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Importance of Physicochemical Properties for the Design of New Pesticides

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ABSTRACT: The physicochemical properties of candidate compounds play important roles in the design of new pesticides. Pesticides must be absorbed by pests, be transported to the target site, and then interact with proteins. Hydrophobicity is very important for these processes. Log P, where P is the partition coefficient in the 1-octanol/water system, is commonly used as a hydrophobic descriptor and correlates with membrane permeation and transport. It was recently reported that permeability by the parallel artificial membrane permeation assay (PAMPA) could be used to predict human oral absorption of passively transported compounds. PAMPA, which is a rapid high-throughput screening system, may be useful to predict pesticide absorption because PAMPA permeability can be calculated using log P and other parameters. Electronic and structural properties as well as hydrophobicity are important factors for protein−ligand interaction. To show the importance of physicochemical properties, the classic QSAR and CoMFA of neonicotinoids and prediction of bioavailability of pesticides in terms of membrane permeability in comparison with drugs are described.

KEYWORDS: physicochemical properties, pesticides, log P, QSAR, neonicotinoids, PAMPA, membrane permeability, bioavailability

■ INTRODUCTION

The physicochemical properties of candidate compounds play important roles in the design of new pesticides as well as therapeutic agents. First, compounds must be absorbed by pests or humans, be transported to the target site, and then interact with the target receptors or enzymes; hydrophobicity is very important for absorption, transport, and interaction with receptors. Electronic and structural properties are also important factors for receptor−ligand interaction.

Quantitative structure−activity relationships (QSAR) have been widely applied to the design of pharmaceuticals and pesticides since the 1960s.[1] In QSAR, variations in biological activities are statistically analyzed using descriptors related to the structural properties of compounds in the form of linear free energy relationships. The Hansch−Fujita approach,[1,2] the so-called classic QSAR, is a representative QSAR method. Log P, which is the logarithm of the partition coefficient of compounds in the 1-octanol/water system,[3] has been used as a hydrophobic parameter. Although the Hammett σ, which is defined on the basis of the ionization constants of substituted and unsubstituted benzoic acids,[4] is the original electronic parameter, descriptors obtained by molecular orbital calculations such as atomic charges are often used instead of Hammett constants with better calculation methods.[5,6] Because molecular properties based on the three-dimensional (3D) structure of compounds may be useful for describing ligand−receptor interactions, 3D-QSAR approaches have been developed. Comparative molecular field analysis (CoMFA) developed by Cramer et al.[7] is a representative of 3D-QSAR. In recent years a large number of modern QSAR approaches have been reported with the rapid improvement of computer power;[8−10] however, classic QSAR and CoMFA with physicochemical descriptors are very useful at the point of giving physicochemical meaning for the protein−ligand interaction mechanism.

Recently we have reported that permeability by the parallel artificial membrane permeation assay (PAMPA)[11] could be used to predict the human oral absorption of passively transported compounds.[12−15] PAMPA, which is a rapid high-throughput screening system, may be useful to predict pesticide absorption even if PAMPA permeability can be calculated using log P and other parameters.

In this paper, to show the importance of physicochemical properties, the classic QSAR and CoMFA of neonicotinoids and prediction of the bioavailability of pesticides in terms of membrane permeability in comparison with drugs are described.

■ QSAR OF NEONICOTINOIDS

Neuroblocking Activity. Neonicotinoids such as imidacloprid are synthetic insecticides that act on nicotinic acetylcholine receptors (nAChRs) in insect neuronal systems.[16] These insecticides have been used because of their fast action and safety for humans. Kagabu et al.[17] reported neuroblocking and insecticidal activities of neonicotinoids against cockroaches in 2007. The compounds were chloronicotinyl and chlorothiazolyl derivatives in which the imidazolidine moiety was also modified. The structures of these compounds are shown in Figure 1. In their paper, QSARs of these activities were also performed according to the Hansch−Fujita method. The QSAR equation for neuroblocking activity derived by Kagabu et al.[17] is as follows.

$$\log (1/BC) = -7.65\,(\pm 8.61) + 1.98\,(\pm 0.74) \log P$$
$$- 29.9\,(\pm 20.5)Q_{O2}(\text{gaus}) \qquad (1)$$

