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Conference Paper

A QSAR Study of 3-(Phthalimidoalkyl)-pyrazolin-5-ones

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A group of 17 new 3-(phthalimidoalkyl)-pyrazolin-5-ones were tested for their mitodepressive activity upon the growth of *Lepidium sativum L.* seeds (*Cresson*). All of them have shown mitodepressive effect on the growth of the plant. Four topological indices (the Wiener index, the valence-connectivity index, the Balaban index and the information-theoretic index) were used in QSAR studies (inhibition of plant growth in % and cytostatic activity in ED_{50}) on these compounds. We obtained QSAR models that can predict cytostatic activity on the HeLa cells (in ED_{50}) with considerable accuracy.

INTRODUCTION

Topological indices may be used directly as simple numerical descriptors in quantitative structure-property relationships (QSPR) and structure-activity relationships (QSAR) with an aim to find the quantitative relationship between these descriptors and the biological properties or biological activity of the compounds.[1] These relationships are mathematical models that enable the prediction of properties and/or activities from the structural parameters. QSAR modelling is a major tool in contemporary drug design.[2–4] Therefore, the combination of QSAR methodology with the intuition and experience of drug designers allows a much faster appearance of novel drugs for human, animal and plant therapy.

Derivatives of pyrazolin-5-ones exhibit interesting biological and chemical properties which may eventually lead to valuable applications. They possess antibacterial,[5] hypoglycemic,[6], antidiabetic,[7] anti-inflammatory[8,9] and antineoplastic[10,11] activities. Their cytostatic activity was studied in this work.

The compounds analyzed in this report are 17 new derivatives of 3-(phthalimidoalkyl)-pyrazolin-5-ones recently synthesized.[12] All studied compounds were tested by

the method of Gagiu *et al.*[13] for their mitodepressive activity upon the growth of *Lepidium sativum L.* seeds (*Cresson*).[13,14] We have used four topological indices[1,15] (the Wiener index, W,[16–18] the valence-connectivity index, χ^v,[19,20] the Balaban index, J,[21,22] and the information-theoretical index, I,[23,24]) with an intention to derive QSAR models that can predict cytostatic activity (ED_{50}) on the *HeLa cells*. In order to establish the initial models, we used a group of some substituted pyrazoles which showed significant cytostatic activity on the HeLa cell cultures.[11]

METHODS

Investigation of Mitodepressive Effect[13,14]

About 30 seeds of *Lepidium sativum L.* were placed on filter paper in a Petri dish, and 15 ml of H_2O was added. After the seeds were incubated for 24 hours at 25±1 °C, H_2O was replaced by a solution of the studied phthalimido-pyrazolin-5-ones. The concentration was 0.05 mg/ml (0.5% *v/v* dimethlyformamide in H_2O). One sample, where seeds were left in the solvent, was used as a blank. After further incubation of 24 hours at the same temperature, the liquid was decanted and the seeds fixed with a solution containing 2 g salicylic acid, 2 g $ZnSO_4$, freshly prepared concentrated solution of phenolate (15 drops) and distilled H_2O (100 ml.). After fixation, 20 seed radicals of each sample were measured by means of mm paper and lens and compared with the blank. The mean value of the measured radical lengths was found for each particular sample and the inhibition (%) of growth was calculated by the following equation

$$\text{Inhibition (\%)} = \frac{L_B - L_x}{L_B} 100 \tag{1}$$

were L_B is the length of blank radicals and L_x is the length of radicals incubated in the solution of phthalimido-pyrazolin-5-one.

Calculations of Topological Indices

The Wiener index, W(G)

The Wiener index of the investigated compounds was calculated from the distance matrix of the corresponding hydrogen-depleted chemical graph (G) according to[1,15–18]

$$W = \frac{1}{2} \sum_{i,j} D_{ij}(\mathrm{G}) \tag{2}$$

where D_{ij}(G) represents elements of $\boldsymbol{D}$(G) and they are weighted (1 for single bond, 2 for double bond).

