QSAR Study of 1,8-Naphthyridin-4-ones As Inhibitors of Photosystem II

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The effect of substituents on in vitro activity of 20 1,8-naphthyridin-4-ones, a novel class of photosystem II inhibitors, was studied. A four-parameter QSAR model based on the molecular connectivity indices was developed which accounts for about 87% of the variations in inhibitory potencies of these compounds. The model suggests that the position, size, and polarity of substituents are factors that predominantly control their activity. By using physicochemical constants, a quantitative model for both 1,8-naphthyridin-4-ones and structurally related 2-trifluoromethyl-4-hydroxyquinoline derivatives was proposed.

1. INTRODUCTION

Nearly one-third of all herbicides on the market act as inhibitors of photosynthesis.[1] Most of them block electron transport in chloroplast, by displacing the secondary electron acceptor Q_B, a plastoquinone molecule, from its binding site on photosystem II complex. These structurally different compounds can be roughly classified in the serine and the histidine families.[2] It is assumed that serine type herbicides (like ureas and triazines) are oriented in the receptor cavity toward serine 264 and members of histidine family (to which belong phenol type herbicides) toward histidine 215. The two types of inhibitors respond differently in experiments with tris-treated chloroplasts and herbicide resistant plants. Thus, while the treatment of chloroplasts with tris buffer reduces the inhibitory potency of serine type inhibitors, the activity of histidine type inhibitors remains unchanged. Also, the plants tolerant to the serine type inhibitors are sensitive or even supersensitive to the inhibitors of the histidine family.

In an effort to learn more about ligand−receptor interactions numerous QSAR (quantitative structure−activity relationship) studies have been carried out for these type of photosynthetic inhibitors.[3,4] In this paper we present a QSAR study on 1,8-naphthyridin-4-ones,[5] a novel class of photosystem II inhibitors, which display a rather unusual progressive inhibition of the Hill reaction.[5,6] We consider here only the initial inhibition of the Hill reaction by the naphthyridinones, which corresponds to the standard procedure for determination of in vitro activity of photosystem II inhibitors.

The molecular structure of the naphthyridinones is described by two types of molecular descriptors: nonempirical[7] molecular connectivity indices[8,9] that have proven to be useful in various QSAR studies[9,10−14] and physicochemical constants. The separate models based on these descriptors are generated, and their performances are compared. Structural similarities between 1,8-naphthyridin-4-ones and hydroxyquinoline derivatives, whose QSAR study was recently published,[15] prompt us to attempt to generate a common model for both groups of the compounds. In addition to the standard regression models, models based on orthogonalized[16] descriptor variables are also generated.

2. METHODS OF CALCULATION AND EXPERIMENTAL DATA

2.1. Molecular Connectivity Indices.[7−9] Simple and valence molecular connectivity indices are calculated from the non-hydrogen part of a substituent. The simple molecular connectivity indices are calculated from the corresponding δ values of the skeletal atoms, which denote the number of adjacent non-hydrogen atoms bonded to a particular atom. The valence molecular connectivity indices are calculated from the valence delta values (δ^v) of the skeletal atoms, which are defined by the equation

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

where Z^v is the number of valence electrons in an atom, Z is its atomic number, and h is the number of hydrogen atoms attached to those atoms. The simple ($^0\chi$) and valence ($^0\chi^v$) zero-order molecular connectivity indices are defined as

$$^0\chi = \Sigma(\delta_i)^{-0.5} \quad (2)$$

$$^0\chi^v = \Sigma(\delta_i^v)^{-0.5} \quad (3)$$

where the sums are over all non-hydrogen atoms.

