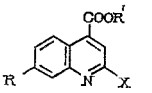
SYNTHESIS AND BIOLOGICAL TESTING OF 4-CARBOXYQUINOLYL-2-ALDEHYDE DERIVATIVES

N. M. Sukhova, I. K. Shprunka,
M. Yu. Lidak, and A. A. Zidermane

Continuing our work on the biological properties of quinoline derivatives, we have synthesized a series of previously unreported oximes and substituted hydrazines of 4-carboxyquinoline-2-aldehyde in order to study their antitumor and tuberculostatic properties.



I-XIX

I: R=Cl, R'=H, X=CHO;
II: R=R'=H, X=CHO;
III: R=R'=H, X=CH=NNHC(=NH)NH$_2$;
IV: R=Cl, R'=H, X=CH=NNHC(=HN)NH$_2$;
V: R=R'=H, X=CH=NNHCSNH$_2$;
VI: R=R'=H, X=NNHCSNH$_2$;
VII: R=Cl, R'=H, X=CH=NNHCSNH$_2$;
VIII: R=H, R'=Na, X=CH=NNHCSNH$_2$;
IX: R=Cl, R'=H, X=CH=NNHCH$_3$;
X: R=R'=H, X=CH=NNHCH$_3$;
XI: R=R'=H, X=CH=NNHCSNHNH$_2$,
XII: R=R'=H, X=CH=NNHCH$_2$CH$_2$OSO$_3$H,
XIII: R=Cl, R'=H, X=CH=NNHCH$_2$CH$_2$OSO$_3$H,
XIV: R=R'=H, X=CH=NNHC$_2$H$_5$,
XV: R=R'=H, X=CH=NOH,
XVI: R=Cl, R=H, X=CH=NOH,
XVII: R=H, R'=Na, X=CH=NOH,
XVIII: R=R'=H, X=CH=NNHCO-(furan)-NO$_2$,
XIX: R=Cl, R'=H, X=CH=NNHCOCH=CH-(furan)-NO$_2$

Starting materials were I and II and these were obtained in high yields by the oxidation of derivatives of 2-methylquinoline-4-carboxylic acid with selenium dioxide.

The condensation of II with hydroxylamine or a substituted hydrazine proceeded slowly in neutral solution and it was therefore necessary to heat the reaction mixture; compound I reacted more quickly. In weakly acid medium, no difference between the reactions of I and II was observed; products were formed almost instantaneously as reported in [1].

The enzyme L-asparaginase was acetylated with the acetyl chloride of V; only the partial acylation of L-asparaginase by acetic, maleic, succinic anhydride, or phenacetyl chloride had previously been reported [2].

Compounds (I-V), (VII), (IX-XIII), and (XVIII) (see Table 1), were isolated as monohydrates; they are crystalline substances ranging in color from colorless to orange, and, with the exception of VIII and XVII, which are water-soluble, they are soluble with difficulty in water and common organic solvents. The composition and structures of the compounds were confirmed by elemental analysis and IR spectral data; the spectra show absorptions at 1653-1698 cm^{-1}, characteristic of the C=N bond, and at 2950-3430 cm^{-1} from the hydroxyl and amino groups. The IR spectra of V, VI, and VII have no absorption bands at 2650-1500 cm^{-1} corresponding to the SH group [3], but strong bands are present at 1104-1068 cm^{-1}, characteristic of the C=S group [4]. The presence of an azomethyne bond was shown by qualitative analysis [5].

EXPERIMENTAL PHARMACOLOGICAL PART

The acute toxicity of the compounds was determined on noninbred white mice weighing 18-22 g using a single intraperitoneal injection of the compound. Each dose was tested on a minimum of six mice, which were kept under observation for 21 days. The acute toxicity was evaluated quantitatively from the LD_{50}, determined by the method of Litchfield and Wilcoxon; confidence limits of $P \geq 0.05$ were obtained from Z. Roth's nomogram.

Institute for Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 2, pp. 169-173, February, 1982. Original article submitted July 17, 1981.