The Molecular Connectivity Index, χ^v(G)

The molecular connectivity index of graph, χ(G) of G, is defined by Randić[19] as

$$\chi(\mathrm{G}) = \sum_{\text{edges}} [\, \mathrm{d}(i)\, \mathrm{d}(j)\,]^{-0.5} \tag{3}$$

where d(i) and d(j) are the valences of vertices i and j making up the edge i–j.

In the case of heterosystems, the connectivity index is given in terms of valence delta values $\delta(i)$ and $\delta(j)$ of atoms i and j and is denoted by χ^v. This version of the connectivity index is called the valence-connectivity index and is defined as[1,15,20]

$$\chi^v = \sum_{ij} [\delta(i)\,\delta(j)]^{-0.5} \tag{4}$$

where the sum is taken over all bonds i–j of the molecule. Each edge of G has, in this case, a weight of $\delta(i)\delta(j)$.

The modified Balaban index, J(G)

Balaban proposed a topological index, named distance-sum connectivity index, which is defined as follows[1,15,21]

$$J(\mathrm{G}) = \frac{M}{\mu+1} \sum_{edges} (\mathrm{d}_i \mathrm{d}_j)^{-0.5} \tag{5}$$

where M is the number of edges in G, μ is the cyclomatic number of G and (d_i) (i = 1,2, $\cdots$, N; N is the number of vertices in G) is the distance-sum. The distance sum for a vertex i represents the sum of all entries in the corresponding row (or column) of the distance matrix $\boldsymbol{D}$.

$$\mathrm{d}_i = \sum_{j=1}^{N} \boldsymbol{D}_{ij} \tag{6}$$

The cyclomatic number μ of a polycyclic graph G is equal to the minimum number of edges necessary to be erased from G in order to transform it into the related acyclic subgraph:

$$\mu = M - N + 1 \tag{7}$$

The Balaban index for heterosystems was modified by Barysz and co-authors.[22] The elements of the modified distance matrix for heterosystems are given by:

(a) for the diagonal elements

$$\boldsymbol{D}_{ii} = 1 - \frac{Z_c}{Z_i} \tag{8}$$

where $Z_c = 6$ and Z_i is the atomic number of the given element.

(b) for the off-diagonal elements

$$\boldsymbol{D}_{ij} = \sum_{r} k_r \tag{9}$$

where the summation is over bonds. The bond parameter k_r is given by

$$k_r = \frac{1}{b_r} \frac{Z_c^2}{Z_i Z_j} \tag{10}$$

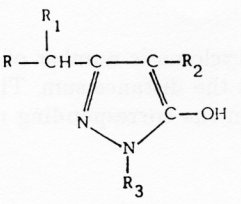
where b_r is the bond weight with values: 1 for single bond, 2 for double bond. The values of $\boldsymbol{D}_{ii}$ for various atoms, and k_r for various types of heterobonds are taken from the literature.[26]

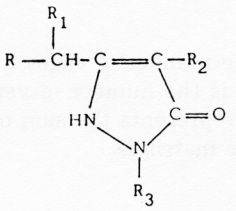
The Information-Theoretic Index, I(G)

The information-theoretic index I(G) was calculated by applying the information-theoretic formalism on chemical graph,[1] by means of the modification of Shannon's relation[23,24]

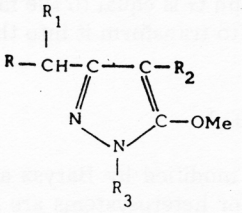
$$I(\mathrm{G}) = -\sum_{i=1}^{n} \frac{2N_i}{N(N-1)} \log_2 \frac{2N_i}{N(N-1)} \tag{11}$$

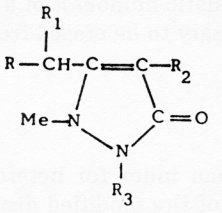
where n is the number of different sets of elements, N_i is the number of elements in the i-th set of elements and the sum is over all sets of elements. The logarithm is taken



