SYNTHESIS AND TRANSFORMATIONS OF POLYHEDRAL COMPOUNDS.

XIII. SEARCH FOR ANTITUMOR AGENTS AMONG THE INDOLYL-1,3-DIAZAADAMANTANES

A. A. Chachoyan, V. A. Shkulev,
Yu. B. Pisarskii, G. S. Saakyan,
Ts. E. Agadzhanyan, and B. T. Garibdzhanyan

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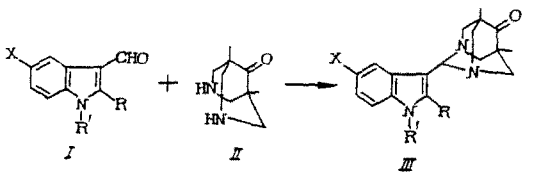
In earlier published work, we described the role of the carboxyl group on the sulfonamide-substituted indole molecule in the manifestation of anti-blastemic activity [7]. With the aim of producing effective antitumor materials, we carried out the replacement of the carboxyl group in these compounds with the 1,3-diazaadamantane residue, other derivatives of which also show experimental antitumor activity [1]. The compounds were obtained by condensation of 3-formyl-5-dimethylaminosulfonylindoles (I) with 1,5-dimethyl-9-oxo-3,7-diazabicyclo[3,3,1]-nonane (II) analogously with our earlier synthesis of 2-(indolyl-3)-5,7-dimethyl-6-oxo-1,3-diazaadamantane (IIIa) [5]. We also synthesized a series of compounds with substituents in positions 1, 2, and 5 of the indole ring (IIIb-l) to show the role of the indole ring substituents on the manifestation of antitumor activity (Table 1).



I II III

R=R'=H (a, e g, i, k, l); R=H, R'=CH_3 (b, h, j); R=CH_3, R'=H (c); R=R'=CH_3 (d, f), X=H (a-d), OCH_3 (e, f), $SO_2N(CH_3)_2$ (g, h), $SO_2N(C_2H_5)_2$ (i, j), $SO_2N(CH_2CH_2Cl)_2$ (l), SO_2-morpholin (k).

EXPERIMENTAL (CHEMICAL)

IR spectra were determined with an UR-20 spectrometer in Vaseline oil, and the ^1H NMR spectra on a Varian T-60 instrument with working frequency of 60 MHz and TMS as internal standard. The mass spectra were obtained with an MX-1320 spectrometer. TLC was carried out on Silufol UV-254 plates in n-butanol-acetic acid-water = 3:1:1 (A), or chloroform-acetone = 3:1 (B), with visualization by means of 20% ethanol solution of ninhydrin. The elemental analysis data agreed with the calculated values.

2-(1,2,5-Substituted indolyl-3)-5,7-dimethyl-9-oxo-1,3-diazaadamantanes (IIIb-l). A solution of equimolar concentrations of II and the corresponding substituted 3-formylindole I in ethanol was boiled for about 10 h until the I disappeared (TLC). After cooling, the resulting precipitate was filtered off and the precipitate was washed on the filter with small quantities of ethanol and water and recrystallized from ethanol (IIIb-f), or from a 5:1 mixture of ethanol and DMF (IIIg-l). The structures of IIIb-l were verified by IR and ^1H NMR data, and in some cases (IIIb, c, e-h, k, l) by mass spectra. In the mass spectra of the indicated compounds, the molecular ion peak was visible. The IR spectra of IIIb-l showed absorptions for the C=O group in the 1690-1710 cm^{-1} region, absorptions for the indole ring at 1610 and 1565 cm^{-1}, and for IIIc, e, g, i, k, l absorptions connected with the NH in the 3400-3440 cm^{-1}. Compounds IIIg-l also were characterized by absorptions at 1330-1340 and 1140-1160 cm^{-1} connected with the valence oscillations of the sulfamide groups.