2.2. Physicochemical Constants. The physicochemical (lipophilic, steric, and electronic) substituent constants were taken from the literature.[17] The π value for isoamyl was calculated according to Hansch additivity rules.[17]

2.3. Orthogonalization Procedure. The molecular connectivity indices and physicochemical constants are orthogonalized by the method recently proposed by Randić.[16] The method is based on the sequential removing of the redundant

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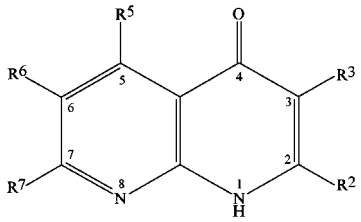

Figure 1. Structure of 1,8-naphthyridin-4-one derivatives.

information from the set of correlated variables. For the arbitrarily selected order of orthogonalization, the construction of orthogonalized descriptors goes as follows:[16,18] The information content of the first orthogonal (Ω) descriptor remains unchanged. It is an original variable, say it is X_1.

$$X_1 = \Omega(X_1) \tag{4}$$

The second orthogonal descriptor $\Omega(X_2)$ is the residual (e_1) of X_2 obtained after its regression against X_1:

$$X_2 = a_1 + b_1X_1 + e_1 \tag{5}$$

$$e_1 = X_2 - (a_1 + b_1X_1) = \Omega(X_2) \tag{6}$$

The third orthogonal descriptor $\Omega(X_3)$ is the residual (e_2) of X_3 when it is regressed against X_1 and X_2

$$X_3 = a_2 + b_2X_1 + b_3X_2 + e_2 \tag{7}$$

$$e_2 = X_3 - (a_2 + b_2X_1 + b_3X_3) = \Omega(X_3) \tag{8}$$

and so on. The procedure continues until all variables from the set are orthogonalized.

2.4. QSAR Calculation. Multiple regression analysis was carried out using statistical package SAS (statistical analysis system).[19] In all regression equations n is the number of compounds used in the analysis, r^2 is the squared correlation coefficient, s is the standard deviation of the estimates and F is the Fisher's variance ratio. The 95% confidence intervals for the regression coefficients are shown in parentheses. The significance of all the derived models and the regression coefficients is above 95% level.

2.5. Experimental Data. The inhibitory activities of the 1,8-naphthyridin-4-ones and 2-trifluoromethylhydroxyquinolines were taken from studies of Mitchell et al.[5] and Draber et al.,[15] respectively. They are expressed as pI_{50}, the negative logarithm of concentration required for 50% inhibition of the Hill reaction. The pI_{50} values are sensitive to the concentration of chloroplasts used in an experiment.[20] Consequently, they may vary from laboratory to laboratory for the same compound. The inhibitory potencies for the naphthyridinone and the hydroxyquinoline derivatives are determined under somewhat different experimental conditions, yet it seems that their pI_{50} values are comparable, since both laboratories were reported a similar value for the inhibitory potency of diuron (7.4 and 7.1, respectively).

3. RESULTS AND DISCUSSION

3.1. QSAR Models for 1,8-Naphthyridin-4-ones. The substitution pattern for 21 1,8-naphthyridin-4-ones (Figure 1) and their observed and calculated pI_{50} values are summarized in Table 1. The compound 21 whose experimental pI_{50} value is not determined has been excluded from regression analysis. The molecular connectivity indices used in the developed model are displayed in Table 2. As is seen from Table 1, substituents at position 3 for the compounds 1−13, and substituents at positions 5−7 for compounds 14−20 were mostly varied. The other substituent positions were generally held constant.

Table 1. Substituent Pattern and the Observed and Calculated Inhibitory Potencies of 21 1,8-Naphthyridin-4-ones

