Quantitative relations between structure and pesticidal activity of new pyridazinyl thiophosphates

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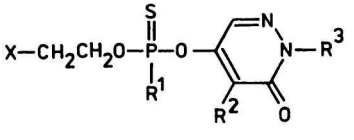
Quantitative structure—activity relationships in the series of 1,6-dihydro--4-pyridazinyl thiophosphates were investigated by Hansch and Free—Wilson methods. Insecticidal, acaricidal, and fungicidal activities were correlated with experimental physicochemical data and topological steric index. Compounds were classified into active and inactive groups by the cluster analysis. The quantitative activity contributions of the substituents were obtained by the Free—Wilson method.

С помощью методов Ганша и Фри—Вильсона исследована количественная взаимозависимость между строением и активностью ряда 1,6-дигидро-4-пиридазиниловых эфиров тиофосфорной кислоты. Инсектицидная, акарицидная и фунгицидная активности этих соединений были сопоставлены с опытными физико-химическими показателями и топологическим пространственным индексом. С помощью кластерного анализа исследуемые соединения были отнесены к группе активных или неактивных веществ. Количественный вклад заместителей в проявляемую активность был оценен с помощью метода Фри—Вильсона.

In connection with the research of new pesticides, based on the derivatives of thiophosphoric acid, the 1,6-dihydro-4-pyridazinyl esters of this acid have been synthesized and biologically tested [1]. These esters are of the following structural type



The measured data permit a correlation between structure and analysis according to the model of *Hansch* and *Fujita* [2] which has been completed using the following formula

$$B = a + \Sigma b_i p_i$$

where B represents the biological activity, p_i are physicochemical parameters.

With respect to the compounds studied, in which the basic skeleton is conserved and only groups X, R^1, R^2, and R^3 are changed, we have also carried out calculations based on the model of *Free* and *Wilson* [3] modified by *Fujita* and *Ban* [4].

The cluster analysis has been carried out in view of the most significant physicochemical parameters obtained by the Hansch method.

Experimental

Biological activity

Since derivatives of the thiophosphoric acid show a wide spectrum of biological activity, several biological tests have been performed [1]:

a) insecticidal activity on *Aphis fabae* $I = \log(10^4/LC_{50})$;

b) acaricidal activity on *Tetranychus urticae* $A = \log(10^4/LC_{50})$;

c) fungicidal activity on *Erisiphe graminis* $F = \log(10^4/ED_{50})$.

The respective data are listed in Table 1.

Physicochemical data

The partition coefficients P have been measured experimentally for all compounds studied in the system octanol—water [1].

Since the compounds studied are structurally relatively complicated species, on which several skeleton substituents are changed, we also studied the electronic effects of those substituents *via* experimentally measured quantities. Eventually, in order to have the possibility to determine the character of interaction taking place at the biological site of action, we used in correlations physicochemical characteristics of different types, as follows:

a) the dipole moment μ;

b) the absorption bands in UV spectra, namely UV_1 — the shortwave band in the region of $\lambda = 209$—219 nm and UV_2 — the longwave band in the region of $\lambda = 280$—330 nm;

c) the wavenumbers of the characteristic vibrations in IR spectra, namely ν_1(P=S), ν_2(P=S), ν(POC), ν(CO);

d) the ^{31}P chemical shift in NMR spectra.

The experimental data are published in [1].

For the description of steric effect we used the topological index MSD (the minimal steric difference), introduced by *Balaban et al.* [5]. This index characterizes the interaction of an effector molecule with a biological receptor. The molecule with the largest activity models the cavity of the receptor (MSD = 0). The difference between this ideal form of an effector and the virtual form of a molecule represents that part of the molecule, which does not interact with the biological receptor and decreases the activity (MSD > 0). The

Table 1

Survey of the compounds studied, topological steric indices for insecticidal (MSD_I), acaricidal (MSD_A), fungicidal (MSD_F) activity and measured values of insecticidal (*I*), acaricidal (*A*), and fungicidal (*F*) activity

