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ELECTRONIC STRUCTURE–ACTIVITY RELATIONSHIPS (ESAR) FOR DERIVATIVES OF PROPENONE. PART 1. 4-CARBOXYVINYLENECHALCONES AND 3-CINNAMOYLCOUMARINS

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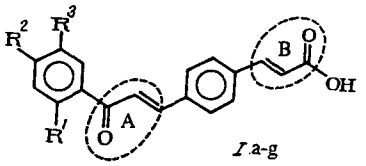
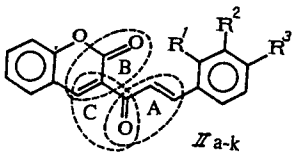
The contribution of the propenone fragment to the display of biological activity by complex chalcone molecules was first recorded by W. Geiger and J. Conn [12]. There are many compounds in which a propenone fragment is crucial for the display of structural and biological characteristics. Previously we have studied derivatives of chalcone, flavone, chromone, cinnamic acids, coumarins, and triterepene derivatives of the ursane, oleanane, and lupane series. Investigations were carried out on the development of rules for the quantitative links of structure and activity using a logical structural approach and subsequent regression analysis based on physicochemical and empirical parameters [5-7]. It therefore became possible to correlate structural and biological information on the compounds indicated.

Subjects chosen for investigation in the present work were the 4-carboxyvinylenechalcones (Ia-g), information on the properties and biological activity of which has been presented by us previously [7], and the newly synthesized derivatives of 3-cinnamoylcoumarin (IIa-k).



I a-g



II a-k

The joint study of these two groups of compounds arose from the appreciable similarity of their compositions and by the presence of common structural features.

The synthesis of 3-cinnamoylcoumarin derivatives is justified for the following reasons.

1. Coumarin is a potential pharmacophore and antiallergic and neurostimulating action has been established for various derivatives of it [2, 3, 11, 13]. The biological activity of these compounds is linked with their ability to inhibit phosphodiesterase and leucotriene biosynthesis [9].

2. The introduction of a cinnamoyl substituent into position 3 of the coumarin nucleus leads to the formation of an additional conjugation chain including the vinylene group of the heterocycle and the exocyclic propenone fragment which

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TABLE 1. Properties and Biological Activity of Compounds

Compound	R^1	R^2	R^3	Empirical formula	mp, °C	Method	AA[a] 25 mg/kg	NS[b] 10 mg/kg
Ia	H	H	H	-	-	-	0,115	-
Ib	OH	H	H	-	-	-	0,169	-
Ic	H	Br	H	-	-	-	0,157	-
Id	H	OMe	H	-	-	-	0,164	-
Ie	OH	OH	H	-	-	-	0,203	-
If	OH	OH	Br	-	-	-	0,360	-
Ig	OH	OH	Ac	-	-	-	0,427	-
IIa	H	H	H	$C_{12}H_{12}O_3$	170	A	0,217	0,326
IIb	H	H	OMe	$C_{19}H_{14}O_4$	169	A	0,468	0,306
IIc	H	H	OH	$C_{18}H_{12}O_4$	249	A,B	0,245	0,387
IId	H	OMe	OMe	$C_{20}H_{16}O_5$	187	A	0,514	0,398
IIe	OMe	H	H	$C_{19}H_{14}O_4$	167	A	0,484	0,296
IIf	OMe	OMe	H	$C_{20}H_{16}O_6$	144	A	0,543	0,245
IIg	H	H	NMe_2	$C_{20}H_{17}O_3N$	218	A	0,559	0,450
IIh	H	H	Br	$C_{18}H_{11}O_3Br$	197	B	0,249	0,316
IIi	H	H	NO_2	$C_{18}H_{11}O_5N$	268	B	0,226	0,429
IIj	H	NO_2	H	$C_{18}H_{11}O_5N$	224	B	0,240	0,173
IIk	NO_2	H	H	$C_{18}H_{11}O_5N$	211	B	0,239	0,306
Caffeine	-	-	-	-	-	-	-	0,163
Intal	-	-	-	-	-	-	0,330[c]	-

[a]Antiallergic activity, % inhibition of RPCA/100.

[b]Neurostimulating activity, $A_0 - A_i/A_0$ (A_0 is control, A_i experimental, in minutes of sleep).

[c]Dose 50 mg/kg.

generate additional centers of complementarity with the biosubstrate. This is in agreement with the data obtained previously on the properties of the 4-carboxyvinylenechalcones [7].

Synthesis of the 3-cinnamoylcoumarin derivatives was effected by the condensation of 3-acetylcoumarin with various aromatic aldehydes in the presence of a basic or acidic catalyst. Biological testing of the compounds obtained revealed marked antiallergic and neurostimulating activity for some of them. The data on the compounds synthesized and their biological activity is given in Table 1.