						pI_{50}		
no.	R^2	R^3	R^5	R^6	R^7	(exp.)	eq 9	eq 11
1	CH_3	H	CH_3	H	CH_3	5.89	5.92	5.74
2	C_2H_5	H	CH_3	H	CH_3	6.15	5.92	5.74
3	*i*-C_3H_7	H	CH_3	H	CH_3	5.68	5.92	5.74
4	CH_3	CH_3	CH_3	H	CH_3	6.56	6.45	6.38
5	CH_3	C_2H_5	CH_3	H	CH_3	6.85	6.57	6.60
6	CH_3	*n*-C_3H_7	CH_3	H	CH_3	6.44	6.47	6.52
7	CH_3	*i*-C_3H_7	CH_3	H	CH_3	6.12	6.42	6.53
8	CH_3	*i*-C_4H_9	CH_3	H	CH_3	6.12	6.05	6.03
9	CH_3	*i*-C_5H_{11}	CH_3	H	CH_3	5.49	5.46	5.37
10	CH_3	Cl	CH_3	H	CH_3	6.77	6.49	6.48
11	CH_3	Br	CH_3	H	CH_3	6.98	6.56	6.56
12	-$(CH_2)_3$-		CH_3	H	CH_3	6.22	6.47	6.41
13	-$(CH_2)_4$-		CH_3	H	CH_3	6.74	6.55	6.47
14	CH_3	CH_3	CH_3	Br	CH_3	7.40	7.52	7.40
15	CH_3	C_2H_5	CH_3	Br	CH_3	7.52	7.64	7.62
16	CH_3	C_2H_5	H	H	CH_3	5.55	6.03	5.94
17	CH_3	C_2H_5	H	Br	CH_3	7.10	7.10	6.96
18	CH_3	C_2H_5	CH_3	H	NH_2	5.57	5.52	5.59
19	CH_3	C_2H_5	CH_3	H	NHC_2H_5	5.95	6.06	6.33
20	CH_3	C_2H_5	CH_3	H	$N(C_2H_5)_2$	6.27	6.25	6.95
21	CH_3	C_2H_5	CH_3	H	H	nd[a]	6.57	6.28

[a] nd = not determined.

Table 2. Substituent Molecular Connectivity Indices Used in Deriving Eq 9[a]

substituent	$^0\chi^v$	substituent	$^0\chi^v$
H	0.000	*i*-C_4H_9	3.284
Br	1.961	*i*-C_5H_{11}	3.992
Cl	1.132	$(CH_2)_3$	2.121
CH_3	1.000	$(CH_2)_4$	2.828
C_2H_5	1.707	NH_2	0.577
C_3H_7	2.414	NHC_2H_5	2.207
i-C_3H_7	2.577	$N(C_2H_5)_2$	3.861

[a] $(^0\chi - {}^0\chi^{v})(R^7)$ for H = 0.000, CH_3 = 0.000, NH_2 = 0.423, NHC_2H_5 = 0.207, $N(C_2H_5)_2$ = 0.130.

Initially we investigated the effect of substituents on the inhibitory activity of the naphthyridinones by using the molecular connectivity indices as predictor variables. The following structural descriptors were probed in the process of the model building: the valence zero-order molecular connectivity index, $^0\chi^v$, for substituents R^2-R^7, $(^0\chi^v)^2$, for substituent R^3, and the difference between the simple and the valence zero-order molecular connectivity indices[21] $^0\chi$-$^0\chi^v$ for R^7. The valence zero-order molecular connectivity index describes primarily the size of the substituent, while the differential molecular connectivity index $^0\chi$-$^0\chi^v$ encodes information on noncarbon sp^3 atoms and their topology.[21] Compounds 12 and 13 differ from the rest of the naphthyridinone derivatives: the positions 2 and 3 of these compounds are joined by three and four methylene groups, respectively, forming another ring. Consequently, it would be convenient to take the sum of the molecular connectivity indices for the substituents at these positions ($^0\chi^v$ (R^2+R^3)) as a predictor variable. Unfortunately, the position-specific

substituent effect precludes that. Thus, the numerical values of the variable $^0\chi^v$ (R^5+R^6) for compounds 3 and 5 are similar, whereas the activities of these compounds differ for more than 1 order of magnitude. Hence, in the case of compounds 12 and 13, we assigned to the substituent positions 2 and 3 half of the descriptor value for the methylene groups connecting them.