Compound	X	R^1	R^2	R^3	MSD_I	MSD_A	MSD_F	*I* mg dm^{-3}	*A* mg dm	*F* mg dm^{-3}
I	Cl	i-C_4H_9O	CH_3S	CH_3	1.5	2.5	1.5	4.59	3.89	3.69
II	Cl	i-C_4H_9O	CH_3O	C_5H_{11}	5.0	6.0	5.0	4.83	3.33	5.00
III	Cl	C_2H_5O	Cl	C_6H_5	10.5	6.5	7.5	3.33	3.68	2.66
IV	Cl	i-C_4H_9O	Cl	CH_3	5.5	3.5	2.5	5.17	3.62	3.10
V	Cl	$(C_2H_5)_2N$	CH_3O	CH_3	6.0	2.0	3.0	3.70	3.76	4.09
VI	Cl	i-C_4H_9O	C_2H_5O	C_6H_5	10.0	8.0	7.0	3.48	2.95	3.37
VII	Cl	i-C_4H_9O	Cl	C_3H_7	7.5	5.5	4.5	3.91	3.92	2.98
VIII	Cl	i-C_4H_9O	CH_3O	$C_6H_5CH_2$	10.0	6.0	7.0	4.31	3.65	3.42
IX	Cl	CH_3O	CH_3O	CH_3	5.0	1.0	2.0	3.72	5.68	5.43
X	Cl	i-C_4H_9O	C_2H_5O	C_5H_{11}	9.0	7.0	6.0	5.37	2.93	3.86
XI	Cl	C_2H_5O	CH_3O	C_6H_5	9.0	5.0	6.0	4.83	3.91	3.60
XII	Cl	C_4H_9NH	CH_3O	CH_3	2.0	2.0	1.0	5.65	3.53	3.17
XIII	Cl	i-$C_5H_{11}O$	CH_3O	CH_3	3.0	3.0	2.0	5.85	3.19	5.31
XIV	Cl	*sec*-C_4H_9O	CH_3O	CH_3	4.0	2.0	1.0	5.92	3.58	4.67
XV	Cl	C_2H_5O	CH_3O	CH_3	4.0	0.0	1.0	6.21	6.17	54
XVI	Cl	i-C_4H_9O	CH_3S	C_6H_5	9.5	8.5	6.5	3.28	3.95	2.99
XVII	Cl	i-C_4H_9NH	CH_3O	CH_3	4.0	2.0	1.0	5.57	3.55	3.09
XVIII	Cl—CH_2	i-C_4H_9O	CH_3O	CH_3	5.0	3.0	2.0	5.54	3.89	5.09
XIX	Cl	i-C_3H_7O	CH_3O	CH_3	5.0	1.0	2.0	6.27	5.84	.33
XX	Cl	n-C_4H_9O	CH_3O	CH_3	2.0	2.0	1.0	4.47	3.87	.42
XXI	Cl	i-C_4H_9O	CH_3O	C_6H_{11}	9.0	7.0	6.0	4.06	3.34	4.57
XXII	Cl	i-C_4H_9O	CH_3O	C_4H_9	7.0	5.0	4.0	4.84	3.22	4.73
XXIII	Cl	i-C_4H_9O	Cl	$C_6H_5CH_2$	11.5	9.5	8.5	3.43	3.66	2.07
XXIV	Cl	i-C_4H_9O	Cl	*m*-$CF_3C_6H_4$	12.5	11.5	9.5	3.34	3.75	2.71
XXV	Cl	i-C_4H_9O	Cl	CH_2=CH—CH_2	7.5	5.5	4.5	3.30	3.65	2.83
XXVI	Cl	i-C_4H_9O	CH_3O	CH_3	4.0	2.0	1.0	6.25	3.55	.69

Table 1 (Continued)