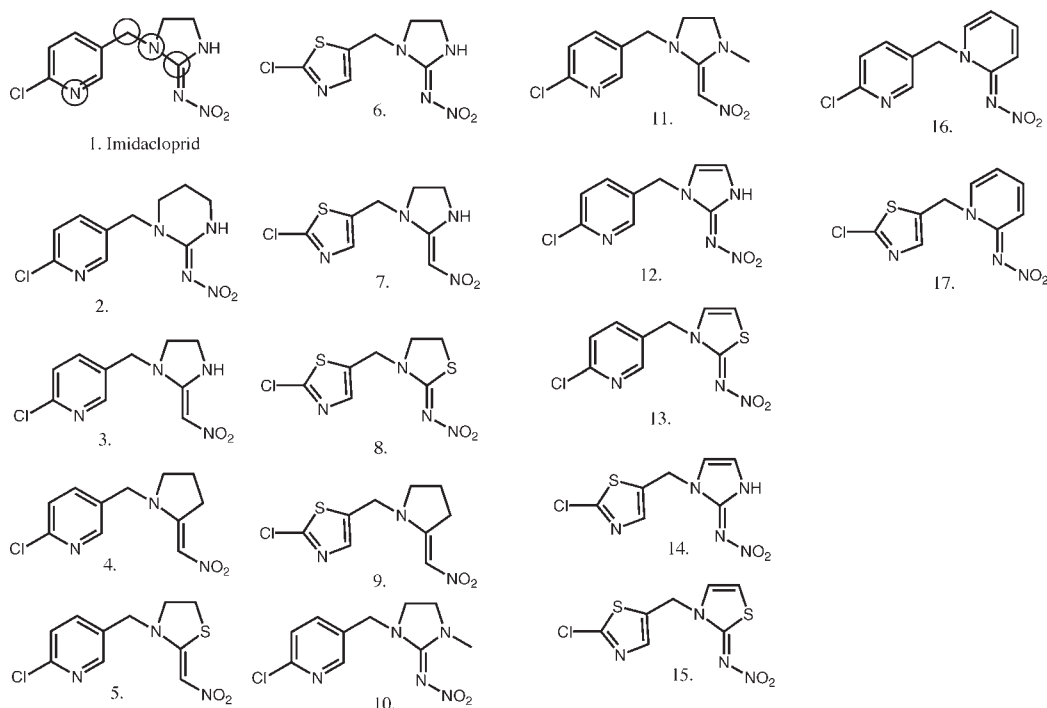$$n = 17 \quad s = 0.48 \quad r^2 = 0.70 \quad q^2 = 0.60$$

Figure 1. Structures of imidacloprid and derivatives. Atoms used for superposition are indicated by open circles on imidacloprid.

In this and the following equations, n is the number of compounds, s is the standard deviation, r is the correlation coefficient, q is the cross-validated (leave-one-out) correlation coefficient, and the figures in parentheses are 95% confidence intervals. BC means the neuroblocking concentration (M), and Q_{O2}(gaus) represents the Mulliken charges of compounds at one of the nitro oxygen atoms calculated by Gaussian 98, B3LYP/6-31G(d) level.[18] The activity and parameter values are listed in Table 1. They also derived eq 3 excluding two compounds, the log (1/BC) values of which were much lower than those calculated by eq 1.

$$\log (1/BC) = -8.53\ (\pm 5.79) + 1.98\ (\pm 0.50) \log P$$
$$- 32.3\ (\pm 13.8) Q_{O2}(\text{gaus}) \qquad (2)$$

$$n = 15\ \ s = 0.31\ \ r^2 = 0.86\ \ q^2 = 0.79$$

Because a larger log (1/BC) means higher activity, eqs 1 and 2 show that the higher log P and more negative charge of one of the nitro-oxygen atoms are favorable for activity. Hydrophobicity is considered to be important for the penetration of a compound through the nerve cords of an insect, although the effect on the interaction of compounds with receptors may be also involved. The negative charge of the nitro-oxygen atom should strengthen the interaction with receptors.

We reanalyzed the activity using newly calculated MNDO electrostatic potential charges, Q_{O2}(MNDO-esp)[19] with log P. The fully optimized conformation of the molecules was assumed to be the active conformation for binding. As the starting coordinate, the crystal structure of imidacloprid (PDB: 2ZJU[20]) was used. The 3D structure of other compounds was constructed on the basis of the imidacloprid structure using the SYBYL ver. 7.3[21] standard values for bond lengths and angles. A systematic search in SYBYL was applied to all rotatable bonds. The low-energy conformer of each compound obtained by a systematic search was then optimized by the semiempirical PM3 method.[22] For the optimized coordinates of all compounds, atomic charges were calculated using MNDO.[19] Molecular electrostatic potentials of the molecules were computed from the MNDO atomic charges, and eq 3 was obtained.