Multiple regression analysis led to the following "best" four-parameter model:

$$pI_{50} = 5.37(\pm0.35) - 0.22(\pm0.09)(^0\chi^v)^2(R^3) + 0.76(\pm0.33)^0\chi^v(R^3) + 0.55(\pm0.18)^0\chi^v(R^5+R^6) - 2.48(\pm1.21)(^0\chi-^0\chi^v)(R^7) \quad (9)$$

$$n = 20,\ r^2 = 0.869,\ s = 0.247,\ F^{4,15} = 24.9$$

Similarity of regression coefficients with variables $^0\chi^v$ (R^5) and $^0\chi^v(R^6)$ have permitted to combine them in one parameter in eq 9. From the derived model and experimental data follow that the position, size, and polarity of the substituents mainly determine the inhibitory potencies of the naphthyridinones. In general, more substituted derivatives show higher activity. The compound 16, with the unsubstituted vicinal positions 5 and 6, is the least active derivative. The activity parabolically increases with the size of R^3 substituent until an optimal value is reached and then decreases. The optimal size for R^3 is closely related to that for ethyl and bromine. Bromine at position 6 greatly enhances activity; the three most active derivatives are 6-bromo derivatives (compounds 14, 15, and 17). The negative coefficient with the difference between $^0\chi$ and $^0\chi^v$ for R^7 indicates that a polar amino group decreases activity and that this detrimental effect diminishes with the degree of substitution of the amino group. Namely, the numerical value of this term increases with the increasing number of heteroatoms in the substituent and decreases with the degree of substitution of the heteroatoms. It is worth noting that the effect of substituents R^2 is not statistically significant, although the experimental pI_{50} value for compound 3 suggests that substituents bulkier than ethyl at the 2-position tend to reduce activity.

The inhibitory potencies of the naphthyridinones were also correlated with a number of physicochemical descriptors, i.e., with hydrophobic substituent parameters π for R^2-R^7 (Table 3), the squared term of π for R^3 plus molar refractivity (MR) and electronic σ values for R^7. The four-parameter model with a somewhat poorer fit relative to eq 9 was obtained from regression analysis:

$$pI_{50} = 4.97(\pm0.49) - 0.47(\pm0.25)(\pi)^2(R^3) + 1.01(\pm0.63)\pi(R^3) + 1.31(\pm0.48)\pi(R^5+R^6) + 0.47(\pm0.34)\pi(R^7) \quad (10)$$

$$n = 20,\ r^2 = 0.808,\ s = 0.300,\ F^{4,15} = 15.7$$

The examination of residuals showed that lipophilic properties alone were not sufficient to adequately describe the interactions of R^7 substituents with the receptor. Inclusion of a steric term (i.e. MR(R^7)) gives the model (not shown) which accuracy is at the level of the previous one (eq 9). However, the introduction of an additional variable in the model for this relatively small set of compounds is statistically unjustified.

Table 3. Substituent Physicochemical Constants Used in Deriving Eqs 10 and 11[a]

substituent	π	substituent	π
H	0.00	$(CH_2)_3$	1.20
Br	0.86	$(CH_2)_4$	1.39
Cl	0.71	NH_2	−1.23
CH_3	0.56	$N(CH_3)_2$	0.18
C_2H_5	1.02	NHC_2H_5	0.08
C_3H_7	1.55	$N(C_2H_5)_2$	1.18
i-C_3H_7	1.53	CF_3	0.88
i-C_4H_9	2.11	OCF_3	1.04
i-C_5H_{11}	2.55	SCF_3	1.44

[a] L(R^8) for H = 2.06, CH_3 = 2.87, Cl = 3.52, CF_3 = 3.30, SCF_3 = 4.89.

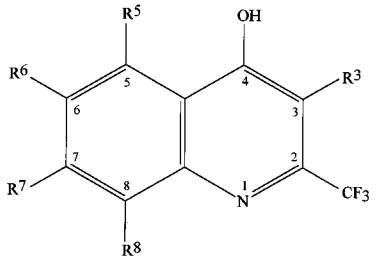

Figure 2. Structure of 2-trifluoromethyl-4-hydroxyquinoline derivatives.

