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Inhibition of Hill Reaction by 3-Alcoxyuracil Derivatives: QSAR Study With Topological Indices

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This study was undertaken to find a simple and accurate structural parameter for the quantitative description of inhibitory potency of alcoxyuracils in the Hill reaction and to gain more information about the mechanism of inhibition on the molecular level. A very good correlation ($r = 0.987$) was obtained between pI_{50} values (negative logarithm of the concentration that causes 50% inhibition) and the valence first-order and the fifth-order molecular connectivity indices. This model, when compared with the empirical models based on the *n*-octanol/water partition coefficients, shows superior or at least comparable performances in accuracy and range of applicability. In addition, the direct correspondence between molecular structure and the above connectivity indices makes it possible to locate structural features responsible for the inhibitory potency of alcoxyuracils in the Hill reaction and to learn more about the mechanism of inhibition on the molecular level. From our QSAR analysis, the interaction between the chloroplast receptor site and alcoxyuracils, which cause inhibition of Hill reaction, can be viewed as a two-stage mechanism. The first stage is a complex formation beteween the uracil ring and some active site of chloroplast. The second stage is a hydrophobic interaction between the alcoxy chain and a hydrophobic region close to the active site. It is assumed that this stage proceeds by the »zipper« mechanism and that it accounts for the quantitative differences in inhibition found for the studied alcoxyuracils.

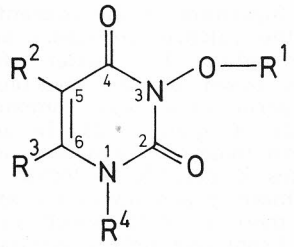
INTRODUCTION

A large number of commercial herbicides function as inhibitors of photosynthesis in chloroplast. The biochemical and biophysical mechanism of photosynthesis is successfully studied in cellfree systems of isolated chloroplast. Thus, it is known that the majority of structurally diverse classes of herbicides (*e. g.* ureas, anilides, s-triazines, as-triazinones, uracils, biscarbamates, pyridazinones, hydroxybenzonitriles, nitrophenols, benzimidazoles, etc.) act as inhibitors

of photosynthetic electron flow on the reducing (acceptor) side of photosystem II.[1] Their inhibitory potency can be determined *in vitro* from their ability to inhibit the Hill reaction. (In Hill reaction an artifical electron acceptor (*e. g.* potassium ferricyanide) is photoreduced by the suspension of isolated chloroplasts.) However, there is no simple relationship between their reactivity in the Hill reaction and herbicidal activity.[2] This is probably caused by the fact that in the Hill test important phenomena, such as transportation and metabolic stability of herbicides, are ignored. In spite of this problem, the reactivity in the Hill test is regularly used as a quantitative measure of herbicidal activity in the design of new herbicides.

In this investigation, the quantitative structure activity relationship (QSAR) will be formulated for the inhibition of the Hill reaction by 3-alcoxyuracils. Topological indices[3–6] will be used as quantitative descriptors of molecular structures. They have been demonstrated to be very successful in formulating numerous QSAR models with physico-chemical properties,[3–8] biological activities,[3–6,9,10] and environmental behavior[3,6,11–21] of chemicals. In addition, these nonempirical structural descriptors can be obtained very quickly, with high precision and the process is inexpensive.

Our primary objective is to develop a quantitative model, based on topological indices, which will predict the inhibitory potency of 3-alcoxyuracils within experimental error. The initial set of 22 compounds will only differ in the size and type of alcoxy group on position 3 (see structure 1).



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The quantitative model obtained for such a training set will be subsequently tested on a smaller group of structurally more diverse 3-alcoxyuracils to assess its predictive power. To check the quality of these predictions, the results of this test will be compared with the inhibitory activities predicted from models based on *n*-octanol/water partition coefficients (log *P*).[2,22] The above results will provide important information about the performance and range of applicability of molecular topology in predicting biological activites of herbicides. In addition, topological indices are used here for the first time to formulate QSAR models for herbicides and to design new herbicides.