 0091-150X/82/1602-0106$07.50 © 1982 Plenum Publishing Corporation

TABLE 1. 4-Carboxyquinolyl-2-aldehydes and Their Derivatives

Compound†	Yield, %	mp, °C	Found, %					Empirical formula	Calculated, %				
			C	H	N	Cl	S		C	H	N	Cl	S
I	90,2	220—221	52,12	3,12	5,30	13,48		$C_{11}H_8NO_4Cl$	52,09	3,18	5,52	13,97	
II	90,4	209—210	60,56	4,01	5,98			$C_{11}H_9NO_4$	60,27	4,14	6,39		
III	96,0	264*	52,29	5,00	25,50			$C_{12}H_{13}N_5O_3$	52,36	4,76	25,44		
IV	96,4	313—314*	46,21	4,08	22,73	11,39		$C_{12}H_{12}N_5O_3Cl$	46,54	3,91	22,61	1,45	
V	99,1	264—265*	49,57	3,94	19,51		11,06	$C_{12}H_{12}N_4O_3$	49,31	4,14	19,17		10,97
VI	83,4	267—268*	52,82	3,72	20,66		12,01	$C_{12}H_{10}N_4O_2$	52,54	3,67	20,43		11,69
VII	98,9	268—270*	43,88	3,09	17,02		11,16	$C_{12}H_{11}N_4O_3Cl$	44,11	3,39	17,15	10,85	9,81
VIII	98,0	300*	45,47	3,79	18,00		10,58	$C_{12}H_{11}N_4O_3Na$	45,86	3,53	17,83		10,20
IX	77,3	247—248*	51,36	3,88	15,22	12,96		$C_{12}H_{12}N_3O_3Cl$	51,16	4,29	14,92	12,59	
X	76,1	205—206	58,30	5,40	17,09			$C_{12}H_{13}N_3O_3$	58,29	5,30	17,00		
XI	79,1	212—213	47,09	4,53	23,06		10,24	$C_{12}H_{13}N_5O_3$	46,90	4,26	22,79		10,43
XII	87,6	207	44,21	4,07	12,02		8,76	$C_{13}H_{15}N_3O_7$	43,69	4,23	11,76		8,97
XIII	92,0	254—256*	40,42	3,98	11,15	9,42	8,58	$C_{13}H_{14}N_3O_7Cl$	39,85	3,60	10,73	9,05	8,18
XIV	60,0	232*	56,12	4,86	15,35	12,72		$C_{13}H_{12}N_3O_2Cl$	56,22	4,36	15,13	12,77	
XV	56,3	257—259*	61,01	3,78	13,32			$C_{11}H_8N_2O_3$	61,11	3,73	12,95		
XVI	57,1	246—249*	53,07	3,18	11,16	14,29		$C_{11}H_7N_2O_3Cl$	52,71	2,82	11,18	14,14	
XVII	74,2	247—248*	55,11	3,08	11,49			$C_{11}H_7N_2O_3Na$	55,47	2,96	11,76		
XVIII	98,6	277—278*	51,18	3,91	15,49			$C_{16}H_{12}N_4O_7$	51,62	3,25	15,05		
XIX	77,1	303*	57,14	3,27	15,01			$C_{18}H_{12}N_4O_6$	56,85	3,18	14,73		

*Compounds melt with decomposition.

†I, II, XII, and XIII were recrystallized from alcohol; III and IV from acetic acid; V from DMF/alcohol; VI-XI and XIV-XIX from DMF/water.

TABLE 2. Tuberculostatic Activity from *in vitro* Tests, μm/ml

Compound	Number of tests	Drug sensitive		Drug resistant	
		$H_{37}R_V$	Ravenel	Vallee	D
III	13	12,50	10,62	28,00	28,00
V	12	9,37	13,24	41,66	50,00
VIII	4	50,00	50,00	50,00	50,00
X	19	7,58	37,50	37,50	50,00
XII	19	3,51	37,50	50,00	50,00
XV	4	50,00	50,00	50,00	50,00
Streptomycin	17	0,60	0,30	30,00	23,33
Tubazide	30	0,096	0,086	10,71	22,18

The acute toxicity of III-XIX varied widely depending on the nature of the hydrazine component. The most toxic of the compounds was X (LD_{50} 105 mg/kg); less toxic were III, V, and XI (LD_{50} respectively 950, 3200, and 500 mg/kg).

The antitumor activity of the compounds was tested on noninbred white rats weighing 80-140 g and mice weighing 18-22 g. The rats received transplanted tumors: Walter carcinoma, Jensen sarcoma, sarcoma 45, alveolar membrane cancer of the lung PC-1, and Pliss lymphosarcoma; sarcoma 180 and carcinoma HK were transplanted subcutaneously into mice. Treatment of the animals with the fast-growing Walter carcinoma, sarcoma 180, and carcinoma HK was started within 24 hours; the animals with Jensen sarcoma, tumor PC-1, and Pliss lymphosarcoma were treated within 6 days after the transplantation. There were ten animals both in the test group and the control group. Compounds were injected intraperitoneally during the course of 10 days. The growth of sarcoma was inhibited by 54-73% by compounds I and XI, and by 69-74% by compound X. Compound V inhibited the growth of Walker carcinoma by 51-61%. These compounds had negligible effect on Jensen sarcoma, sarcoma 45, carcinoma PC-1, and carcinoma HK (inhibition less than 30-32%). Compound III decreased the growth of carcinoma PC-1 by 42%. Compounds III, IV, V, XI, XIII, XVIII, and XIX had no effect on Ehrlich's ascites, hemocytoblastosis La, leukemia L 1210, leukemia L 5178, and Lewis lung carcinoma. The adduct of chemically modified L-asparaginase caused 22% inhibition of tumor growth in Balb/c mice with implanted lympholeukemia L 51784, i.e., lower than the native enzyme.