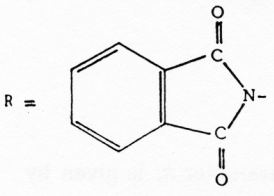


1, 3, 5, 6, 9, 10, 12-15, 17





2, 7, 11, 16 **4, 8**



R_1 = H	**(1-9, 17)**
-CH_3	**(*10*-16)**
R_2 = H	**(5, 9, 13, 14, 17)**
-CO_2Et	**(1-4, 6-8, 10-12, 15, 16)**
R_3 = H	**(1, 2, 4, 5, 10, 11, 13)**
-CH_3	**(3, 12, 14, 17)**
-Ph	**(6-9, 15, 16)**

Figure 1. The structures of substituted 3-(phthalimidoalkyl)-pyrazolin-5-ones.

on basis 2 for measuring the information content in bits. A certain distance of values i ($1 \leq i \leq N-1$) appears $2N_i$ times in the distance matrix. Since the distance matrix is a symmetric matrix, the upper-triangle part contains all the information about the observed system. The total number of elements in the upper-triangle of the distance matrix is $N(N-1)/2$.

DISCUSSION

Quantitative structure-activity relationship (QSAR) studies have been successfully applied to drug design. QSAR modelling is based on the mathematical representation of the connection between the structure of a molecule and its biological activity applicable to various classes of compounds.[27,28] In the first two papers of this series, the synthesis of congeneric series of 3-(phthalimidoalkyl)-pyrazolin-5-ones[12] and QSPR study of these compounds[15] were reported. The structures of 17 studied compounds are shown in Figure 1.

In our work, a molecular modelling technique based on four topological indices (W, χ^v, J, I) for the group of 17 new derivatives of recently synthesized 3-(phthalimidoalkyl)-pyrazolin-5-ones is considered. Molecular mass, mitodepressive activity on *Lepidium sativum L. (Cresson)* as biological activity and values of four topological indices (W, χ^v, J, I) as the structural parameters of the studied compounds are given in Table I.

All tested 3-(phthalimidoalkyl)-pyrazolin-5-ones have shown mitodepressive activity on *Lepidium sativum L. (Cresson)*. The structure-activity modelling based on the Wiener index and the valence-connectivity index gives the appropriate models in the QSAR study of mitodepressive activity of 3-(phthalimidoalkyl)-pyrazolin-5-ones and they are as follows:

$$\text{Inhibition (\%)} = 0.023\ (\pm 0.003)\ W - 3.802\ (\pm 4.820) \qquad (12)$$
$$n = 17,\ r = 0.92,\ s = 7.65,\ F = 38.55$$

TABLE I

Molecular mass, M_r, *mitodepressive activity Inhibition (%), the valence-connectivity index,* χ^v, *the Wiener index,* W, *the information-theoretic index,* I, *and the Balaban index,* J, *of 3-(phthalimidoalkyl)-pyrazolin-5-ones.*

Compound number	Abbreviated name	M_r	Inhibition (%) (0.05 mg/ml)	χ^v	W	I	J
1	Gly-Pyr	315.28	28.40	6.858	1411	3.486	2.066
2	Gly-Pyr-O-Me	329.31	28.00	7.266	1558	3.490	2.081
3	Gly-Pyr-1-N-Me	329.31	30.40	7.305	1503	3.385	2.062
4	Gly-Pyr-2-N-Me	329.31	27.70	7.305	1536	3.471	2.123
5	Gly-Pyr-Decarb	243.22	14.30	5.281	723	3.240	2.033
6	Gly-Ph-Pyr	391.37	68.30	9.052	2581	3.653	1.659
7	Gly-Ph-Pyr-O-Me	405.40	49.40	9.460	2781	3.647	1.691
8	Gly-Ph-Pyr-2-N-Me	405.40	65.20	9.499	2685	3.577	1.685
9	Gly-Ph-Pyr-Decarb	319.31	46.90	7.475	1685	3.678	1.567
10	Ala-Pyr	329.31	29.30	7.312	1520	3.462	2.156
11	Ala-Pyr-O-Me	343.33	28.90	7.721	1673	3.467	2.170
12	Ala-Pyr-1-N-Me	343.33	32.60	7.760	1613	3.363	2.149
13	Ala-Pyr-Decarb	257.25	12.20	5.736	799	3.209	2.115
14	Ala-Pyr-1-N-Me-Decarb	271.27	18.20	6.183	906	3.232	2.104
15	Ala-Ph-Pyr	405.40	71.70	9.506	2734	3.636	1.713
16	Ala-Ph-Pyr-O-Me	419.42	50.60	9.915	2941	3.630	1.744
17	Gly-Pyr-1-N-Me-Decarb	257.25	15.10	5.728	825	3.259	2.018

