STUDY OF THE QUANTITATIVE STRUCTURE – ACTIVITY RELATIONSHIPS IN A SERIES OF THIOSEMICARBAZIDE DERIVATIVES OF PHENYLANTHRANYL ACIDS

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 30, No. 12, pp. 43 – 45, December, 1996.

Original article submitted May 21, 1996.

Phenylanthranyl acid derivatives are widely used in practical medicine as antiinflammatory, analgesic, and antipyretic drugs, and serve as initial substances in the search for new effective drug preparations [1, 2]. However, no systematic investigations into the relationship of the biological activity of these compounds and their physicochemical properties were reported in the literature.

The purpose of this work was to establish quantitative relationships between the biological activity of thiosemicarbazides of substituted phenylanthranyl acids and their physicochemical parameters.

For that purpose, we have synthesized 18 thiosemicarbazides (I – XVIII) using the reaction of acylation [3] of thiosemicarbazide by chloroanhydrides of the corresponding phenylanthranyl acids [4].

The resulting thiosemicarbazides I – XVIII appear as crystalline substances soluble in dioxane, ethanol, benzene, and DMF, and insoluble in water. The proposed structures of synthesized compounds I – XVIII were confirmed by the IR and UV spectroscopic data, and their purity was checked by TLC in the appropriate solvent systems (Table 1).

The IR spectra of compounds I – XVIII contain absorption bands in the regions of 1587 – 1573 cm^{-1} (bending vibrations of the NH groups, amide II), 1653 – 1620 cm^{-1} (stretching vibrations, amide I), and 1253 – 1220 cm^{-1} (vibrations of the C=S group). The UV spectra of the thiosemicarbazides in ethanol are analogous to those of the corresponding phenylanthranyl acids [5].

EXPERIMENTAL CHEMICAL PART

The IR spectra of compounds I – XVIII were measured on a Specord 75 spectrophotometer using samples prepared as KBr disks.

The UV spectra I – XVIII were obtained on an SF-26 spectrophotometer using ethanol solutions.

TLC was performed on Silufol UV-254 plates eluted with a dioxane – hexane (4 : 1) mixture (system 1) or an acetic acid – ethanol (3 : 1) mixture (system 2). The results of elemental analyses agreed with empirical formulas.

Thiosemicarbazide of 4-chloro-N-phenylanthranyl acid (I). A mixture of 1.9 g (0.0074 mole) of 4-chloro-N-phenylanthranyl acid, 6 ml thionyl chloride, and 25 ml of dry benzene was heated on a water bath for 30 min. Excess thionyl chloride, sulfur dioxide, and hydrogen chloride were distilled off in vacuum. The residual chloroanhydride was dissolved in 20 ml of anhydrous dioxane, mixed with a solution of 0.67 g (0.0074 mole) of thiosemicarbazide in 15 ml of anhydrous dioxane, and heated on the water bath for 5 min. After cooling, the mixture is diluted with water. The precipitate was filtered, dried, and triply recrystallized from ethanol to obtain thiosemicarbazide I.

Compounds II – XVIII were obtained by analogous procedures.

EXPERIMENTAL BIOLOGICAL PART

Acute toxicity was studied by intraperitoneal injections to white mice, and the LD_{50} was determined by the Kerber method [6]. The antiinflammatory activity of compounds I – XVIII was assessed in rats by determining the degree of edema inhibition for a model of acute inflammation induced by subplantar injections of 1% carrageenan in the hind paw [7]. The analgesic effect was studied on the model of vinegar writhing in white mice weighing 20 – 22 g [8]. The diuretic effect was determined by the method described in [9] for white male mongrel rats weighing 150 – 180 g. The experimental data were statistically processed by the conventional techniques [6].

The acute toxicities of compounds I – XVIII are close to the LD_{50} values of the corresponding phenylanthranyl acids [10], which allows us to classify these substances as having low toxicity according to the scheme of Sidorov [11].