Table 4. Substituent Pattern and the Observed and Calculated Inhibitory Potencies of 17 2-Trifluoromethyl-4-hydroxyquinolines

						pI_{50}	
no.	R^3	R^5	R^6	R^7	R^8	(exp.)	eq 11
1	H	H	H	H	H	4.1	4.13
2	H	H	Cl	H	H	4.5	4.96
3	H	H	$N(CH_3)_2$	H	H	4.7	4.34
4	Br	H	H	H	CH_3	4.8	5.31
5	H	H	H	H	Cl	4.9	4.89
6	H	H	CF_3	H	H	4.9	5.16
7	H	H	OCF_3	H	H	4.9	5.35
8	Br	H	H	H	H	5.1	4.94
9	Br	H	$N(CH_3)_2$	H	H	5.3	5.15
10	Br	H	H	H	CF_3	5.4	5.56
11	Br	H	CH_3	H	H	5.6	5.60
12	Br	H	Cl	H	Cl	5.9	6.54
13	Br	H	H	Cl	Cl	6.4	6.10
14	Br	H	CF_3	H	H	6.6	5.98
15	Br	H	OCF_3	H	H	6.7	6.17
16	Br	Cl	H	H	Cl	6.7	6.54
17	Br	H	H	H	SCF_3	7.0	6.77

3.2. Common Model for Naphthyridinones and Hydroxyquinolines. Recently, Draber et al.[15] have reported a QSAR model for 2-trifluoromethyl-4-hydroxyquinolines (Figure 2 and Table 4), inhibitors of photosystem II that are structurally related to the naphthyridinones. The quinoline ring system, as compared to the naphthyridine one, lacks a nitrogen atom at the 8-position. The quinoline derivatives were classified in the histidine family of photosystem II inhibitors. Like other members of this family, they do not lose their inhibitory activity in tris-treated chloroplasts or in thylakoids isolated from resistant biotypes. The naphthyridinones have not been classified yet. Their structure can be represented by several tautomeric forms. Which of them is dominant depends on numerous factors, such as for instance the nature of the ring substituents or the polarity of the

medium. In an attempt to formulate a common model for both groups of photosynthetic inhibitors, we assumed that naphthyridinones are oriented in the receptor cavity in a similar way as hydroxyquinolines, that is, that they bind to protein D1 in their enol form. (Recall that the binding patterns for the serine and histidine type inhibitors are supposed to be different.) Here we only present a model based on physicochemical constants since the corresponding molecular connectivity model is statistically of a somewhat lower quality (a six-parameter model with $r^2 = 0.81$). In the screening process, we tested the physicochemical constants appearing in the previous physicochemical model (eq 10) and in the model of Draber et al.[15] (Hammet electronic constant σ (R^6) and Verloop's sterimol width ($B_5(R^6)$) and length ($L(R^8)$) parameters. The parameter $L(R^8)$ is assigned the value zero for naphthyridinones.) We also tested the π constant for the 2-position, the σ constants for positions 2 and 3 plus an indicator variable I which stands for the additional nitrogen atom in the naphthyridinones skeleton. I assumes the value 1 for naphthyridinones and zero for hydroxyquinolines. It is worth noting that the parameters $\sigma(R^2)$, $L(R^8)$, and I are highly intercorrelated, and thus only one of them should enter the final regression equation. The stepwise elimination of statistically insignificant parameters led to the following model:

$$pI_{50} = 4.76(\pm0.40) - 0.66(\pm0.22)(\pi)^2(R^3) + 1.52(\pm0.48)\pi(R^3) + 1.16(\pm0.35)\pi(R^5+R^6) + 0.58(\pm0.35)\pi(R^7) + 0.20(\pm0.07)L^2(R^8) - 0.71(\pm0.28)L(R^8) \quad (11)$$