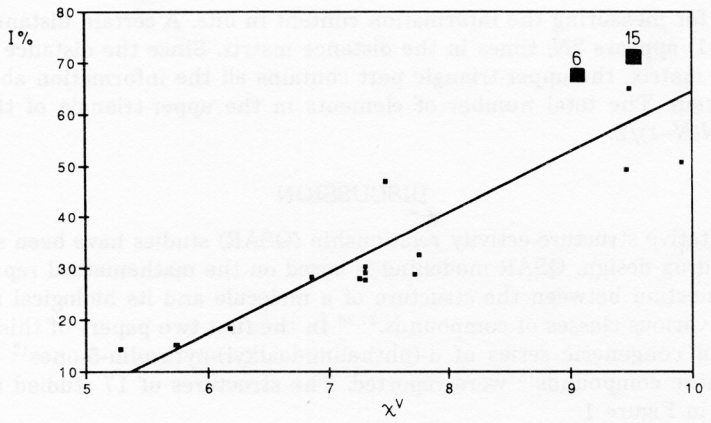
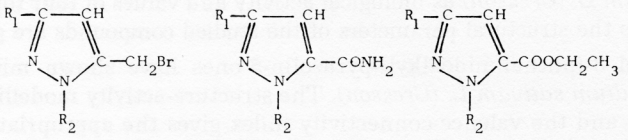


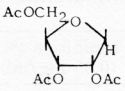
Figure 2. The linear QSAR model between Inhibition (%) of substituted 3-(phthalimidoalkyl)-pyrazolin-5-ones tested on *Lepidium sativum L.* and valence-connectivity index, χ^v.



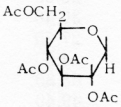
(6,10) (2, 7-9, 12,14) (1, 3-5, 11, 13)

R_1 = - CH_2Br (1-5, 7-9)
- $CONH_2$ (10)
- $COOCH_2CH_3$ (6)
- $CH_2N(CH_2CH_2Cl)_2$ (11 - 14)

R_2 = - H (1, 2, 11, 12)



(5, 9, 10, 13)



(3, 6, 7, 14)

(4, 8)

Figure 3. The structures of some substituted pyrazoles with cytostatic effect.

$$\text{Inhibition } (\%) = 11.780(\pm 1.431)\,\chi^{v} - 53.160(\pm 11.070) \quad (13)$$
$$n = 17,\ r = 0.91,\ s = 8.28,\ F = 67.79$$

The Balaban and the information-theoretic indices are less valuable for this study ($0.8 < r < 0.9$). The linear QSAR model, between inhibition (%) of the studied compounds tested on *Lepidium sativum L.* and valence-connectivity index, χ^{v}, is shown in Figure 2. The mitodepressive activity was significant for two compounds: 1-phenyl substituted pyrazolin-5-ones of glycine (**6**) and of alanine (**15**), which are used in the QSPR and QSAR studies of substituted pyrazoles with known cytostatic activity (ED_{50}) on the *HeLa cells.*[11] The structures of cytostatically active pyrazoles are shown in Figure 3.