Compound	X	R^1	R^2	R^3	MSD_I	MSD_A	MSD_F	I / mg dm^{-3}	A / mg dm^{-3}	F / mg dm^{-3}
XXVII	Cl	C_6H_5O	CH_3O	CH_3	0.0	4.0	3.0	6.31	3.05	3.50
XXVIII	Cl	n-C_3H_7O	CH_3O	CH_3	3.0	1.0	0.0	5.57	5.11	6.27
XXIX	Cl	i-C_4H_9O	C_2H_5S	CH_3	5.5	3.5	2.5	3.90	3.73	4.12
XXX	F	i-C_4H_9O	CH_3O	CH_3	4.5	1.5	0.5	5.63	4.82	4.93
XXXI	Br	i-C_4H_9O	CH_3O	CH_3	4.5	3.0	2.0	4.14	4.22	5.05
XXXII	*a*	i-C_4H_9O	CH_3O	CH_3	5.0	3.0	2.0	3.93	3.47	5.03
XXXIII	Cl	i-C_4H_9O	Cl	C_6H_{11}	10.5	8.5	7.5	3.28	3.65	2.87
XXXIV	Cl	i-C_4H_9O	C_2H_5S	C_2H_5	6.5	4.5	3.5	4.01	2.96	3.32
XXXV	Cl	C_2H_5O	Cl	CH_3	5.5	1.5	2.5	3.79	4.00	3.24
XXXVI	Cl	i-C_4H_9O	Cl	C_4H_9	8.5	6.5	5.5	3.92	3.39	3.32
XXXVII	Cl	C_2H_5O	C_2H_5S	C_6H_5—CH_2	11.5	7.5	8.5	3.75	3.84	2.87
XXXVIII	F	n-C_3H_7O	CH_3O	CH_3				5.85	5.55	6.08
XXXIX	F	C_2H_5O	CH_3O	CH_3				5.92	5.83	5.78
XL	F	n-C_3H_7O	C_2H_5O	CH_3				5.98	5.19	3.35
XLI	Cl	C_2H_5O	C_2H_5O	CH_3						5.56
XLII	Cl	C_2H_5O	CH_3S	C_3H_7						3.48
XLIII	Cl	n-C_3H_7O	CH_3O	C_5H_{11}						5.25
XLIV	Cl	n-C_3H_7O	H	CH_3						3.36
XLV	Cl	n-C_3H_7O	CH_3S	C_3H_7						4.33
XLVI	Cl	i-C_3H_7O	C_2H_5O	CH_3						4.84
XLVII	Cl	i-C_4H_9O	C_2H_5O	CH_3						5.62
XLVIII	Cl	i-C_4H_9O	H	CH_3						5.66
XLIX	Cl	n-C_4H_9O	CH_3O	C_5H_{11}						5.41
L	Cl	C_6H_5O	C_2H_5O	CH_3						4.38

a) Cl—$CH_2(CH_3)CH$.

calculated MSD values for all three types of biological activity, as well as the survey of the compounds studied are listed in Table 1.

Multiparameter regression analysis

It is assumed that the function, which is represented by the respective biological activity, correlates with one or several independent variables, namely with $\log P$, the steric factor MSD and the above-mentioned experimental physicochemical quantities, expressing the electronic effect. The multiparameter correlations have been calculated and their statistical significance characterized by the multiple correlation coefficient r, the standard deviation s, and the F values. In the results only the equations with the best statistical values are reported.

The Free—Wilson method

In order to express quantitatively contributions of particular substituents, we have performed the calculations using the model of *Free* and *Wilson* [3] in version modified by *Fujita* and *Ban* [4]. In this method the total activity is expressed as the sum of the contributions of particular substituents and the reference compound. The contributions of substituents in the reference compound are zero. The advantage of this method is the possibility of predicting the activity of nontested compounds, which corresponds to different combinations of substituents. For the Free—Wilson calculation the series of compounds are extended. In order to achieve statistically significant results, only the substituents which occur in the compounds more than once are included.

Cluster analysis

For classification of compounds into active and inactive groups cluster analysis was used. The compounds are defined as points in an N-dimensional space, coordinates of which are represented by the most significant physicochemical parameters obtained from the Hansch analysis.

In the hierarchal clustering method, the analysis begins with the evaluation of the Euclidean distance d_{ij}, between each pair of points i and j in the space. The closest two points are clustered into a new pseudopoint, and the distances between pairs are calculated again

$$d_{ij} = [\Sigma(x_{ik} - x_{jk})^2]^{1/2}\, i,j = N$$

where the x_{ik} are scale-corrected parameter values for the i-th point and the k-th parameter and the x_{jk} are the cluster averages (or single points on the first run) for the j-th point and k-th parameter type. The scaling is done through the following equations

$$x_{ik} = (a_{ik} - \bar{a}_k)/s_k$$

$$\bar{a}_k = 1/N \Sigma a_{ik}$$

$$s_k^2 = \Sigma(a_{ik} - \bar{a}_k)^2$$

where a_{ik} are the original values of the k-th parameter for the i-th point. The process is repeated until two large clusters representing the active and inactive compounds, are formed [6].

Cluster analysis is not only classification scheme but it allows to predict activities of nontested compounds with similar structure.