The tuberculostatic activity was determined by *in vitro* tests; serial dilutions were carried out in semiliquid modified Model medium using cultures of $H37R_V$ human and Ravenel bovine strains (sensitive to tubazide and streptomycin), and Valle bovine and D human strains (low sensitivity to tubazide and streptomycin).

From the data given in Table 2, it can be seen that the activity of the compounds was dependent on the nature of the hydrazine part of the molecule and was low. The fungistatic activity of VIII, XII, XVI, XVIII, and XIX was negligible.

These results show that some of the 4-carboxyquinoline-2-aldehydes possess antitumor activity.

EXPERIMENTAL CHEMICAL PART

Infrared absorption spectra of suspensions of the compounds in mineral oil, nujol, or hexachlorobutadiene were taken on an IKS-14 spectrograph (KBr, NaCl prisms).

4-Carboxyquinolyl-2-aldehyde Monohydrate (II). A mixture of 1.87 g (0.01 mole) of 2-methylquinoline-4-carboxylic acid, 2.0 g (0.002 mole) of selenium dioxide, and 20 ml of dioxane was stirred vigorously, slowly heated to 100-110°C (1 h), and maintained at this temperature (with vigorous stirring) for 4 h. The selenium was removed by filtration and the filtrate evaporated to dryness in vacuum (water bath temperature 50-60°). The residue was dissolved in 60 ml of ethyl alcohol and boiled with activated charcoal for 15-20 min. The hot solution was filtered from the charcoal and the filtrate cooled to room temperature for 12 h to give 1.98 g of II. The same method was used to prepare I from 7-chloro-2-methylquinoline-4-carboxylic acid.

4-Carboxyquinolyl-2-aldehyde Guanylhydrazone Monohydrate (III). A suspension of 1.36 g (0.01 mole) of aminoguanidine bicarbonate in 15 ml of water was neutralized slowly by the addition of dilute acid, and the solution was filtered, the filtrate heated to 40-50°, and 2.19 g (0.01 mole) of II in 60 ml of hot alcohol slowly added with mixing. The reaction mixture was heated at 70-80° for 30 min, cooled to room temperature, washed with water and alcohol, dried, and recrystallized from acetic acid to give 2.54 g of III.

4-Carboxyquinolyl-2-aldehyde Thiosemicarbazone Monohydrate (V). a) To a solution of 0.91 g (0.01 mole) of thiosemicarbazide in 15 ml of water (or 50 ml of alcohol in the case of the 5-nitrofuran derivative) at 45-50° was added slowly, with mixing, 2.19 g (0.01 mole) of II in 60 ml of ethyl alcohol. The mixture was maintained at 65-70° for 30 min and cooled. The precipitated material was filtered off, washed with water, and recrystallized from dimethylformamide and water to give 2.92 g of V. Compounds VII, IX-XIV, XVIII, and XIX were prepared in the same way.

b) To a solution of 0.91 g (0.01 mole) of thiosemicarbazide in 30 ml of water at 45-50° acidified to pH 3.5 was added slowly with mixing 2.10 g (0.01 mole) of II in 60 ml of alcohol. Crystals started to separate immediately after the addition of the aldehyde. The crystals were filtered off and recrystallized from dimethylformamide and water to give 2.93 g of V. Compounds VI, XV, and XVI were prepared in the same way.

Sodium Salt of 4-Carboxyquinoline-2-aldehyde Thiosemicarbazone. To a solution of 0.23 g (0.01 mole) of metallic sodium in 60 ml of absolute ethyl alcohol was added 2.92 g (0.01 mole) of V in 70 ml of alcohol and the mixture refluxed for 40 min. After cooling, the precipitate was filtered off and washed with alcohol to give 3.07 g of VIII.

Adduct of Chemically Modified L-Asparaginase. A mixture of 162.5 mg of protein (total catalytic activity of L-asparaginase of 19460 ME) in 6 ml of semisaturated sodium acetate solution was added to the hydrochloride of V and stirred with a magnetic stirrer until the reaction was complete (about 1 h). The solution was dialyzed for 24 h against 0.001 M sodium borate buffer at pH 8.5 (3 × 500 ml), then for 24 h against double distilled water, to give 13170 ME of asparaginase activity (66% of activity of native protein); isoelectric point pI 5.24 (native enzyme pI 5.40).

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