The ^1H NMR spectra of IIIb-l showed signals for the protons of the two CH_3 groups in the form of two singlets in the 0.6-0.9 ppm region, a multiplet for the protons of the $(NCH_2C)_4$ in the 2.5-3.6 ppm region and the protons of the NCHN group in the from of a singlet in the 5.3-5.6 ppm region. Protons of the substituted indole nucleus show group characteristic signals in the 7.4-78.4 ppm region, depending upon the substituents. Compounds IIIe, f

Institute of Fine Organic Chemicals, Academy of Sciences of the Armenian SSR, Erevan.
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TABLE 1. 2-(1',2',5'-Substituted Indolyl-3')-5,7-dimethyl-6-oxo-1,3-diazaadamantanes IIIb-l

Compound	Yield, %	mp, °C (ethanol)	Empirical formula	R_f
IIIb	64,1	225—226	$C_{19}H_{23}N_3O$	0,33 (A)
IIIc	53,6	298—301	$C_{19}H_{23}N_3O$	0,82 (B)
IIId	54,1	234—236	$C_{20}H_{25}N_3O$	0,38 (A)
IIIe	67,2	241—243	$C_{19}H_{23}N_3O_2$	0,75 (B)
IIIf	62,4	214—215	$C_{21}H_{27}N_3O_2$	0,86 (B)
IIIg	52,1	277—280	$C_{20}H_{26}N_4O_3$	0,35 (B)
IIIh	54,7	250—253	$C_{21}H_{28}N_4SO_3$	0,43 (B)
		Ethanol-DMF		
IIIi	51,6	195—197	$C_{22}H_{30}N_4SO_3$	0,76 (A)
IIIj	56,3	178—180	$C_{23}H_{32}N_4SO_3$	0,70 (A)
IIIk	58,2	277—280	$C_{22}H_{28}N_4SO_4$	0,46 (A)
IIIl	60,0	227—229	$C_{22}H_{28}Cl_2SO_3$	0,48 (A)

TABLE 2. Toxicity and Antitumor Activity of Compounds IIIa-l, IV and V

Compound	LD_{100}, mg/kg (for mice)	Inhibition of tumor growth, %						
		dose, mg/kg	Sarcoma 45	Pliss lymphosarcoma	Schvets leucose	dose, mg/kg	Sarcoma 180	Sarcoma 37
IIIa	>5000	250	71	—	0	500	Stimulant	—
IIIb	4000	200	36*	—	43	—	—	—
IIIc	4000	200	47*	0	0	500	—	—
IIId	>5000	250	19*	0	0	500	—	55,5
IIIe	>5000	250	37*	0	Stimulant	—	—	—
IIIf	5000	250	45*	Stimulant	45,5	500	55	65,7
IIIg	3500	160	0	29	21,7	350	45,8	—
IIIh	5000	250	62	27,5	42	500	54	58
IIIi	5000	250	34*	28	34,8	—	—	—
IIIj	5000	250	29*	32	0	500	—	—
IIIk	5000	250	56,5	36	39	—	—	—
IIIl	5000	250	0	44	24*	500	41,6	—
IV	5000	250	65	45	—	—	—	—
V	1100	50	52	0	0	—	—	—

*Nonsignificant ($\alpha < 0.95$).

TABLE 3. Influence of Derivatives of Indolyl-1,3-diazaadamantanes on the Resistivity of Erythrocyte Membrane under the Action of 0.1 N HCl (time for 50% lysis of cells, min)

Compound	Concentration, mg/ml				
	control	0,01	0,1	1,0	10.
IIIf	10,24±1,52 (12)	10,22±2,88 (4)	8,25±1,89 (6)	7,01±0,86 (5)	Lysis
IIIa	10,24±1,52 (12)	9,76±3,11 (5)	8,76±3,22 (4)	8,02±1,33 (5)	5,58±2,1 (6)

Note. Number of experiments in parentheses.

also showed signals for the OCH_3 group at 3.7-3.8 ppm; IIIb, d, f, h, k, signals for the CH_3N group at 3.8-3.9 ppm; compounds IIIc, g, e, signals for the 2-CH_3 groups at 2.5-2.6 ppm; compounds IIIj, h, signals for the $SO_2N(CH_3)_2$ at 2.5 ppm; IIIi, j, a quartet at 3.2 ppm and a triplet at 1.5 ppm for the $SO_2N(C_2H_5)_2$, and for IIIk, two multiplets at 2.9 and 3.6 ppm for the morpholine ring.