$$n = 37,\ r^2 = 0.863,\ s = 0.349,\ F^{6,30} = 31.5$$

The model obtained strongly supports our assumption that naphthyridinones act like histidine type inhibitors. The model suggests that naphthyridinone and hydroxyquinoline derivatives occupy the same binding area of the receptor. Again, the lipophilic effects of R^2 substituents are statistically insignificant. Their electronic contributions however, cannot be completely excluded due to high intercorrelation between parameters $\sigma(R^2)$ and $L(R^8)$, as mentioned earlier. Draber et al.[15] found that bromine at the 3-position is important for strong inhibitory potency of the hydroxyquinolines. This conclusion follows straightforwardly from our model, since the optimal lipophilicity for R^3 substituents, calculated from eq 11, corresponds to those of ethyl and bromine. The magnitudes of the regression coefficients associated with $\pi(R^5+R^6)$ in eqs 10 and 11 do not differ significantly although the variations of substituents R^5 and R^6 in the combined data set are greater than that for the naphthyridinones. The positive contribution of chlorine at R^7 to the potency of hydroxyquinolines demonstrates that both groups of photosynthesis inhibitors prefer lipophilic substituents at this position. The nonlinear relationship between the length of R^8 and inhibitory activity shows that the replacement of the nitrogen in the pyridine ring of the naphthyridinones with a CH group results in a somewhat reduced activity of the corresponding quinoline derivatives, whereas substitution of position 8 increases the activity of quinolines. As the basic skeletons of naphthyridinones and hydroxyquinolines can be considered isosteric it may be speculated that interaction of the nitrogen with the receptor via a hydrogen bond make the naphthyridinones somewhat more potent inhibitors relative to 8-hydrogen quinolines. The parabolic increase of the activity with the length of the substituents R^8 may be rationalized by the assumption that the nonspecific interactions of these substituents with the receptor are disturbed by a small steric barrier or a limited polar region.

Table 5. Correlation Matrix between Orthogonalized (Ω) and Original Molecular Connectivity Indices

	$\Omega({}^0\chi^v(R^5+R^6))$	$\Omega(({}^0\chi\text{-}{}^0\chi^v)(R^7))$	$\Omega(({}^0\chi^v)^2(R^3))$
${}^0\chi^v(R^5+R^6)$	1.00	0.00	0.00
$({}^0\chi\text{-}{}^0\chi^v)(R^7)$	−0.11	0.99	0.00
${}^0\chi^v(R^3)$	−0.07	0.04	0.00
$({}^0\chi^v)^2(R^3)$	−0.12	−0.07	0.36

3.3. Models with Orthogonalized Descriptors. The recently proposed procedure for sequential removing of overlapping information from a set of correlated descriptors makes it possible, in some cases, to obtain the model with the reduced number of predictor variables.[22] If the orthogonalization is performed in all possible orderings (for n variables there are n! possibilities), one can find that some of the so obtained orthogonal descriptors contain essentially no relevant information to describe the variations in the dependent variable. In another words, the relevant information contained in the given set of correlated variables can be compressed to the reduced number of orthogonal descriptors. As it was discussed in some detail elsewhere,[14,18] the orthogonalization of variables can be viewed as two parallel processes running simultaneously. On one hand, the superfluous information is progressively removed from the correlated variables, whereas on the other hand the "joint effect of the variables"[23] remains preserved in the orthogonalized descriptors. By the term "joint effect of variables" is meant that the sum of r^2 of individual descriptors may amount to less than r^2 of the model comprising all these variables.