When analyzing the structural features of the compounds we first picked out the main fragments which presumably determine the interaction with the biosubstrate (denoted by dotted lines).

The presence of a large number of probable centers of interaction with the biosubstrate in this particular series of compounds enables the common structural feature, which has the minimum size and maximum information on the electronic environment characteristic of the given molecule, to be defined. It is assumed that the local characteristics of the fragment (charge, relative reactivity, Wiberg indices, etc.) must reflect the total sum of interactions in the molecule. This also applies when considering systems such as the combination of an atomic framework and electron density, which is distributed as a function of the shape and geometry of the atoms. The high pair correlation coefficients (0.80-0.95) between the local characteristics and such parameters as the GMO energy indicate that it is wrong in our opinion to separate quantum chemical characteristics into like groups in the classes studied. The exception is dipole moment, which depends to a large extent on the geometry of the molecule. The fragments shown in Table 1 correspond with this condition exactly. Each of these may be characterized by a combination of the resulting electronic properties (a single conjugation chain) of all the atoms of an individual molecule.

Although the work that has been devoted to the study of the relationship of electronic structure to activity (ESAR) is important, most of it is based on the methodology developed by Hammett and Hansch and is limited to revealing regularities within series. In the communications proposed by us we are extending the groups of compounds studied by exposing common structural features in the various classes of compounds by parameterizing the structures by SSP LCAO MO and studying ESAR.

There are several approaches when investigating structure–activity correlations for related compounds and establishing links between series. However, neither Hansch–Fujita analysis nor the application of the theory of sample discrimination can give a satisfactory answer to a problem like explaining the biological importance of the various structural elements by virtue of the fact that it is caused mainly by electronic effects.

TABLE 2. Analysis of ESAR

Dependent variables	Independent variables, coefficients, and characteristics of the methods				
	W	Q_1	Q_2	R	U
AA-I	13,074	2,188	-	-	-0,331
	±1,828	±0,166	-	-	±0,042
	p = 0,00	p = 0,00	-	-	p = 0,00
	F = 778,96	F = 106,1	-	-	F = 61,59
n = 7; R^2 = 0,993; S = 0,0218; F = 315,56; p = 0,0000					
AA-I	19,744	-1,885	-	-7,870	-
	±1,558	±0,68	-	±0,49	-
	p = 0,00	p = 0,00	-	p = 0,00	-
	F = 2371,0	F = 866,8	-	F = 257,5	-
n = 11; R^2 = 0,980; S = 0,0160; F = 1165,41; p = 0,0009					
NS-II	21,063	-2,084	-20,786	-	-
	±4,869	±0,711	±6,794	-	-
	p = 0,00	p = 0,00	p = 0,00	-	-
	F = 561,9	F = 67,67	F = 8,42	-	-

n = 11; R^2 = 0.986; S = 0,0437; F = 159,88; p = 0,0000.

Recently superpositional computer methods have been applied for this purpose, particularly to explain anti-allergic activity [20]. Regardless of the high level of these studies the solution goes no further than a qualitative assessment of substance–biosubstrate interactions.

It is known that the spectrum of physicochemical and biological properties is secondary to the electronic structure [16]. A combination of the methods of quantum chemistry and regression analysis for isolating or confirming quantitatively the effect of intuitively determined minimum pharmacophores is the optimum way to solve this problem. We considered the following when choosing a means of calculating electronic structures. The application of x-ray methods does not give a precise quantitative estimate of electronic parameters and the application of *ab initio* calculations is at present inadequate for the main purpose of ESAR analysis, viz. to reduce the volume of pharmacological screening. Calculation of the electronic structure of compounds was carried out by a PPDP semi-empirical approach, which gave good reproducibility with values of electronic parameters obtained by nonempirical methods.

After preliminary processing the characteristics obtained (50-60 for each compound) were checked for conforming to the normal distribution rule. The coefficients of asymmetry and excess of individual variables did not exceed standard limits. Correlation coefficients for pairs exceeding a value of 0.89 enabled one of the mutually dependent parameters to be excluded from the subsequent analysis. The number of parameters was reduced to 44 for each compound by this procedure.

Stepwise multiple regression analysis was used to reveal the statistically significant parameters. The size of the biological activity was considered to be a dependent variable. After passing the preliminary selection the quantum chemical parameters of compounds are independent variables.

The following regularities emerged in the course of analysis. Of the three delineated fragments in the series of coumarin derivatives (see Table 1) only the parameters of fragment A enabled the dispersion of values of the activity to be described with a confidence greater than 95%. Similarly, in the series of 4-carboxyvinylenechalcone derivatives the electronic characteristics of fragment A proved to be significant for explaining antiallergic activity. Indirect confirmation of these results is the fact that unsubstituted cinnamic acid and coumarin do not display neurostimulating and antiallergic activity.