METHOD OF CALCULATION AND EXPERIMENTAL DATA

Several extensive reviews of the theory and method of calculation of molecular connectivity indices have been published recently.[3-6] Thus, only a brief description of the calculation of topological indices used in the nonempirical models discussed in this study is given here.

The first-order valence molecular connectivity indices ($^1\chi^v$) are calculated from the non-hydrogen part of the molecule. Each non-hydrogen atom is described by its atomic δ^v value, which is calculated from the following equation:

$$\delta^v = (Z^v - h)/(Z - Z^v - 1) \tag{1}$$

where Z is its atomic number, Z^v is the number of valence electrons in the atom and h is the number of hydrogen atoms bound to the same atom. The $^1\chi^v$ indices are then calculated from the atomic δ^v values by equation 2.

$$^1\chi^v = \sum_n (\delta_i^v \cdot \delta_j^v)^{-0.5} \tag{2}$$

where i and j correspond to the pairs of adjacent non-hydrogen atoms and the summation is over all bonds between non-hydrogen atoms.

The fifth-order molecular connectivity indices ($^5\chi$) are also calculated from the non-hydrogen part of the molecule and the corresponding δ values (the number of adjacent non-hydrogen atoms) by equation 3,

$$^5\chi = \sum_n (\delta_i \cdot \delta_j \cdot \delta_k \cdot \delta_l \cdot \delta_m \cdot \delta_n)^{-0.5} \tag{3}$$

where i, j, k, l, m, and n correspond to six consecutive non-hydrogen atoms and the summation is over all sequences of five adjacent bonds between non-hydrogen atoms. In all valence type molecular connectivity indices the effect of unsaturation is taken into account only by using a different value for h, which is reversely proportional to the degree of unsaturation. Thus, molecules with a higher degree of unsaturation will have smaller valence molecular connectivity indices providing that all other structural features are identical.

The Wiener number (W) was defined[23] as the number of bonds between all pairs of non-hydrogen atoms in a molecule. It can be easily calculated from the distance matrix of the molecular graph and it is equal to half the sum of its off-diagonal elements.

Molecular connectivity indices were calculated by the GRAPH III computer program on an IBM PC/XT personal computer.[3] Minimum hardware and software requirements for this program are an IBM PC or a compatible computer, 256 KB memory, a double sided/double density disk drive, and PC-DOS or MS-DOS operating system version 2.1 or higher. The use, of mathematical coprocessor is higly recommended. In its present version, GRAPH III can calculate molecular connectivity indices up to the tenth order for molecules with 35 non-hydrogen atoms or less. It is possible to extend the program to handle larger molecules if sufficient memory is available.

Regression analysis was carried out using the statistical analysis system (SAS). To test the quality of regression equations the following statistical parameters were used: the correlation coefficient (r), the standard error of the estimates (s). a test of the null hypothesis (F-test) and the amount of explained variance (EV).

Inhibitory activities of 3-alcoxyuracils are taken from the study of Brown *et al.*[2] They are expressed as pI_{50}, the negative logarithm of concentrations causing 50% inhibition in the Hill reaction. Their experimental errors are in the range of 1—5%.

RESULTS AND DISCUSSION

Molecular connectivity indices and Wiener numbers were calculated for 22 alcoxyuracil derivatives shown in Table I.

TABLE I

Wiener Numbers, the First-order Valence, and Fifth-order Molecular Connectivity Indices Plus the Observed[2] and Calculated (eq. 5) Inhibitory Potencies (pI_{50}) of 22 Alcoxyuracils in the Hill Reaction. Alcoxyuracils Used in This Study are Described by Structure 1, Where R^2=Br, R^3=methyl and R^4=H, and only Substituent R^1 is Indicated in This Table.