All the compounds depicted in Figure 3 were evaluated as cytostatic agents against the *HeLa cell* culture.[10] All the bromomethylpyrazole nucleosides showed significant activities, while the corresponding bromomethylpyrazolic bases were completely inactive. However, most of the related pyrazole nitrogen mustard nucleosides were inactive. Substitution of the bromine atom of the bromomethyl group by the amino group caused a total loss of activity. The cytostatic activity data of pyrazoles are taken from the literature.[11] The »in vivo« cytostatic evaluation was estimated by a previously described method.[10,25] 6-Mercaptopurine was always included as a positive control ($ED_{50} = 0.1\ \mu g/ml$).

Experimental and calculated values (based on the Wiener index) of the cytostatic activity of pyrazoles (in ED_{50}), molecular mass and values of four topological indices (W, χ^{v}, J, I) as structural parameters are given in Table II.

The QSPR model of molecular mass for the pyrazoles with cytostatic activity shows similarity between the structures of two phthalimido-pyrazolin-5-ones (compounds **6** and **15** in Table I) and these pyrazoles. The most accurate mathematical model for molecular mass (M_r), based on the valence-connectivity index, is as follows

TABLE II

Molecular mass, M_r, *experimental*[11] *and calculated cytostatic activities,* ED_{50}, *the Wiener index,* W, *the valence-connectivity index,* χ^{v}, *the information-theoretic index,* I, *and the Balaban index,* J, *of cytostatically active pyrazoles*

Compound number	M_r	$(ED_{50})_{exp}$	$(ED_{50})_{calc}$	W	χ^{v}	I	J
1	232.99	100	72.293	255	4.635	2.945	2.892
2	203.98	100	78.958	156	3.659	2.745	2.994
3	491.11	2	4.361	2594	10.258	3.526	2.909
4	491.11	2.5	4.034	2547	10.258	3.476	2.816
5	534.13	4	12.842	3124	10.258	3.458	3.049
6	550.13	3	4.502	2087	9.282	3.411	2.849
7	462.10	2	4.233	2122	9.282	3.429	2.799
8	462.10	2	3.990	2159	9.282	3.493	2.790
9	294.07	18	41.552	791	6.883	3.429	2.792
10	265.03	20	53.470	564	5.907	3.282	2.771
11	552.16	100	64.704	4325	12.506	3.760	2.839
12	595.18	100	127.985	5166	13.007	3.786	3.022
13	523.15	50	33.741	3739	11.529	3.761	2.801
14	611.19	35	35.288	3774	11.529	3.777	2.776

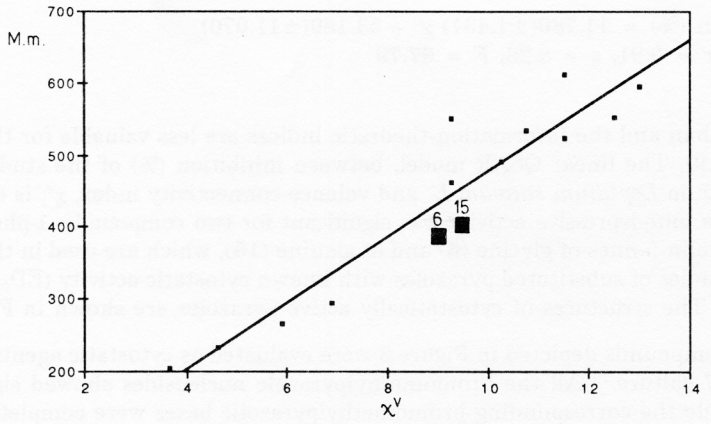


Figure 4. The linear QSPR model of molecular mass, M_r, of substituted pyrazoles based on the valence-connectivity index, χ^v.

