SYNTHESIS AND ANTITUMOR ACTIVITY OF NEW THIOSEMICARBAZONES OF SALICYLALDEHYDE AND 4-DIETHYLAMINOBENZALDEHYDE

É. R. Dilanyan,[1] T. R. Ovsepyan,[1] F. G. Arsenyan,[1] and B. T. Garibdzhanyan[1]

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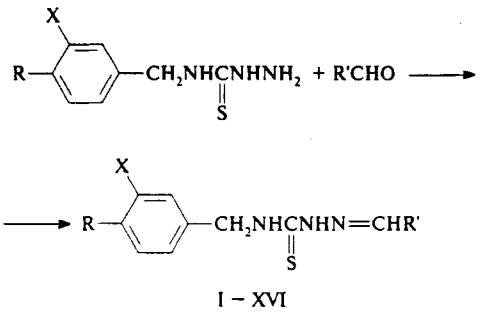
Previously we reported on the synthesis of new bis-thiosemicarbazones of methylglyoxal, 3-ethoxy-2-oxo-butanal, and glucosone, possessing pronounced antitumor activity [1 – 4]. In continuation of that work, we have synthesized new substituted thiosemicarbazones on the basis of salicylaldehyde and 4-diethylaminobenzaldehyde and studied their antitumor properties. The synthesis was performed according to the following scheme:



I – XVI

I – IV: R = MeO, EtO, *i*-PrO; R′ = 2-HOC_6H_4; X = H;
V, VI: R = MeO, EtO, *i*-Pr; R′ = 2-HOC_6H_4; X = Br;
VII, VIII: R = MeO, EtO; R′ = 2-HOC_6H_4; X = NO_2;
IX – XIV: R = MeO, EtO, *p*-PrO, *i*-PrO, *i*-BuO, NO_2;
R′ = 4-$Et_2NC_6H_4$; X = H;
XV, XVI: R = MeO, EtO; R′ = 4-$Et_2NC_6H_4$; X = Br.

The initial 4-[3-hydro(bromo, nitro)-4-alkoxybenzyl]thiosemicarbazides were obtained from the corresponding substituted benzylthiocyanates, synthesized by the method described in [5]. Interaction of the substituted thiosemicarbazides with salicylaldehyde and 4-diethylaminobenzaldehyde in an alcohol medium led to the corresponding thiosemicarbazones I – XVI. The products appeared as chromatographically pure crystalline substances with the proposed structures confirmed by IR, UV, and mass-spectrometric data. For example, the IR spectra exhibited characteristic absorption bands in the region of 1545 – 1525 cm^{-1}, attributed to the vibrations of C=N groups.

It was found that compounds I – VII and IX – XV were of low toxicity, with a maximum tolerable dose (MTD) exceeding 2500 mg / kg. For this reason, the chemotherapeutic experiments on sarcoma 45 and Walker carcinosarcoma (WCS) were performed with a drug dose of 100 – 150 mg / kg, and the experiments on sarcoma 180 involved a dose of 200 – 250 mg / kg.

According to the results of our chemotherapeutic experiments, a moderate antitumor activity with respect to all the model tumors was demonstrated by compound V, as charac-

TABLE 1. Yields and Physicochemical Characteristics of Substituted Thiosemicarbazones I – XVI

Compound	Yield, %	M.p., °C	R_f	Empirical formula*	UV spectrum in ethanol, λ_{max}, nm
I	88	202 – 204	0.56	$C_{16}H_{17}N_3O_2S$	336
II	78	191 – 193	0.86	$C_{17}H_{19}N_3O_2S$	335
III	56	183 – 185	0.61	$C_{18}H_{21}N_3O_2S$	336
IV	76	218 – 220	0.77**	$C_{15}H_{14}N_4O_3S$	325
V	59	156 – 158	0.69**	$C_{16}H_{16}BrN_3O_2S$	358
VI	75	187 – 189	0.60	$C_{17}H_{18}BrN_3O_2S$	335
VII	58	107 – 109	0.49	$C_{16}H_{16}N_4O_4S$	335
VIII	54	153 – 155	0.60	$C_{18}H_{20}N_4O_4S$	336
IX	71	158 – 160	0.73	$C_{20}H_{26}N_4OS$	366
X	70	117 – 119	0.61	$C_{21}H_{28}N_4OS$	367
XI	44	187 – 189	0.58	$C_{22}H_{30}N_4OS$	401
XII	57	181 – 183	0.81	$C_{22}H_{30}N_4OS$	398
XIII	73	191 – 193	0.68	$C_{23}H_{32}N_4OS$	400
XIV	80	179 – 181	0.72	$C_{19}H_{23}N_5O_2S$	405
XV	74	175 – 177	0.73	$C_{20}H_{25}BrN_4OS$	404
XVI	59	184 – 186	0.63	$C_{21}H_{27}BrN_4OS$	404

* Data of elemental analyses (C, H, Br, N, S) agree with the calculated values.