Results and discussion

Insecticidal activity

The statistical characteristics in the Hansch analysis are not satisfactory. Relatively the most significant parameters are MSD_I and the longwave band in UV spectrum

$$I = -0.180\,MSD_I - 0.023\,UV_2 + 12.383$$

$$n = 37 \quad r = 0.747 \quad s = 0.695 \quad F = 21.47$$

These parameters served as the coordinates of the Euclidean space for classification of compounds by the cluster analysis. The results are shown in Fig. 1 in a picture form. Axes x and y represent a distance from the centre of the

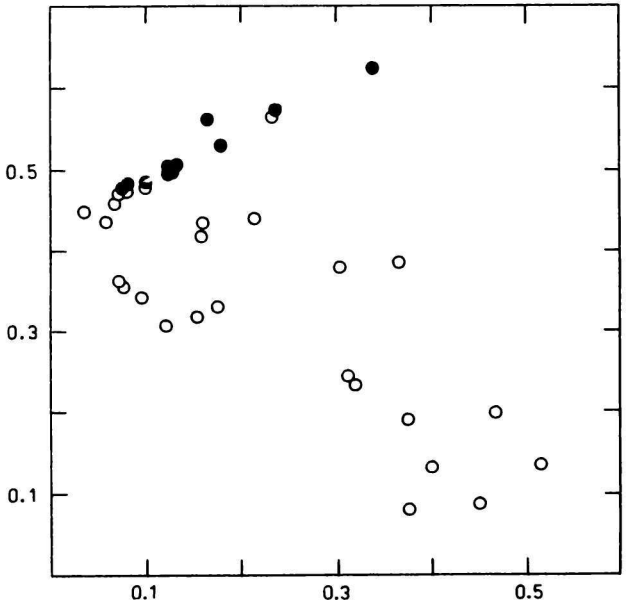


Fig. 1. Cluster analysis for insecticidal activity.
The full points represent compounds with the highest experimental values of insecticidal activity I.

active and inactive compounds cluster, respectively. Points corresponding to the most active insecticides are gathered at the left top of the figure. The least active compounds are collected at the right bottom of the figure. The experimental values I do not make possible an explicit distribution of compounds to active and inactive, hence the frontier between clusters is not distinct.

In Table 2 the quantitative values of the substituent contributions to the total insecticide activity are listed, which have been calculated on the basis of the Fujita—Ban model.

The insecticidal activity is little influenced by the substituent in position X. In position R^1 the largest contribution has the C_2H_5O group, from R^2 substituents the CH_3O and C_2H_5O groups and CH_3 group in R^3 position.

Acaricidal activity

We have not obtained the statistically significant linear dependences of the acaricidal activity on the parameters studied.

The numerical values of contribution for the particular substituents X, R^1, R^2, and R^3 to the total activity are listed in Table 3.

Table 2

Insecticidal activity contributions of substituents calculated by the Fujita—Ban method ($n = 24$, $r = 0.934$, reference compound activity = 5.638 mg dm^{-3}, X = Cl, R^1 = i-C_4H_9O, $R^2 = CH_3O$, $R^3 = CH_3$ in reference compound)

X	$Z(X)$ / mg dm^{-3}	R^1	$Z(R^1)$ / mg dm^{-3}	R^2	$Z(R^2)$ / mg dm^{-3}	R^3	$Z(R^3)$ / mg dm^{-3}
F	0.102	C_2H_5O	0.272	C_2H_5O	−0.116	C_5H_{11}	−0.480
		n-C_3H_7O	0.133	CH_3S	−0.957	C_4H_9	−0.689
				Cl	−1.138	$C_6H_5CH_2$	−1.043
				C_2H_5S	−1.427	C_6H_{11}	−1.399
						C_6H_5	−1.491

Table 3

Acaricidal activity contributions of substituents calculated by the Fujita—Ban method ($n = 24$, $r = 0.912$, reference compound activity = 4.049 mg dm^{-3}, X = Cl, R^1 = i-C_4H_9O, $R^2 = CH_3O$, $R^3 = CH_3$ in reference compound)

X	$Z(X)$ / mg dm^{-3}	R^1	$Z(R^1)$ / mg dm^{-3}	R^2	$Z(R^2)$ / mg dm^{-3}	R^3	$Z(R^3)$ / mg dm^{-3}
F	0.727	C_2H_5O	0.920	CH_3S	0.252	$C_6H_5CH_2$	−0.338
		n-C_3H_7O	0.884	Cl	−0.347	C_6H_{11}	−0.381
				C_2H_5O	−0.403	C_4H_9	−0.571
				C_2H_5S	−0.555	C_5H_{11}	−0.718
						C_6H_5	−0.762

A smaller activity of the reference compound was observed when compared with insecticidal activity. In position X the highest contribution to the activity has fluorine, in position R^1 alkoxy groups with short chain (C_2 and C_3) exhibit a large contribution to the activity. From substituents R^2 CH_3S group has the largest contribution. CH_3 group is the most active from R^3 substituents.