Thiosemicarbazides I – XVIII exhibit an antiinflammatory effect comparable with that of voltaren (note that the ac-

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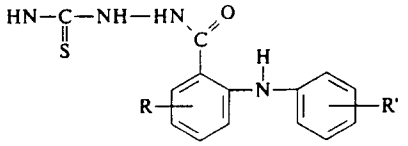
0091-150X/96/3012-0764$15.00

TABLE 1. Physicochemical Characteristics of Thiosemicarbazides



I – XVIII

Compound	R	R'	Yield, %	M.p., °C	Empirical formula	IR spectrum, ν, cm^{-1}			UV spectrum, λ_{max}, nm	R_f^1	R_f^2
						Amide I	Amide II	$\nu_{C=S}$			
I	4-Cl	H	70	183 – 185	$C_{14}H_{13}ClN_4OS$	1613	1540 – 1527	1220	286, 346	0.72	0.77
II	4-Cl	2-Me	75	100 – 102	$C_{15}H_{15}ClN_4OS$	1647	1560 – 1527	1227	278, 346	0.79	0.77
III	4-Cl	3-Me	74	158 – 160	$C_{15}H_{15}ClN_4OS$	1640	1560 – 1527	1213	286, 346	0.73	0.76
IV	4-Cl	4-Me	74	159 – 161	$C_{15}H_{15}ClN_4OS$	1600	1547 – 1533	1200	282, 346	0.80	0.74
V	4-Cl	2-OMe	76	208 – 210	$C_{15}H_{15}ClN_4O_2S$	1640	1547 – 1507	1207	283, 309, 351	0.74	0.76
VI	4-Cl	4-OMe	62	188 – 190	$C_{15}H_{15}ClN_4O_2S$	1613	1540 – 1535	1207	282, 346	0.73	0.75
VII	4-Cl	3.4-Me_2	75	128 – 130	$C_{16}H_{17}ClN_4OS$	1620	1553 – 1547	1200	294, 360	0.80	0.76
VIII	4-Cl	3.5-Me_2	69	136 – 138	$C_{16}H_{17}ClN_4OS$	1627	1547 – 1540	1200	290, 348	0.80	0.79
IX	4-Cl	4-OEt	70	134 – 136	$C_{16}H_{17}ClN_4O_2S$	1633	1547 – 1540	1233	284, 354	0.70	0.75
X	4-NO_2	2-Me	58	146 – 148	$C_{15}H_{15}N_5O_3S$	1673	1587 – 1540	1234	276, 425	0.78	0.77
XI	4-NO_2	4-Me	65	208 – 210	$C_{15}H_{15}N_5O_3S$	1653	1587 – 1534	1220	274, 425	0.63	0.78
XII	4-NO_2	4-OMe	57	138 – 140	$C_{15}H_{15}N_5O_4S$	1673	1587 – 1547	1253	470, 430	0.62	0.78
XIII	4-NO_2	3.4-Me_2	55	158 – 160	$C_{15}H_{17}N_5O_3S$	1673	1580 – 1533	1220	278, 430	0.63	0.77
XIV	4-NO_2	3-Br	52	203 – 205	$C_{14}H_{12}BrN_5O_3S$	1653	1580 – 1560	1234	294, 340	0.68	0.77
XV	4-NO_2	2-Cl	63	214 – 216	$C_{14}H_{12}ClN_5O_3S$	1653	1583 – 1534	1227	248, 400	0.61	0.77
XVI	4-NO_2	4-Cl	58	204 – 206	$C_{14}H_{12}ClN_5O_3S$	1666	1600 – 1547	1227	284, 415	0.66	0.79
XVII	4-NO_2	H	55	185 – 187	$C_{14}H_{13}N_5O_3S$	1680	1606 – 1587	1200	276, 415	0.69	0.78
XVIII	4-NO_2	2-OMe	63	200 – 202	$C_{15}H_{15}N_5O_4S$	1667	1593 – 1554	1234	250, 271, 430	0.70	0.78