R^1	W	$^1\chi^v$	$^5\chi$	pI_{50}	
				exp.	calc.
3-O-methy	181	3.927	1.716	2.6	2.8
3-O-ethyl	234	4.514	2.172	3.9	3.8
3-O-(2-chlroethyl)	300	5.108	2.248	4.4	5.0
3-O-*n*-propyl	300	5.014	2.248	4.9	4.8
3-O-*iso*-propyl	289	4.909	2.478	4.5	4.3
3-O-allyl	300	4.624	2.248	4.3	4.0
3-O-propargyl	300	4.450	2.248	3.6	3.6
3-O-*n*-butyl	380	5.514	2.323	5.4	5.6
3-O-*sec*-butyl	358	5.447	2.540	5.0	5.2
3-O-*iso*-butyl	368	5.370	2.326	5.5	5.3
3-O-*n*-pentyl	475	6.014	2.457	5.8	6.1
3-O-*n*-hexyl	586	6.514	2.582	6.3	6.6
3-O-*n*-heptyl	714	7.014	2.707	6.8	6.9
3-O-*n*-octyl	860	7.514	2.832	7.3	7.2
3-O-*n*-nonyl	1025	8.014	2.957	7.8	7.5
3-O-*n*-decyl	1210	8.514	3.082	7.9	7.6
3-O-*n*-undecyl	1416	9.014	3.207	7.9	7.8
3-O-*n*-dodecyl	1644	9.514	3.332	8.0	7.9
3-O-*n*-tridecyl	1895	10.014	3.457	7.9	8.0
3-O-*n*-tetradecyl	2170	10.514	3.582	7.9	8.0
3-O-*n*-hexadecyl	2796	11.514	3.832	7.8	8.1
3-*sec*-butyl (bromacil)	280	5.287	2.233	5.9	5.3

From the correlation diagrams it was easy to conclude that the exponential relation is apparent between the topological indices and the inhibitory potencies of alcoxyuracils. Thus, single variable models (hyperbolic, exponential, and logarithmic) were calculated for the zero- and first-order molecular connectivity indices and Wiener numbers to find an index that would most adequately describe the influence of alcoxy chains on the inhibitory potencies of alcoxyuracils. (Their linear and quadratic models were also tested but, as expected from the correlation diagrams, were found to be less successful.) The best relationship was obtained between pI_{50} and the hyperbolic function of the first-order valence molecular connectivity index ($^1\chi^v$). The regression equation and statistical parameters describing this quantitative model are the following:

$$pI_{50} = 11.5(\pm 0.3) - 33.8(\pm 1.6)/^{1}\chi^{v} \quad (4)$$

$$N = 22 \quad r = 0.978 \quad s = 0.351 \quad F^{1,20} = 440 \quad EV = 95.4\%$$

The statistical paraemters show that eq. 4 is statistically significant above the 99% level and it accounts for more than 95% of the variation in the pI_{50} data. (The 95% confidence intervals are shown in parentheses.) The two variable models were screened to find if any higher-order molecular connectivity index would significantly improve the quality of eq. 4. The result of this search is presented by the following equation:

$$pI_{50} = 17.7(\pm 1.7) - 48.9(\pm 4.3)/^{1}\chi^{v} - 1.4(\pm 0.3) \cdot {}^{5}\chi \quad (5)$$

$$N = 22 \quad r = 0.987 \quad s = 0.268 \quad F^{2,19} = 366 \quad EV = 97.2$$

The introduction of the second variable ($^{5}\chi$) made statistically significant improvements in our model. The standard eror (s) is lower by the huge amount of 24%. The value of F-test clearly shows that improvements are real and not caused by the sole fact that more variables are used. Equation 5 accounts for more than 97% of the variation in the pI_{50} data and this is probably as good as can be expected since the average experimental error in the pI_{50} data is 2—3%. A comparison of the observed and predicted inhibitory potency of alcoxyuracils, Table I, clearly demonstrates that the molecular connectivity model (eq. 5) is very accurate in predicting their pI_{50} data. The average difference between the predicted and observed pI_{50}'s is only 0.2 log units (factor 1.58) and only two compounds are predicted outside the two standard deviations. The high accuracy of the molecular connectivity model in predicting the inhibitory potency of alcoxyuracils is also shown in Figure 1 where the observed *vs.* predicted pI_{50} data of test compounds from Table I are plotted.

The highly satisfactory performance of the molecular connectivity model (eq. 5) in predicting the inhibitory potency of alcoxyuracils in the Hill reaction prompted us to examine its predictive ability and its range of applicability. This task will be performed on nine alcoxyuracils shown in Table II along with their observed and calculated pI_{50} data, plus, corresponding molecular connectivity indices and n-octanol/water partition coefficients.