Fungicidal activity

The Hansch analysis shows that relatively the most significant factor is the parameter MSD_F and dipole moment μ.

$$F = -0.174\,MSD_F - 1.294\,\mu + 9.068$$

$$n = 37 \quad r = 0.711 \quad s = 0.788 \quad F = 17.38$$

Fig. 2 presents results of the cluster analysis for fungicides. MSD_F and μ were used as the coordinates of the Euclidean space. Description of the figure is the same as in the case of insecticides.

The calculated additive contributions of substituents to the total activity are presented in Table 4.

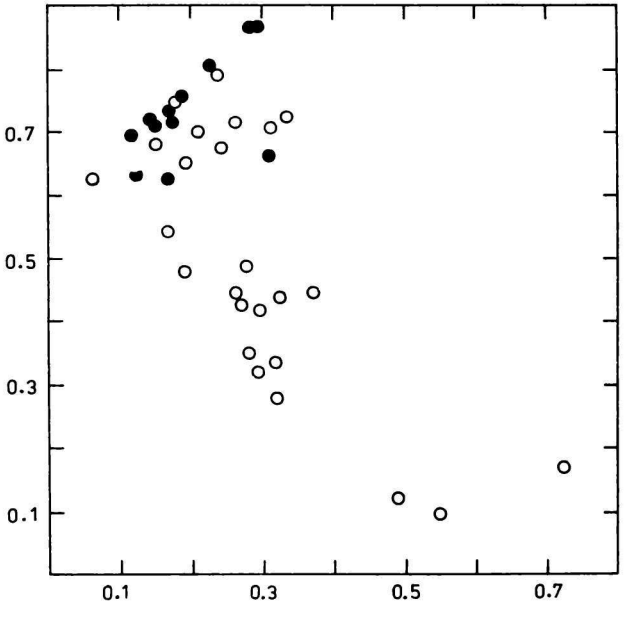


Fig. 2. Cluster analysis for fungicidal activity.

Table 4

Fungicidal activity contributions of substituents calculated by the Fujita—Ban method ($n = 38$, $r = 0.918$, reference compound activity = 5.371 mg dm^{-3}, X = Cl, R^1 = i-C_4H_9O, $R^2 = CH_3O$, $R^3 = CH_3$ in reference compound)

X	$Z(X)$ / mg dm^{-3}	R^1	$Z(R^1)$ / mg dm^{-3}	R^2	$Z(R^2)$ / mg dm^{-3}	R^3	$Z(R^3)$ / mg dm^{-3}
F	0.025	n-C_4H_9O	0.345	C_2H_5O	−0.221	C_4H_9	−0.424
		n-C_3H_7O	0.324	H	−1.023	C_3H_7	−0.466
		C_2H_5O	0.129	C_2H_5S	−1.121	C_5H_{11}	−0.603
		i-C_3H_7O	−0.176	CH_3S	−1.267	C_6H_{11}	−0.729
		C_6H_5O	−1.321	Cl	−1.845	C_6H_5	−1.448
						$C_6H_5CH_2$	−1.639

From substituents R^1 alkoxy groups (n-C_4H_9O and n-C_3H_7O) exhibit the largest contribution. The activity is mostly influenced by the R^2 and R^3 substituents, from R^2 the most suitable are the CH_3O and C_2H_5O groups and from R^3 substituents only the CH_3 group.

Conclusion

The results of the statistical treatment of the insecticidal, acaricidal, and fungicidal activity of 1,6-dihydro-4-pyridazinyl thiophosphates, using Hansch and Free—Wilson methods, are in all three cases so different that a different mechanism of biological activity may be assumed.

From the statistical point of view, MSD_I and the longwave band in UV spectrum are connected with insecticidal activity, $\log P$ with acaricidal activity and the relatively most important factors reflecting fungicidal activity are MSD_F and the dipole moment.

This preliminary set of compounds can serve for classification of nontested molecules with a similar structure. Their MSD_I values and the wavelengths of UV_2 band determine their correspondence to the active or inactive group of insecticides. Similarly MSD_F and dipole moment value classify fungicides into active and inactive ones.

Quantitative contributions of substituents X, R^1, R^2, and R^3 calculated by the Fujita—Ban method are different in all cases. In individual cases it was possible to determine the substituents exhibiting a significant contribution to the total activity.

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