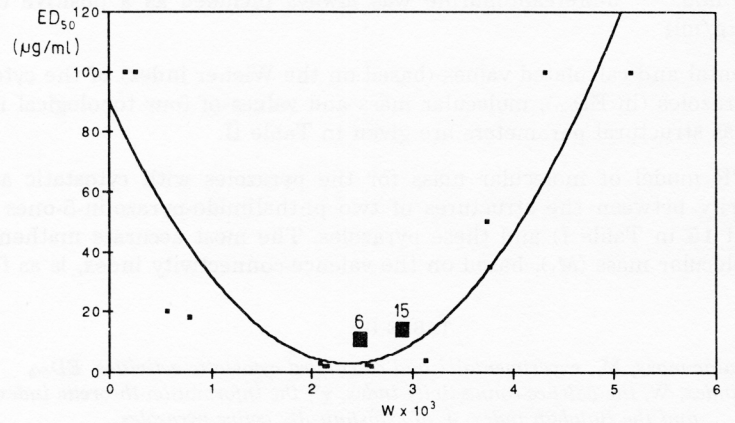


Figure 5. The parabolic QSAR model of cytostatic activity, ED_{50}, of substituted pyrazoles based on the Wiener index, W.

$$M_r = 45.805(\pm 4.109)\chi^v + 19.783(\pm 39.325) \quad (14)$$
$$n = 16,\ R = 0.95,\ s = 42.86,\ F = 124.27$$

Correlations of other indices with M.m. produced less satisfactory results ($r < 0.9$). The linear model based on the valence-connectivity index for molecular mass is shown in Figure 4.

The QSAR study of cytostatic activity (ED_{50}) of pyrazoles[11] gives the most accurate mathematical model based on the Wiener index as follows:

$$ED_{50} = 1.6 \times 10^{-5}(\pm 3 \times 10^{-6})\ W^2 - 0.074(\pm 0.013)\ W + 90.295(\pm 14.531) \quad (15)$$
$$n = 14,\ r = 0.88,\ s = 21.89,\ F = 19.29$$

This model enabled prediction of the cytostatic activity (ED_{50}) for two phthalimido-pyrazolin-5-ones previously evaluated as good cytostatic agents on *Lepidium sativum L. (Cresson)*. The calculated ED_{50} activities for compounds **6** and **15** are 4.263 and 5.744, respectively. The plot of cytostatic activity (ED_{50}), based on the Wiener index, is shown in Figure 5. The parabolic QSAR model based on the valence-connectivity index gives lesser standard deviation (s = 14.44) and coefficient of correlation (r = 0.95), but in this consideration it is not accepted, because the values of ED_{50} of some tested compounds showed a negative rate merit.

CONCLUDING REMARKS

Several molecular modelling techniques for the group of 17 new derivatives of recently synthesized 3-(phthalimidoalkyl)-pyrazolin-5-ones have been considered. All tested 3-(phthalimidoalkyl)-pyrazolin-5-ones have shown mitodepressive activity on *Lepidium sativum L. (Cresson)*. The activity was significant for two compounds: 1-phenyl substituted pyrazolin-5-ones of glycine and of alanine. The structural parameters were four topological indices (W, χ^v, J, I). The structure-property-activity models based on the valence-connectivity index are most widely used in QSPR[29–31] and QSAR[20] studies. Thus, the structure-activity model based on the valence-connectivity index and the Wiener index as significant models for the QSAR study of 3-(phthalimidoalkyl)-pyrazolin-5-ones appeared in this work. The parabolic QSAR model enables prediction of cytostatic activity on the *HeLa cell* for yet untested phthalimido-pyrazolin-5-ones.

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SAŽETAK

QSAR 3-(ftalimidoalkil)-pirazolin-5-ketona

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Mitodepresivna aktivnost 17 novosintetiziranih 3-(ftalimidoalkil)-pirazolin-5-ona istraživana je na biljkama *Lepidium sativum L. (Cresson).* Svi testirani spojevi pokazuju mitodepresivni efekt na rast te biljke. Četiri topologijska indeksa (Wienerov indeks, indeks valencijske povezanosti, Balabanov indeks i informacijsko-teorijski indeks) uporabljena su u istraživanjima QSAR (inhibicija rasta biljaka istražena u %, citostatska aktivnost izražena kao ED_{50}, tih spojeva. Predloženi QSAR-modeli omogućuju predviđanje citostatske aktivnosti na HeLa stanicama za istraživane spojeve.