This table is composed of two groups of compounds: (a) alcoxyuracil derivatives, whose pI_{50} data are still uncertain (reported only as smaller than), and (b) alcoxyuracil derivatives, whose ring substitution pattern differs from those of alcoxyuracils shown in Table I. The molecular connectivity model (eq. 5) gave qualitatively correct prediction for the inhibitory potency (pI_{50}) of 3-hydroxy-5-bromo-6-methyluracil. Its performance is very satisfactory for alcoxyuracil derivatives where bromine is substituted by hydrogen or SCN group. This result shows that substituents at position 5 do not interact with an active site of chloroplast but rather influence the inhibitory activity, either by the steric effect or some nonspecific interaction. Other alcoxyuracil derivatives from Table II have n-propyl and methyl groups in place of the methyl group (position 6) and hydrogen (nitrogen position 1), respectively. In both cases, a larger substituent leads to a significant loss of activity. This suggests that the loss of activity is caused by an unfavorable steric effect, where larger alkyl groups partially obstruct interaction between alcoxyuracils and the hypothetical receptor site. In the case of nitrogen substitution the loss

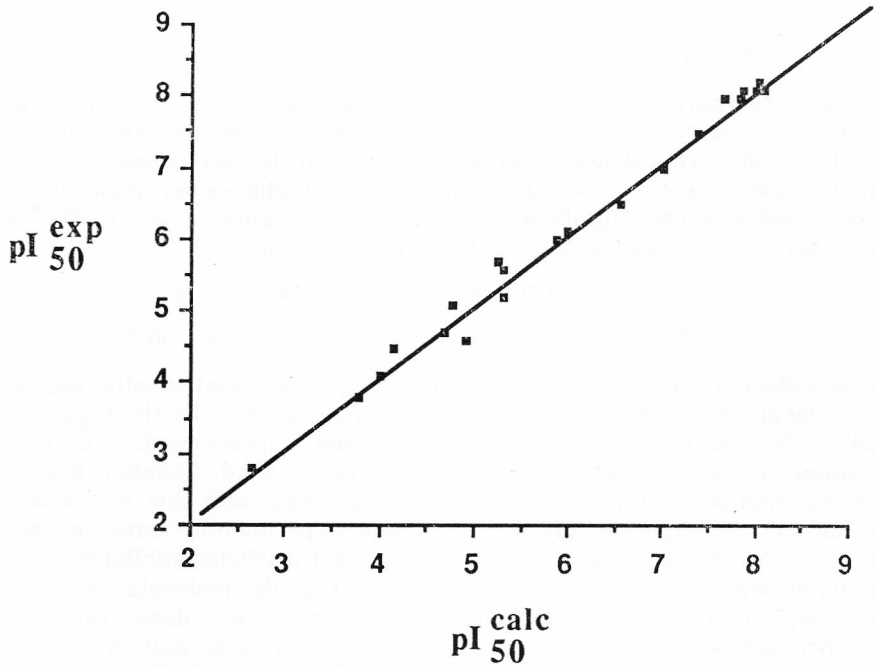

Figure 1. Correlation between the observed and predicted inhibitory potencies (pI_{50}) of 22 alcoxyuracils from Table I. The solid line presents their linear regression model. Predicted inhibitory potencies are calculated by eq. 5, which is based on molecular connectivity indices.

TABLE II

Comparison of the Observed[a] and Calculated (eqs. 5, 6, and 7) Inhibitory Potencies (pI_{50}) of Substituted Alcoxyuracils, Plus Their First-order Valence and Fifth-order Molecular Connectivity Indices and n*-Octanol/Water Partition Coefficients (log* P*). The Calculated pI_{50} Data are Calculated From a Model Based on Molecular Connectivity Indices (eq. 5) and Models Based on* n*-Octanol/Water Partition Coefficients (eqs. 6 and 7).*