The procedure for stepwise selection was carried out both by the direct and reverse methods and also by the basic set method.

The electronic parameters selected and included in the regression equations and the statistical characteristics of the models are given in Table 2. All the parameters pertain to the atoms of fragment A, where W is the Wiberg index estimated from the size of the interaction [19] of the carbonyl oxygen and the β-carbon atom, Q_1 the charge on the carbonyl carbon atom, Q_2 the charge on the β-carbon atom, R the reactivity of the oxygen in the terms of the calculation method, and V the valence activity of the β-carbon atom. In addition to those given 11 models were obtained (with coefficients within the limits 0.75-0.89) which scored a low percentage when explaining the scatter of activity values and are therefore not cited. The following must be taken into account when interpreting the experimental results.

1. For the best assessment of the contribution of each parameter the significant regression relationships are given in their renormalized form, i.e. without the independent term. The correctness and need for just such a form of representation of the mathematical modelling data was shown in [14] and has been used successfully by other authors [17].

2. The "rule of five" as formulated in [18] was not observed in the equations (the presence of not less than five compounds at one degree of freedom in the regression equation), however this apparent disadvantage is refuted by [8] where exhaustive points are made for using a smaller number of compounds (experiments), and for proceeding from the limiting values of the determination coefficients. The "rule of five" may serve as a serious limitation when the main regularities become apparent with the aid of a minimum number of pharmacological experiments. These are then transposed to uninvestigated compounds with the aim of sifting out those of little promise and the subsequent prediction of compounds with maximum activity.

It follows from analysis of the equations that the values of W and Q_1 are the decisive variables for all the interactions, explaining up to 70-80% of the dispersion of the activity values. The remaining three are additional and less reliable (cf. the partial Fisher criterion). However these parameters are necessary in individual cases to explain delicate interactions.

As an example of the modeling efficiency it is possible to cite compounds (IIb) and (IIk) having equal neurostimulating activity but opposing substituent effects. The ESAR analysis enables prediction of the disparity with high precision (prognosis 0.334 and 0.328 respectively, error $< 9\%$, overall error of the model 4.4%). The ortho nitro group reduces significantly the charge on the β-carbon atom (from 0.0144 to 0.0079) and the contribution of parameter Q_2 proves to be decisive.

In those cases when a clear discrepancy occurred between the predicted and calculated values of the biological activity it may be assumed that the effect of substituents showing a comparatively small influence on the electron density distribution may be displayed in their ability to change the outer electrostatic field of the molecule [1] and lead correspondingly to a probable change in the character of the ligand–receptor interaction.

From the results obtained it may be assumed that the propenone fragment is probably the structural fragment determining neurostimulating and antiallergic activity in the series of compounds being considered. The electronic characteristics of the carbonyl oxygen, the carbonyl carbon atom and the β-carbon atom are the decisive parameters for explaining the scatter of the biological activity values. The α-carbon atom presumably does not participate in interactions. The recurrence of the parameters in the equations explaining the differences in the form of the activity and their transferability between both types of compound indicate the universally decisive nature of the electronic effects of the propenone fragment and gives grounds to suggest a single molecular mechanism for the biological activity. A similar conclusion is in agreement with the work of [10].

EXPERIMENTAL

Synthesis of 3-Cinnamoylcoumarins. Method A. A mixture of 3-acetylcoumarin (0.01 mole) and the aromatic aldehyde (0.012 mole) was dissolved with heating in n-butanol (10 ml). Acetic acid (0.3 ml) and the same quantity of piperidine were then added. The reaction mixture was boiled for 4 h, then cooled. The solid which precipitated was filtered off and crystallized from the appropriate solvent (yield 40-60%).

Method B. A mixture of 3-acetylcoumarin (0.01 mole) and the aromatic aldehyde (0.012 mole) was dissolved in glacial acetic acid (10 ml). Concentrated sulfuric acid (1-2 drops) was added. The reaction mixture was boiled for 15 min. A solid separated after cooling and was crystallized from the appropriate solvent (yield 52-58%).

The structures of the compounds obtained were confirmed by IR, UV, and PMR spectral methods and by the data of elemental analysis.

Calculations of the electronic structures of the compounds being investigated were carried out by the PPDP/2 semiempirical approach according to the program of [15]. Input data were worked out with the ChemCad 1.0 package, and data of x-ray structural analysis were used to describe the geometric characteristics [4]. Operations of transforming the initial data, statistical and graphical analysis, and stepwise multiple regression analysis were carried out with the Statistical Graphics System 5.0 package.

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