With the exception of the variable ${}^0\chi^v(R^3)$ and its square term which are highly correlated, the molecular connectivity indices used in eq 9 are almost independent (pairwise correlation is not shown). By the orthogonalization of the descriptor variables from eq 9 in all possible orderings, it was found that for the orthogonalization sequence ${}^0\chi^v(R^5+R^6)$, $({}^0\chi\text{-}{}^0\chi^v)(R^7)$, ${}^0\chi^v(R^3)$, $({}^0\chi^v)^2(R^3)$, one can obtain a three-parameter model,

$$pI_{50} = 5.59(\pm0.24) + 0.66(\pm0.17)\Omega({}^0\chi^v(R^5+R^6)) - 1.64(\pm1.12)\Omega(({}^0\chi\text{-}{}^0\chi^v)(R^7)) - 0.22(\pm0.08)\Omega(({}^0\chi^v)^2(R^3)) \quad (12)$$

$$n = 20,\ r^2 = 0.868,\ s = 0.241,\ F^{3,16} = 35.0$$

which has statistics comparable with that of eq 9. In this and the following equation Ω denotes an orthogonalized descriptor and the variable from which the descriptor is derived is given in parentheses. The correlations between the original (eq 9) and the orthogonalized (eq 12) molecular connectivity indices are displayed in Table 5. Comparison of r^2 values of the individual molecular connectivity indices and their orthogonalized analogues is given in Table 6. It is seen that removing of $\Omega({}^0\chi^v(R^3))$ from eq 12 reduces its r^2 for only 0.1%. On the other hand increase in r^2 for

Table 6. Comparison of Contribution of Original and Orthogonalized (Ω) Molecular Connectivity Indices to the Explained Variability in pI_{50} Values (Eqs 9 and 12)

	r^2		r^2
$^0\chi^v(R^5+R^6)$	0.540	$\Omega\ (^0\chi^v(R^5+R^6))$	0.540
$(^0\chi\text{-}^0\chi^v)(R^7)$	0.130	$\Omega\ ((^0\chi\text{-}^0\chi^v)(R^7))$	0.080
$^0\chi^v(R^3)$	0.010	$\Omega\ (^0\chi^v(R^3))$	0.001
$(^0\chi^v)^2(R^3)$	0.078	$\Omega\ ((^0\chi^v)^2(R^3))$	0.248

Table 7. Correlation Matrix for Descriptor Variables Used in Eq 11

	$\pi(R^3)$	$\pi^2(R^3)$	$\pi(R^5+R^6)$	$\pi(R^7)$	$L(R^8)$	$L^2(R^8)$
$\pi(R^3)$	1.00					
$\pi^2(R^3)$	0.90	1.00				
$\pi(R^5+R^6)$	0.03	0.02	1.00			
$\pi(R^7)$	0.19	0.21	0.14	1.00		
$L(R^8)$	−0.24	−0.27	−0.40	−0.47	1.00	
$L^2(R^8)$	−0.14	−0.20	−0.42	−0.36	0.94	1.00

Table 8. Correlation Matrix between Original and Orthogonalized (Ω) Descriptors from Eq 13

	$\Omega(\pi(R^{5+}R^6))$	$\Omega(\pi(R^7))$	$\Omega(L^2(R^8))$	$\Omega(\pi(R^3))$
$\pi(R^5+R^6)$	1.00	0.00	0.00	0.00
$\pi(R^7)$	0.14	0.99	0.00	0.00
$\pi^2(R^3)$	0.02	0.21	0.00	0.00
$L(R^8)$	−0.40	−0.42	0.00	0.00
$L^2(R^8)$	−0.42	−0.31	0.32	0.00
$\pi(R^3)$	0.03	0.19	0.11	0.43

Table 9. Comparison of Contributions of Original and Orthogonalized (Ω) Descriptors to the Explained Variability in pI_{50} Values (Eqs 11 and 13)

	r^2		r^2
$\pi(R^5+R^6)$	0.244	$\Omega(\pi(R^5+R^6))$	0.244
$\pi(R^7)$	0.205	$\Omega(\pi(R^7))$	0.152
$\pi^2(R^3)$	0.012	$\Omega(\pi^2(R^3))$	0.000
$L(R^8)$	0.110	$\Omega(L(R^8))$	0.002
$L^2(R^8)$	0.017	$\Omega(L^2(R^8))$	0.273
$\pi(R^3)$	0.121	$\Omega(\pi(R^3))$	0.192

$\Omega((^0\chi^v)^2(R^3))$ implies that the preserved "joint effect of variables" is to a great extent comprised in this variable.