Compound (R^1, R^2, R^3, R^4)[a]	$^1\chi^v$	$^5\chi$	pI_{50} Calc. (eq. 5)	pI_{50} Exp.	pI_{50} Calc. (eq. 7)	pI_{50} Calc. (eq. 6)	log *P*
OH, Br, methyl, H	3.536	1.523	1.8	<2.5	2.5	2.9	—1.12
-O-*n*-propyl, H, methyl, H	4.111	1.943	3.1	2.5	4.1	4.3	0.30
-O-*n*-octyl, H, methyl, H	6.456	2.403	6.8	5.6	7.0	6.8	2.92
-O-*n*-propyl, SCN, H, H	5.479	2.840	4.8	3.4	3.5	3.8	—0.22
-O-*n*-octyl, SCN, methyl, H	7.979	3.425	6.8	6.9	6.4	6.3	2.40
-O-*n*-propyl, Br, *n*-propyl, H	6.075	2.873	5.6	3.8	5.7	5.7	1.73
-O-*n*-octyl, Br, *n*-propyl, H	8.575	3.458	7.1	6.4	7.9	8.2	4.35
-O-*n*-propyl, Br, methyl, methyl	5.409	2.467	5.2	<2.5	4.6	4.7	0.72
-O-*n*-octyl, Br, methyl, methyl	7.909	3.052	7.2	<3.6	7.4	7.2	3.34

[a] For substitutio pattern see structure 1.

of activity may be also associated with the inability of such compounds to generate a hydrogen bond or charge transfer complex. Since our molecular connectivity model does not account for the above properties of alcoxyuracils, it is no wonder that it cannot predict correctly the inhibitory potency for such derivatives.

To additionally check the quality of the above predictions of our molecular connectivity model, we will now examine the predictive ability of QSAR models based on the *n*-octanol/water partition coefficients. The reported linear[2] and bilinear[22] models are described by eqs. 6 and 7, respectively.

$$pI_{50} = 0.96 \cdot \log P + 4.02 \qquad (6)$$
$$N = 13 \quad r = 0.99 \quad s = 0.18$$

$$pI_{50} = 1.12 \cdot \log P - 1.15 \cdot \log (\beta \cdot 10^{\log P} + 1) + 3.78 \qquad (7)$$
$$N = 22 \quad r = 0.991 \quad s = 0.261 \quad \log \beta = -3.76$$

The results of their predictive ability are shown in Table II. The inhibitory potency calculated by the linear model (eq. 6) is shown for global comparison with other models since this model is applicable only to alcoxyuracils whose $\log P$ data are in the range of 0—4 and it was derived for less than 60% of alcoxyuracil derivatives of our training set (Table I). In general, the predictive ability of the bilinear model (eq. 7) is inferior to our molecular connectivity model (eq. 5). Detailed analysis shows that the molecular connectivity model performs better in all cases except 3-propoxy-5-SCN-uracil and 1-methyl-3-propoxy-5-bromo-6-methyluracil. It is fair to conclude that the molecular connectivity model is clearly superior in accuracy and range of applicability to models based on *n*-octanol/water partition coefficients. However more work is necessary to improve its accuracy and range of applicability.

In this paragraph, we will discuss the mechanism of interaction between the »receptor site« of chloroplast and alcoxyuracil derivatives in the Hill reaction with particular emphasis on its relationship to our topological QSAR model. From experimental data[2] and the results of our and previous QSAR analyses,[2,22] interactions between the chloroplast receptor site and the studied alcoxyuracils, which cause inhibition of the Hill reaction, can be viewed as a two-stage mechanism. The first stage is a »complex formation« between the uracil ring (or part of it) and some active site of chloroplast. This stage is responsible for the inhibitory activity of alcoxyuracils and can be obstructed, to a high degree, by unfavorable ring substitution (*e. g.* large substituents at ring positions 1 and 6). The second stage is a hydrophobic interaction between the alcoxy chain and a hydrophobic region close to the active site involved in the first stage. This stage accounts for the quantitative differences in the inhibitory potency found for the studied alcoxyuracils (Table I). Since the alcoxy group posesses a high degree of conformational freedom, it is reasonable to assume that its binding to the hydrophobic region will proceed by the »zipper« mechanism.[24] In this mechanism, it is proposed that the initial interaction (first-stage) is followed by a series of conformational rearrangements of the partially bound alcoxyuracil, leading to the bindig of the remaining segments of the alcoxy chain to their appropriate positions. Such a mechanism allows mutual conformational adjustment of both alcoxyuracil