$$\log (1/BC) = -3.48\ (\pm 3.75) + 2.02\ (\pm 0.56) \log P$$
$$- 14.7\ (\pm 6.58) Q_{O2}(\text{MNDO-esp}) \qquad (3)$$

$$n = 17\ \ s = 0.38\ \ r^2 = 0.81\ \ q^2 = 0.75$$

Although the coefficient of the Q_{O2} term is different because of the difference of charge calculation methods, the meaning of eq 3 is identical to that of eqs 1 and 2; however, the statistical quality of eq 3 including all compounds is better than the corresponding eq 1, showing the effectiveness of the electrostatic potential charges on receptor–ligand interaction.

The same data were analyzed by CoMFA. MNDO electrostatic potential charges were used in CoMFA studies. The optimized conformer of imidacloprid was selected as the reference standard on which the other compounds were superposed. The key atoms for the superposition of imidacloprid were the nitrogen atom of the pyridine ring, the nitrogen atom of the 1-position of the imidazolidine ring, and two atoms adjacent to it (Figure 1). The superposed sets of fully optimized conformers were placed in a 2 Å spaced grid. The potential energy fields of each conformer were calculated at the lattice intersections. The electrostatic and steric energy field parameters were calculated. The biological activity data were then correlated with these parameters by the partial least-squares (PLS) method.[23]

The results of the analysis are shown as a correlation equation with the number of latent variable terms, each of

Table 1. Activities and Physicochemical Properties of Neonicotinoids

compd	log (1/MLD)[a]		log (1/BC)[a]			log P[a]	Q_{O2}(gaus)[a]	Q_{O2}(MNDO-esp)[b]
	measured [a]	calcd, eq 6	measured[a]	calcd, eq 3	calcd, eq 4			
1 [c]	10.15	10.05	5.64	5.74	5.55	0.53	−0.398	−0.553
2	10.12	9.91	5.35	5.14	5.50	0.57	−0.401	−0.507
3	10.19	10.01	5.02	5.08	5.22	−0.18	−0.435	−0.605
4	10.44	10.52	6.43	6.20	6.29	0.45	−0.426	−0.595
5	10.37	10.37	6.19	6.15	6.19	0.47	−0.427	−0.589
6	9.62	9.57	5.97	5.38	5.70	0.61	−0.398	−0.518
7	10.24	10.13	5.73	5.44	5.59	0.03	−0.435	−0.601
8	8.91	9.76	6.00	5.69	6.29	0.80	−0.391	−0.513
9	10.06	10.28	6.31	6.43	6.50	0.64	−0.426	−0.585
10	8.62	8.83	3.81	3.97	3.89	−0.07	−0.399	−0.515
11	8.07	8.04	3.84	3.75	3.68	−0.84	−0.432	−0.605
12	8.72	9.36	4.31	5.10	4.75	0.33	−0.416	−0.537
13	10.25	9.52	5.68	5.15	5.31	0.53	−0.403	−0.513
14	8.82	9.01	4.61	4.89	4.68	0.27	−0.416	−0.531
15	8.85	8.75	5.79	6.28	5.71	0.96	−0.403	−0.531
16	9.99	9.78	5.09	5.45	5.28	0.51	−0.397	−0.536
17	9.74	9.27	5.75	5.68	5.39	0.67	−0.397	−0.530

[a] Data were taken from ref 17. [b] Newly calculated in this study. [c] Imidacloprid.

which was a linear combination of the original independent lattice variables.

$$\log (1/BC) = 4.56 + 1.70 \log P + [\text{CoMFA field terms}] \quad (4)$$

$$n = 17 \quad s = 0.25 \quad r^2 = 0.92 \quad q^2 = 0.63 \quad (3 \text{ components})$$

relative contribution : log P,37.5%; steric, 43.2%;

electrostatic, 19.2%

To show favorable and unfavorable regions for activity, the variables are displayed as contour diagrams of coefficients of the corresponding field descriptor terms at each lattice intersection as shown in a later section.