TABLE 2. Pharmacological Properties and Physicochemical Parameters of Thiosemicarbazides of Phenylanthranyl Acids

Compound	Σσ	Σπ	LD_{50}, mg/kg	Antiinflammatory activity			Analgesic activity		
				log BA	log BA by equation 6	Δlog BA	log BA	log BA by equation 3	Δlog BA
I	0.227	0.72	148.5	1.351	1.378	– 0.027	1.866	1.915	0.051
II	0.087	1.20	141.5	1.398	1.417	– 0.019	1.940	1.939	0.001
III	0.158	1.34	71.5	1.465	1.475	– 0.010	1.982	1.933	0.049
IV	0.057	1.28	71.5	1.451	1.422	0.029	1.952	1.944	0.008
V	0.043	0.80	179.5	1.332	1.321	0.011	1.960	1.937	0.023
VI	0.041	0.88	141.5	1.308	1.310	– 0.002	1.954	1.939	0.015
VII	0.012	1.90	270.5	1.407	1.434	– 0.027	1.977	1.959	0.018
VIII	0.089	1.96	171.5	1.512	1.472	0.040	1.964	1.952	0.012
IX	0.041	1.38	337.0	1.377	1.377	0.000	1.908	1.947	0.039
X	0.638	0.26	108.0	1.473	1.473	0.000	1.875	1.863	0.012
XI	0.608	0.34	139.0	1.483	1.470	0.013	1.876	1.868	0.008
XII	0.510	– 0.06	136.0	1.371	1.376	– 0.005	1.841	1.872	– 0.031
XIII	0.539	0.96	78.0	1.501	1.523	– 0.022	1.843	1.886	– 0.043
XIV	1.169	0.69	64.0	1.771	1.767	0.006	1.778	1.813	– 0.035
XV	0.988	0.20	84.0	1.619	1.619	0.000	1.812	1.825	– 0.013
XVI	1.005	0.50	141.1	1.668	1.666	0.002	1.871	1.828	0.043
XVII	0.778	0.22	187.0	1.461	1.469	– 0.008			
XVIII	0.508	– 0.14	111.0	1.388	1.364	0.024			

TABLE 3. Correlation Equations for the Relationship between the Antiinflammatory Activity of Thiosemicarbazides of Phenylanthranyl Acids and Their Physicochemical Parameters ($n = 18$)

No.	Equation	R	S^2_{res}	F
1	$\log BA = 1.36 + 0.25\sigma$	0.779	0.006	2.544
2	$\log BA = 1.38 + 0.15\sigma$	0.520	0.011	1.337
3	$\log BA = 1.18 + 0.41\sigma + 0.14\pi$	0.973	0.001	19.049
4	$\log BA = 1.21 + 0.29\sigma + 0.12\pi + 0.10\sigma\pi$	0.976	0.001	21.351
5	$\log BA = 1.38 + 0.14\pi - 0.02\pi^2$	0.466	0.011	1.277
6	$\log BA = 0.18 + 0.38\sigma + 0.13\pi + 0.03\pi^2$	0.986	0.001	35.312
7	$\log BA = 1.21 + 0.32\sigma + 0.13\pi + 0.07\sigma^2$	0.973	0.001	19.004
8	$\log BA = 1.21 + 0.31\sigma + 0.14\pi + 0.07\sigma^2 + 0.01\pi^2$	0.945	0.002	9.335
9	$\log BA = 1.19 + 0.30\sigma + 0.14\pi + 0.06\sigma^2 - 0.07\pi^2 - 0.01\sigma\pi$	0.846	0.005	4.378

TABLE 4. Correlation Equations for the Relationship between the Analgesic Activity of Thiosemicarbazides of Phenylanthranyl Acids and Their Physicochemical Parameters ($n = 16$)