EXPERIMENTAL (BIOLOGICAL)

The antitumor activity of compounds IIIa-l was determined by known methods [3] on rats with Sarcoma 45, Pliss lymphosarcoma, Shvets leucose and on mice with Ehrlich ascites carcinoma. The effectiveness of these compounds was determined also on mice with Sarcomas 180 and 37. A single therapeutic dose of each of the materials was calculated on the basis of their acute toxicity (LD_{100}) upon one-time intraperitoneal injection into white mice weighing 18-21 g, and observation of the animals for 10 days. Compounds IIIb, c, e, i-l, were intro-

duced into the animals in the form of suspensions in 0.5% of carboxymethylcellulose solutions, and IIIa, d, f-h in isotonic sodium chloride solutions, initially dissolved in 0.1 ml of 96% ethyl alcohol. The therapeutic effect of the compounds was evaluated according to the percent of inhibition of the growth of solid tumor (T, %) and the prolongation of the life of mice with ascites (P-L, %). The results were worked up statistically, at a confidence level of $\alpha \geq 0.95$.

The membranetropic activity of the indolyl-1,3-diazaadamantanes was studied by the earlier-described method [4] in doses of 0.01, 0.1, 1, and 10 mg/ml and evaluated by their ability to change the stability of erythrocytes to the action of hemolytic agents and regulation of the peroxide oxidation of lipids (POL).

Antioxidant activity (AOM) was evaluated by the ability of the compounds to inhibit the accumulation of malonic dialdehyde (MDA), one of the final products of induced POL, in lecithinic liposomes [6]. Proteins of liposomes prepared from egg yolks according to the method of A. Bangham et al. [2] were used for standardization. The reaction was initiated by the introduction of divalent iron.

All of the experiments were carried out with 344 nonhybrid rats and 278 mice of both sexes.

The antitumor activities of the indolyl-1,3-diazaadamantanes IIIa-l were compared to the effectiveness of the earlier-studied I with 5-(dimethylaminosulfonyl)indol-3-carboxylic acids (IV) and the hydrochloride of 5,7-dimethyl-6-oxo-1,3-diazaadamantanes (V) (Cf. Table 2).

It was established that, independently of the position and character of the substituent on the indole ring of the substituted indol-1,3-diazaadamantanes and IV, the materials are mainly of low toxicity (LD_{100} – 5000 mg/kg) (Table 2). A somewhat lower toxicity is shown by compounds IIIb, c, g (LD_{100} 3500-4000 mg/kg). Thus, substitution of the carboxyl group in the sulfonamidoindol-3-carboxylic acid by the 1,3-diazaadmantane nucleus does not lead to a significant change in toxicity.

The chemotherapeutic studies showed that the nonsubstituted indol-1,3-diazaadmantane IIIa, as well as IV showed a noticeable antitumor activity upon treatment of rats with Sarcoma 45 (T = 71%, $\alpha > 0.95$) and exceeded the activity of V on this strain. With regard to Sarcoma 180 and Ehrlich ascites carcinoma, compound IIIc as well as IV and V did not show significant antitumor effects.

Substitution in position 5 of the indole nucleus of the indole-1,3-diazaadamantane by alkylaminosulfonyl (methyl = IIIg, ethyl = IIIi, morpholinyl = IIIk, chloroethyl = IIIl) or methoxyl (IIIe) groups leads to weakened (from 70 to 30%), and in the case of dimethylsulfonyl (IIIg), to a loss of antitumor activity with respect to Sarcoma 45 with a one-time weak therapeutic effectiveness on Leucose Shvets and Sarcoma 180 (T = 30-40%). The introduction of methyl groups into position 1 or 1 and 2 of the indole ring of compounds IIIe, g leads to the formation of materials IIIf, d, showing noticeable antitumor activity with respect to Sarcoma 37 (T = 58-65%). Analogous modification of the structure of IIIi did not show a corresponding influence on the therapeutic effect of the compound IIIj obtained.