Insecticidal Activity. Kagabu et al. [17] attempted to derive a Hansch–Fujita QSAR equation for insecticidal activity using physicochemical parameters. Although it was difficult to develop an appropriate equation, they derived the following eq 5 about the relationship between insecticidal and neuroblocking activities.

$$\log (1/MLD) = 5.63(\pm 1.18) + 0.85(\pm 0.23) \log (1/BC)$$
$$- 1.30(\pm 0.71) (\log P)^2 - 0.52(\pm 0.38) I_{ClTh} \quad (5)$$

$$n = 17 \quad s = 0.32 \quad r^2 = 0.86 \quad q^2 = 0.77$$

MLD represents the minimum lethal dose in moles against male adult cockroaches with synergists to avoid the metabolism of compounds, and I_{ClTh} is the indicator variable that takes unity for chlorothiazolyl derivatives. Equation 5 shows that the higher the neuroblocking activity, the higher the insecticidal activity. In addition, log P is parabolically related to the insecticidal activity, and compounds containing a chlorothiazolyl moiety show lower activity (almost one-third) than the corresponding chloronicotinyl compounds.

We attempted QSAR analysis for insecticidal activity using CoMFA and obtained the significant eq 6.

$$\log (1/MLD) = 9.22 + 1.19 \log P - 1.17 (\log P)^2$$
$$+ [\text{CoMFA field terms}] \quad (6)$$

$$n = 17 \quad s = 0.40 \quad r^2 = 0.76$$
$$q^2 = 0.44 \quad (2 \text{ components}) \quad \log P_{opt} = 0.51$$

relative contribution : log P,25.8%; $(\log P)^2$,

15.1%; steric, 43.0%; electrostatic, 16.0%

In eq 6, log P and $(\log P)^2$ as well as CoMFA steric and electrostatic field terms were significant. The optimum log P is 0.51, which is very close to the imidacloprid log P.

CoMFA Potential Contour Maps. Figure 2 shows an overlay of the structure of compound **4** having the highest activity with the major electrostatic and steric potential contour maps drawn according to eqs 4 (neuroblocking activity) and 6 (insecticidal activity). The red areas in Figure 2 indicate regions where negative electrostatic interactions with the receptor binding site increase activity, whereas the blue areas show the reverse. The green areas in Figure 2 indicate regions where submolecular bulk is well accommodated with an increase in activity, whereas the yellow areas indicate regions where submolecular bulk is unfavorable for activity. The favorable and unfavorable regions were very similar for both neuroblocking and insecticidal activities. Red areas near the nitro group show that negative charges of nitro-oxygen atoms are favorable for both activities, being consistent with the results of the classic QSAR eqs 3 and 5, whereas positive charges of the nitro-nitrogen atom and the CH group or imino-nitrogen atom are favorable as shown by blue areas. Green regions show that the nitromethylene-CH group is sterically better than the nitroimine-imino group for the activity. The yellow regions around the CH_2 group of the 5-membered ring show that the compounds having an N−CH₃ group at that

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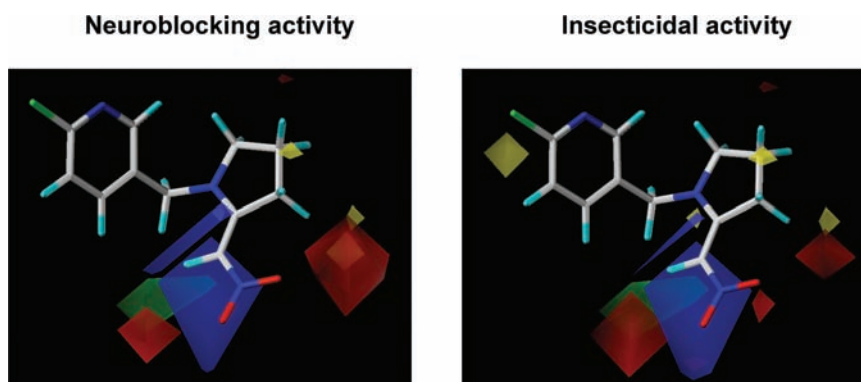dx.doi.org/10.1021/jf102525e |*J. Agric. Food Chem.* 2011, 59, 2909–2917

Figure 2. CoMFA potential contour maps of steric and electrostatic fields wfth compound 4. See the text for an explanation of the contours.

position have low activity. The only difference in the regions between the two activities was that yellow regions appeared around the Cl atom of the pyridine ring for insecticidal activity. Because the Cl atom of the chlorothiazolyl moiety is located in these yellow regions, the regions show the negative effect of the chlorothiazolyl moiety as shown by the indicator variable, I_{ClTh}, for the moiety in eq 5. Calculated activity values are listed in Table 1.

