J = 7.40); 4.15 s, 2 H ($Ar-CH_2-S$); 3.65 s, 2 H ($S-CH_2COOH$); 1.52 t, 3 H ($COOCH_2CH_3$, J = 7.40)
VIIa	8.55 – 7.55 m, 8 H (Ar–H); 4.55 q, 2 H ($COOCH_2CH_3$, J = 7.30); 4.05 s, 2 H ($Ar-CH_2-S$); 3.50 – 2.71 m, 4 H ($S-CH_2CH_2COOH$); 1.50 t, 3 H ($COOCH_2CH_3$, J = 7.40)
VIIIa	8.55 – 7.56 m, 8 H (Ar–H); 4.60 q, 2 H ($COOCH_2CH_3$, J = 7.50); 4.15 s, 2 H ($Ar-CH_2-S$); 3.75 q, 1 H ($CH(CH_3)COOH$, J = 7.10); 1.70 – 1.35 m, 6 H ($COOCH_2CH_3$ and $CH(CH_3)COOH$)
VIIIb	8.14 – 7.15 m, 7 H (Ar–H); 4.08 s, 3 H ($COOCH_3$); 3.89 – 3.51 m, 3 H ($Ar-CH_2-S$ and $CH(CH_3)COOH$); 1.50 d, 3 H ($CH(CH_3)COOH$, J = 6.50)
IXa	8.20 – 7.10 m, 8 H (Ar–H); 4.80 s, 1 H (OH); 4.35 q, 2 H ($COOCH_2CH_3$, J = 7.40); 3.73 t, 2 H (CH_2CH_2OH, J = 6.90); 3.46 s, 2 H ($Ar-CH_2-S$); 2.75 t, 2 H (CH_2CH_2OH, J = 7.00); 1.36 t, 3 H ($COOCH_2CH_3$, J = 7.40)
Xa	8.25 – 7.22 m, 8 H (Ar–H); 4.65 s, 2 H ($Ar-CH_2-O$); 4.35 q, 2 H ($COOCH_2CH_3$, J = 7.50); 2.20 s, 3 H ($O-CO-CH_3$); 1.33 t, 3 H ($COOCH_2CH_3$, J = 7.50)
Xb	10.80 s, 1 H (OH, exchangeable with D_2O); 8.28 – 6.72 m, 7 H (Ar–H); 4.71 s, 2 H ($Ar-CH_2-O$); 3.93 s, 3 H ($COOCH_3$); 2.08 s, 3 H ($O-COCH_3$)
XIb	10.80 s, 1 H (OH, exchangeable with D_2O); 8.28 – 6.71 m, 7 H (Ar–H); 4.74 s, 2 H ($Ar-CH_2-O$); 3.94 s, 3 H ($COOCH_3$); 2.35 q, 2 H ($O-CO-CH_2CH_3$, J = 6.70); 1.15 t, 3 H ($CO-CH_2CH_3$, J = 6.60)

H-5′ and H-6′); 4.25 s, 2 H (Ar-CH_2Cl); 3.96 s, 3 H ($ArCOOCH_3$). For $C_{17}H_{13}ClN_2O_4$ (344.7) calculated: 59.23% C, 3.80% H, 8.12% N; found: 58.91% C, 3.87% H, 8.51% N.

Synthesis of Compounds *IV*, *V*, *IX*; General Procedure

To a stirred solution of the appropriate *IIIa* or *IIIb* (0.01 mol) and anhydrous potassium carbonate (0.005 mol) in dry acetone (30 ml), the appropriate thiol (0.01 mol) was added. The reaction mixture was refluxed for 3 h. Acetone was removed in vacuo and water (100 ml) was added. The crude product was filtered, washed, dried and recrystallized from ethanol to afford compounds *IV*, *V* and *IX* (Tables I, II).

Synthesis of Compounds *VI* – *VIII*; General Procedure

To a stirred solution of the appropriate *IIIa* or *IIIb* (0.01 mol) and anhydrous potassium carbonate (0.01 mol) in dry acetone (30 ml), the appropriate thioacid (0.01 mol) was added. The reaction mixture was refluxed for 3 h and the solvent was evaporated in vacuo. Acetic acid (5%, 100 ml) was added and the precipitated solid was filtered, washed with water, air dried and recrystallized from ethanol to afford compounds *VI* – *VIII* (Tables I, II).

Mass spectrum of *VIa*: 398 (M^+ 1.3), 353 (4.0), 308 (67.9), 307 (100.0), 293 (4.9), 265 (8.2), 235 (15.0), 234 (15.2).

IR spectrum of *VIb*: 1 600 (C=N); 1 665 (amide C=O); 1 695 (carboxylic C=O); 1 715 (ester C=O); 2 650 – 3 100 (combination bands and overtones embodying the C–H stretching); 3 350 (OH, hydrogen bonded); 3 650 (free OH).

Mass spectrum of *VIIa*: 412 (M^+ 0.2), 367 (3.0), 339 (4.4), 308 (90.3), 307 (100.0), 279 (8.2), 265 (12.5), 235 (13.4), 234 (18.1).

Mass spectrum of *VIIb*: 414 (M^+ 0.4), 397 (7.1), 396 (13.0), 383 (2.4), 310 (97.0), 309 (100.0), 278 (86.0), 250 (44.3), 249 (18.4), 236 (1.4).

Mass spectrum of *VIIIa*: 412 (M^+ 0.4), 367 (2.5), 339 (1.9), 308 (90.3), 307 (100.0), 279 (16.3), 265 (19.6), 235 (13.8), 234 (12.0).

Synthesis of Compounds *X*, *XI*; General Procedure

To a stirred solution of silver acetate or silver propionate (0.01 mol) in glacial acetic acid or propionic acid (20 ml), the appropriate *IIIa* or *IIIb* (0.01 mol) was added. The reaction mixture was refluxed for 2 h, cooled and poured onto sodium carbonate solution (10%, 100 ml). The residue was filtered, washed with water, dried and crystallized from benzene–petroleum ether (1 : 1) to afford compounds *X* and *XI* (Tables I, II).

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