Thus, the indole-1,3-diazaadamantanes IIIf,h have other spectra of therapeutic activity, noting that they show antitumor activity against mouse tumors.

Physicochemical and other biological properties of the comparatively active compounds IIIf,h were studied similarly.

It was established that the values of the distribution coefficients for compounds IIIf, h in the octanol-water system ($K_{o/w}$) vary between the limits of 5 to 8, which places them in the class of surface-active compounds. Based upon the data obtained, it may be said that these materials may interact with the biomembranes by means of adsorption into the lipid bilayer.

Study of the membranotropic activity of these compounds established that at the indicated dosages (0.01, 0.1, 1, and 10 mg/ml) they did not have an influence on the resistance of the erythrocyte membrane to 0.1 N HCl and a mixture of plant saponins. However, in view of their high relationship to biological membranes the compounds sensitize and decrease the resistivity of erythrocyte membranes, and in a dose of 10 mg/ml, show hemolyzing action (Table 3). As shown in the tables, the most hemolytic and sensitizing activity is shown by compound IIIf, which possesses an elevated $K_{o/w}$.

It also was established that compounds IIIf and IIIh possessed significant antioxidant activity, inhibiting Fe-induced POL of liposomes prepared from egg lecithin. The AOA of these compounds was comparable with the AOA of the known antioxidant ionol at a dose of 0.1 mg/ml .

On the basis of the results obtained it may be said that compounds IIIf and IIIh displayed significant membrane-active activity, apparently connected with their antitumor activity.

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A NEW TYPE OF PLATINUM (2+) ANTITUMOR COMPLEX

K. I. Yakovlev, A. I. Stetsenko,
G. M. Alekseeva, A. F. Imsyrova,
A. L. Konovalova, N. S. Kamaletdinov,
and T. Yu. Glazkova

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At the present time cis-dichlorodiammineplatinum(2+) (DDP) is widely used in tumor chemotherapy [3]. However, the drug is nephrotoxic and poorly soluble in water (2 mg/ml), which complicates its clinical use and the technology of manufacture of the lyophilized drug form. Therefore, the search for new water-soluble and less toxic Pt complexes is urgent.

For this purpose we synthesized, investigated the structure, and studied the antitumor activity of cationic complexes of platinum(2+) of the triammine type with a cis-structure – $[Pt(NH_3)_2LCl]Cl$, where L represents purine or pyrimidine ligands. The presence of a lipophilic heterocyclic ligand in the inner sphere promotes their membrane permeability. The structural difference from DDP (positive charge, presence of one labile chloride ion in the inner sphere) permits us to expect a different type of interaction with DNA for the electrolyte complexes. The advisability of searching for active compounds in the series of monofunctional cationic complexes is indicated in [4-6].

We synthesized triammine complexes with a cis-structure, containing monodentately coordinated molecules of cytosine – Cty, cytidine – Cyd, 2-amino-4-hydroxypyrimidine (isocytosine – i-Cyt), 2-amino-4-hydroxy-6-fluoropyrimidine (6-fluoroisocytosine – 6-F-i-Cyt), 2,6-dioxo-1,3,7-trimethylpurine (caffeine – Coff), and 2,6-dioxo-1,7-dimethylpurine (theobromine – Thb) in the inner sphere.

Compounds (I-VI) with the composition $cis[Pt(NH_3)_2LCl]Cl$, where L represents Cyt (I), Cyd (II), i-cyt (III), 6-F-i-Cyt (IV), Coff (V) and Thb (VI), were obtained by heating in aqueous medium in the interaction of the initial cis-complex of DDP with the indicated ligands in a 1:1 mole ratio.

Leningrad Chemico-Pharmaceutical Institute. All-Union Oncologic Science Center, Academy of Medical Sciences of the USSR.

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