We have previously reported CoMFA for the binding activity of imidacloprid derivatives.[24,25] Even if the activity is different from this paper, the CoMFA potential contour maps in Figure 2 were consistent with previous maps. In addition, we have performed homology modeling of the complex of imidacloprid with the insect nAChR based on the complex structure of acetylcholine binding protein and imidacloprid (PDB: 2ZJU[20]). The binding mode of imidacloprid revealed by the modeled structure was also consistent with the favorable and unfavorable regions drawn according to CoMFA. Please refer to Matsuda's review[26] and related papers for our studies on the interaction of neonicotinoids with insect nAChRs.

The complementary information about the binding site of neonicotinoids obtained from QSAR of neonicotinoids and homology modeling of nAChR will be useful for not only design of a new neonicotinoid but also clarification of the neonicotinoid–protein interaction.

PHYSICOCHEMICAL PROPERTIES FOR BIOAVAILABILITY

Prediction of Membrane Permeability of Diverse Compounds. In our previous papers,[12−15] PAMPA[11] was developed as a model for the prediction of transcellular permeation in the process of drug absorption. We measured the PAMPA permeability of peptide-related compounds, diverse drugs, and pesticides (molecular mass ≤ 500) and derived a QSAR equation for permeability coefficients by the PAMPA of structurally diverse compounds with simple physicochemical parameters, hydrophobicity at an experimental pH (log P and $|pK_a - pH|$), hydrogen-accepting ability (SA_{HA}), and hydrogen-donating ability (SA_{HD}).[13] However, the PAMPA permeability of hydrophobic compounds decreased with its apparent hydrophobicity because of the barrier of the unstirred water layer on membrane surfaces and the membrane retention, so the bilinear QSAR model[27,28] was introduced to explain the PAMPA permeability of a whole set of compounds with the same physicochemical parameters as those used for the linear model.[14]
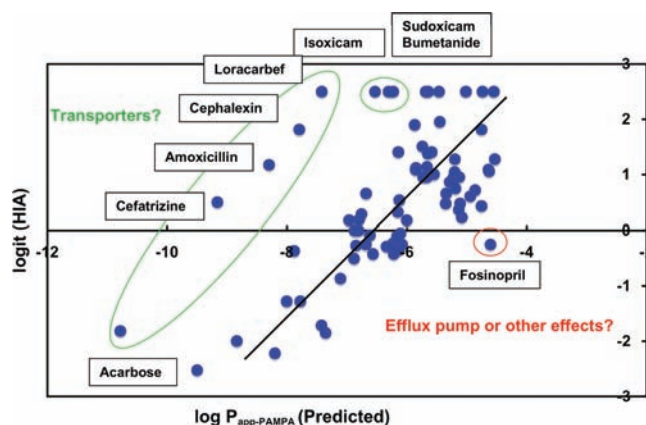

Figure 3. Relationship between the predicted PAMPA permeability coefficient and percent oral absorption.

Group 1 (relatively hydrophilic compounds):

$$\log P_{app\text{-}PAMPA} = 0.42\ (\pm 0.09)\log P - 0.28\ (\pm 0.07)|pK_a - pH|$$
$$- 1.20\ (\pm 0.47)\ SA_{HA} - 1.11\ (\pm 0.40)\ SA_{HD}$$
$$- 4.79\ (\pm 0.30) \tag{7}$$

$$n = 71\quad s = 0.35\quad r^2 = 0.76\quad q^2 = 0.72$$

Group 2 (relatively hydrophobic compounds):

$$\log P_{app\text{-}PAMPA} = -0.62\ (\pm 0.19)\log P + 0.39\ (\pm 0.19)|pK_a - pH|$$
$$- 3.12\ (\pm 0.63) \tag{8}$$

$$n = 31\quad s = 0.42\quad r^2 = 0.63\quad q^2 = 0.55$$

Combining groups 1 and 2 (bilinear model):

$$\log P_{app\text{-}PAMPA} = 0.53\ (\pm 0.10)\log D_{app}$$
$$- 1.43\ (\pm 0.24)\log (\beta 10^{\log D_{app}} + 1) - 0.82\ (\pm 0.37)\ SA_{HA}$$
$$- 1.17\ (\pm 0.42)\ SA_{HD} - 4.99\ (\pm 0.25) \tag{9}$$

$$n = 102\quad s = 0.39\quad r^2 = 0.71\quad q^2 = 0.67$$

$$[\log D_{app} = \log P - 0.67|pK_a - pH|];\ \log D_{app}(\text{optimum})$$
$$= 2.09;\ \log \beta = -2.32$$