After the orthogonalization of the predictor variables from eq 11 (in the following orthogonalization sequence, $\pi(R^5+R^6)$, $\pi(R^7)$, $\pi^2(R^3)$, $L(R^8)$, $L^2(R^8)$, $\pi(R^3)$, and removing of statistically insignificant parameters ($\Omega(\pi^2(R^3))$, $\Omega(L(R^8))$), a four-parameter model was obtained which has an accuracy slightly better than that of eq 11:

$$pI_{50} = 5.37(\pm0.20) + 1.13(\pm0.31)\ \Omega(\pi(R^5+R^6)) + 0.84(\pm0.29)\ \Omega(\pi(R^7)) + 0.26(\pm0.07)\Omega(L^2(R^8)) + 1.52(\pm0.47)\Omega(\pi(R^3)) \quad (13)$$

$$n = 37,\ r^2 = 0.861,\ s = 0.340,\ F^{4,32} = 49.6$$

The correlation matrix for the predictor variables used in eq 11 is presented in Table 7. The pairwise correlations between the nonorthogonalized (eq 11) and orthogonalized (eq 13) predictor variables are given in Table 8. The coefficients of determination (r^2) of the individual physicochemical constants before and after the orthogonalization are shown in Table 9.

3.4. Comparison of Models Describing the Inhibitory Potency of Photosystem II Inhibitors. In this paragraph, we compare the models obtained for the naphthyridinone and hydroxyquinoline derivatives with those we recently proposed for the serine type inhibitors, 3-alkoxyuracils[10] and triazines,[11,13,14] and for 4-hydroxypyridines[12] that belong to the histidine family of photosynthetic inhibitors. The models show that the inhibitory potency of these compounds is essentially controlled by their size or lipophilicity. Except for the 4-hydroxypyridines, inhibitory potency is exponentially related to the size of the molecules. Optimal size varies from one group of inhibitors to the other. For 3-alkoxyuracils, optimal size corresponds to an alkoxy chain with nine carbon atoms. The optimal combination of alkylamino substituents for 2-azidotriazines and 2-methylthiotriazines is ethyl plus *tert*-butyl and ethyl plus hexyl for 2-difluoromethylthiotriazines. Ethyl or bromine is the optimal choice for positions 3 of the naphthyridinone and quinoline derivatives, while in the case of 4-hydroxypyridines the optimum size value is not reached. The additional factors that influence the activity of the above groups of inhibitors are also different, i.e., the flexibility of the alkoxy chain for 3-alkoxyuracils, the polarity of the alkylamino substituents and/or the degree of branching on the α-carbon atom of the larger alkylamino substituent for triazine derivatives, the electron-withdrawing capacity of the ring substituents for 4-hydroxypyridines, and the polarity of substituents and steric constraints for naphthyridinones and hydroxyquinolines. Thus, while it is evident that each group of the inhibitors interacts with distinct lipophilic regions of the receptor, it appears that specific modes of binding for serine and histidine type inhibitors cannot be deduced from the parametric structure of the corresponding QSAR models.

4. CONCLUSIONS

By using the molecular connectivity indices, a four-parameter QSAR model was developed that reasonably well describes the inhibitory potency of 1,8-naphthyridin-4-one derivatives. From the model and experimental data follow that the position, size, and polarity of the substituents are structural features which primarily influence their activity. Small substituents are preferable for the positions 2 and 3, while polar substituents at position 7 substantially reduce the activity. It seems that bromine at the 6-position is important for high potency of these compounds. A common model based on physicochemical constants for 1,8-naphthyridin-4-ones and structurally related 2-trifluoromethyl-4-hydroxyquinolines implies that both groups of the photosynthetic inhibitors may have similar structural requirements for optimal activity.

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