** In the methanol – acetone (5 : 1) system; the other data refer to the benzene – dioxane – acetic acid (90 : 25 : 4) system.

[1] Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of the Republic of Armenia, Erevan, Armenia.

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terized by the tumor growth inhibition (TGI) level of 42 – 54% ($p < 0.05$), and by compounds IX – XIII and XV with TGI up to 48% ($p = 0.05$). Compound XIV was efficient only with respect to WCS (TGI = 54%, $p < 0.05$). Compounds I, II, and IV showed a weak antimalignant effect in experiments with sarcomas 45 and 180 (TGI up to 38%, $p = 0.05$), and a somewhat higher activity with respect to WCS (TGI = 57 and 46%, $p < 0.05$).

Antistaphylococcal tests showed that compounds I, IV, V, X, XIV, and XV possessed no antimicrobial activity.

EXPERIMENTAL CHEMICAL PART

The IR absorption spectra were measured on an UR-20 spectrophotometer (Germany) using samples prepared as nujol mulls. The UV spectra were recorded on a Specord UV-VIS spectrophotometer. The mass spectra were obtained on an MX-1303 spectrometer with direct introduction of the sample into the ionization zone of the ion source, operating at an ionizing electron energy of 30 eV and a sample admission temperature 30 – 40°C below the melting point. The melting temperatures were determined on a Boethius 72 / 2064 microscopic heating stage. TLC chromatograms were obtained on Silufol UV-254 plates developed by iodine vapors. Data on the properties of the synthesized compounds are given in Table 1.

4-[3-Hydro(bromo, nitro)-4-alkoxybenzyl]thiosemicarbazones of salicylaldehyde (I – VIII). To a hot solution of 5 mmole hydrazide of the corresponding 4-[3-hydro(bromo, nitro)-4-alkoxybenzyl]thiosemicarbazide in 20 ml of ethanol was added on stirring 0.61 g (5 mmole) of salicylaldehyde, and the mixture was boiled with reflux for 2 h. The precipitate was separated by filtration and recrystallized from ethanol (see Table 1).

For compound I, IR spectrum (ν_{max}, cm^{-1}): 1535 (C=N), 3100 – 3190 (O–H), 3390 (N–H). For compound IV, mass spectrum, m/z (I_{rel}): 237 (100), 224 (62), 195 (9), 147 (44), 121 (50), 93 (44). For compound V, IR spectrum (ν_{max}, cm^{-1}): 1540 (C=N), 3170 (O–H), 3260 – 3280 (N–H). For compound VIII, IR spectrum (ν_{max}, cm^{-1}): 1545 (C=N), 3100 – 3170 (O–H), 3355 (N–H).

4-[3-Hydro(bromo, nitro)-4-alkoxybenzyl]thiosemicarbazones of 4-diethylaminobenzaldehyde (IX – XVI). These compounds are obtained similarly to compounds I – VIII, using 5 mmole of 4-[3-hydro(bromo)-4-alkoxy(nitro)benzyl]thiosemicarbazide and 0.89 g (5 mmole) of 4-diethylaminobenzaldehyde.

For compound IX, mass spectrum, m/z (I_{rel}): 370 M^+ (50), 233 (87), 191 (8), 176 (100), 161 (98), 121 (56). For compound X, IR spectrum (ν_{max}, cm^{-1}): 1525 (C=N), 1250 (C=S). For compound XIV, IR spectrum (ν_{max}, cm^{-1}): 1530 (C=N), 1275 (C=S), 1360 (NO_2 stretching).

EXPERIMENTAL BIOLOGICAL PART

The acute toxicities and antitumor activities of the synthesized compounds were studied by conventional methods [6]. The toxicity was determined by single intraperitoneal injections to white mongrel mice. The antitumor effects were studied on rats and mice inoculated with sarcomas 45 and 180 or Walker carcinosarcoma (WCS). The chemotherapeutic treatment started on the 4 – 5th day of the tumor growth, and the effect was evaluated as the percentage inhibition of the tumor growth. All compounds were injected during 8 (rats) and 6 (mice) days at a daily dose varying from 1 / 6 to 1 / 10 MTD. In view of their poor solubility, all compounds were introduced as suspensions in a 0.5% carbomethylcellulose solution. The data were statistically processed using the Fisher – Student method.

The antibacterial activity of the synthesized compounds was studied on a model of generalized infection in mice, induced by intraperitoneal injections of the Smith staphylococcus strain [6]. The drugs were administered perorally in a single dose of 1000 mg / kg simultaneously with the microbial inoculation. The reliability of differences in the survival of animals with respect to the maximum possible value in the test group was established according to the alternative form of the reaction evaluation, with calculation of the χ^2 criterion. Norsulfazol was used as the reference drug.

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