and the hydrophobic region of chloroplast. The zipper mechanism has also been proposed as an explanation for the double-helix formation in nucleic acids and the receptor binding of peptide hormones,[24] methadone binding to apiate receptor site,[25] and for the specific binding of alkyl alcohols to cytochrome P-450.[26] Our molecular connectivity model shows that the degree of inhibition of the Hill reaction by alcoxyuracils is directly proportional to the size of the alcoxy chain ($^1\chi^v$ index). The inhibitory potency of alcoxyuracils increases with the size of the alcoxy chain until a plateau is reached which corresponds to an *n*-alcoxy chain with nine carbon atoms. This may be a point where the *n*-alcoxy chains begin to extend beyond the limits of the receptor hydrophobic region. (The possibility that at this point a folding of the *n*-alcoxy chain starts to play a significant role should also be entertained.) It is difficult to say something about the influence of branching on the inhibitory potency of alcoxyuracils since only a small number of alcoxyuracils with the branched chain were tested and they do not show consistent behavior. Such behavior can be rationalized by the assumption that the receptor hydrophobic region is very flexible and can adapt itself to optimize the interaction with various types of alcoxy chains. Similar results were obtained for phenylureas,[22] where even a bulky adamantyl group was able to interact strongly with the hydrophobic region of chloroplast. Our molecular connectivity model (eq. 5) is consistent with this assumption about the nature of the hydrophobic region since is does not contain any cluster or path/cluster type connectivity indices highly sensitive to changes in branching.[26,27]

CONCLUSION

In this investigation we have demonstrated that a simple model, based on topological indices, can be used to describe accurately the inhibitory potencies of alcoxyuracils in the Hill reaction. From our QSAR analysis, the interaction between the chloroplast receptor site and alcoxyuracils, which causes inhibition of the Hill reaction, can be viewed as a two-stage mechanism and the size of alcoxy chain accounts for almost all quantitative differences in the inhibitory potency found for the studied alcoxyuracils. In addition, our model is in fine agreement with the experimental[2] and theoretical[22] results on alcoxyuracils and other inhibitors of the Hill reaction.

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SAŽETAK

Inhibicija Hillove reakcije s derivatima alkoksiuracila: »QSAR« istraživanje s topološkim indeksima

Milan Šoškić i Aleksandar Sabljić

Ciljevi istraživanja bili su otkrivanje jednostavnih i preciznih strukturnih parametara za kvantitativan opis inhibitorske snage alkoksiuracila u Hill-ovoj reakciji, te proširenje naših spoznaja o mehanizmu inhibicije na molekulskom nivou. Dobivena je vrlo dobra korelacija ($r = 0.987$) između vrijednosti pI_{50} (negativan logaritam koncentracije koja uzrokuje 50%-tnu inhibiciju) te molekulskih indeksa povezanosti prvoga i petog reda. Iz usporedbe ovog modela s iskustvenim modelima utemeljenim na koeficijentu raspodjele *n*-oktanol/voda proizlazi da je naš model superioran i po preciznosti i po širini područja primjene. Pored toga, neposredna veza između molekulske strukture i navedenih indeksa povezanosti omogućuje nam da odredimo strukturna svojstva molekula koja su odgovorna za inhibitorsko djelovanje alkoksiuracila u Hill-ovoj reakciji. Naša QSAR analiza pokazala je da se proces interakcije između receptora na kloroplastu i alkoksiuracila odvija u dva stupnja. Prvi je stupanj stvaranje kompleksa između uracilnog prstena i aktivnog mjesta na kloroplastu. Drugi je stupanj hidrofobna interakcija između alkoksidnog lanca i hidrofobnog područja kloroplasta koje se nalazi u blizini aktivnog mjesta. Pretpostavlja se da se drugi stupanj odvija preko »zipper« mehanizma i da je odgovoran za kvantitativne razlike u aktivnostima proučavanih alkoksiuracila.