No.	Equation	R	S^2_{res}	F
1	$\log BA = 1.95 - 0.12\sigma$	0.737	0.002	2.189
2	$\log BA = 1.94 - 0.08\pi$	0.549	0.003	1.432
3	$\log BA = 1.93 - 0.11\sigma + 0.02\pi$	0.728	0.002	2.131
4	$\log BA = 1.92 - 0.05\sigma + 0.02\pi - 0.05\sigma\pi$	0.711	0.002	2.022
5	$\log BA = 1.89 - 0.06\pi + 0.05\pi^2$	0.647	0.002	1.720
6	$\log BA = 1.93 - 0.10\sigma + 0.02\pi - 0.01\pi^2$	0.717	0.002	2.057
7	$\log BA = 1.93 - 0.11\sigma + 0.02\pi + 0.01\sigma^2$	0.703	0.002	1.980
8	$\log BA = 1.93 - 0.12\sigma + 0.01\pi + 0.01\sigma^2 + 0.01\pi^2$	0.674	0.002	1.834
9	$\log BA = 1.82 - 0.11\sigma + 0.17\pi - 0.07\sigma^2 - 0.05\pi^2 - 0.21\sigma\pi$	0.694	0.002	1.929

tivity of compound XIV exceeds that of voltaren by 20%). The analgesic properties of I – XVI are higher than those of the corresponding hydrazides [10]. The influence of phenylanthranyl acid compounds I – XVIII on the uropoietic function of kidney was statistically unreliable, which indicates the inexpediency of the search for highly efficient diuretics in this series of compounds.

Taking into account the prospects of design of the pharmacologically active compounds with predicted properties in the series of thiosemicarbazides of phenylanthranyl acids, we have studied the quantitative structure – activity relationships (QSAR) for compounds I – XVIII by the method of multifactor regression analysis [12]. The biological response was evaluated by logarithmic biological activity indices (logBA). There is a large number of physicochemical parameters used for the QSAR investigation [13], of which we selected the additive σ-constants, related to changes in the electron properties of molecules [14], and the π-constants of lipophilicity (Table 2), characterizing the transport properties of biologically active substances and their ability to hydrophobically bind with some parts of receptors [15].

The results of QSAR calculations are presented in Table 3 and 4. It is interesting to note that parameter σ more strongly affects the antiinflammatory activity of thiosemicarbazides than does the lipophilicity parameter π (cf. statistical characteristics of equations 1 and 2 in Table 3). The statistical characteristics are markedly improved when both parametersare taken into consideration (equation 3) and are further increased by introducing a cross term (equation 4).

The best statistical characteristics are observed for equation 6, which implies a linear dependence on the parameter σ and a parabolic dependence of the lipophilicity π. Note that positive values of the coefficients in this equation allow us to predict the further increase in the antiinflammatory activity of the thiosemicarbazide derivatives of phenylanthranyl acid upon introduction of electron-donor and hydrophobic substituents. The antiinflammatory activity characteristics calculated by equation 6 (Table 3) exhibit no significant deviation from the experiment. This result is indicative of a common mechanism of the pharmacological activity of this class of compounds. Attempts to complicate the QSAR relationship (see equations 7 – 9, Table 3) leads to less favorable statistical characteristics.

The QSAR study of the analgesic activity of compounds I – XVI showed that the best description is provided by equation 3 (Table 4), corresponding to a linear dependence of the biological response on both σ and π parameters of the substituents. It must be noted that the predicting ability of QSAR equations with respect to the analgesic activity of thiosemicarbazides (albeit still statistically reliable) is markedly lower than that for the antiinflammatory properties. Opposite signs of the coefficients at σ and π terms (equation 3, Table 4) imply that a higher analgesic activity is expected for thiosemicarbazides having electron-donor substituents with hydrophobic properties.

The above results suggest that the antiinflammatory and analgesic activities of the thiosemicarbazides of phenylanthranyl acids are explained by different mechanisms.

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