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Table 2. PAMPA Permeability Coefficients and QSAR Parameters of Drugs and Pesticides

compd no.	compd name	$\log P_{\text{app-PAMPA}}$ (measured)	$\log P$	$|pK_a-7.3|$	SA_{HA}	SA_{HD}	$\log D_{app}$	$\log P_{\text{app-PAMPA}}$ (calcd)	CLOGP	$|(ACD/pK_a)-7.3|$	TPSA
	drugs										
1	aminopyrine	−4.76	1.00	0	0.266	0.000	1.00				
2	antipyrine	−5.54	0.23	0	0.279	0.000	0.23				
3	coumarin	−4.55	1.39	0	0.330	0.000	1.39				
4	caffeine	−5.41	−0.07	0	0.695	0.000	−0.07				
5	theophylline	−5.31	−0.02	0	0.611	0.135	−0.02				
6	testosterone	−4.95	3.32	0	0.307	0.140	3.32				
7	corticosterone	−4.77	1.94	0	0.517	0.261	1.94				
8	phenytoin	−4.41	2.26	0	0.441	0.267	2.26				
9	acetaminophen	−6.04	0.51	0	0.331	0.293	0.51				
10	hydrocortisone	−5.45	1.61	0	0.560	0.391	1.61				
11	chloramphenicol	−5.41	1.14	0	0.790	0.391	1.14				
12	prednisolone	−5.47	1.62	0	0.561	0.420	1.62				
13	dexamethasone	−5.37	2.01	0	0.587	0.420	2.01				
14	hydrochlorothiazide	−6.69	−0.07	0	0.964	0.549	−0.07				
15	trimethoprim	−5.50	0.91	0	0.658	0.561	0.91				
16	pirenzepine	−6.05	0.10	0.70	0.618	0.147	−0.37				
17	clonidine	−4.98	1.43	0.75	0.182	0.286	0.93				
18	diltiazem	−4.72	2.80	0.76	0.628	0.000	2.29				
19	ranitidine	−6.05	0.27	0.88	0.699	0.222	−0.32				
20	verapamil	−4.64	3.79	1.36	0.717	0.000	2.88				
21	norfloxacin	−6.71	−1.03	2.08	0.560	0.248	−2.42				
22	imipramine	−4.71	4.44	2.10	0.073	0.000	3.03				
23	practolol	−5.98	0.79	2.10	0.435	0.423	−0.62				
24	labetalol	−5.18	3.09	2.10	0.416	0.669	1.68				
25	acebutolol	−6.44	1.71	2.11	0.582	0.424	0.30				
26	piroxicam	−4.96	1.98	2.23	0.798	0.241	0.49				
27	pindolol	−5.31	1.75	2.24	0.257	0.413	0.25				
28	oxprenolol	−4.83	2.10	2.30	0.362	0.262	0.56				
29	propranolol	−4.58	2.98	2.30	0.209	0.274	1.44				
30	alprenolol	−4.94	2.89	2.30	0.211	0.281	1.35				
31	nadolol	−6.15	0.71	2.37	0.409	0.549	−0.88				
32	metoprolol	−5.10	1.88	2.45	0.341	0.281	0.24				
33	ibuprofen	−4.67	3.50	2.92	0.299	0.131	1.54				
34	ketoprofen	−5.55	3.12	3.01	0.471	0.144	1.10				
35	naproxen	−5.30	3.34	3.29	0.401	0.130	1.14				
36	desipramine	−4.77	4.54	3.35	0.048	0.137	2.30				
37	furosemide	−6.47	2.03	3.96	0.868	0.570	−0.62				
38	salicylic acid	−5.92	2.26	4.32	0.444	0.286	−0.63				
	insecticides										
1	imidacloprid	−5.34	0.59	0	0.812	0.126	0.59				
2	RH-5849	−4.78	2.45	0	0.432	0.129	2.45				
3	DMTP	−4.97	2.50	0	0.643	0.000	2.50				
4	salithion	−5.03	2.67	0	0.397	0.000	2.67				
5	chromafenozide	−4.78	2.70	0	0.546	0.133	2.70				
6	BPMC	−4.91	2.78	0	0.264	0.146	2.78				
7	halofenozide	−4.76	3.22	0	0.448	0.132	3.22				
8	fenitrothion	−5.55	3.30	0	0.787	0.000	3.30				
9	diazinon	−5.28	3.30	0	0.587	0.000	3.30				
10	phenthoate	−6.24	3.96	0	0.503	0.000	3.96				
11	methoxyfenozide	−4.72	3.70	0	0.553	0.132	3.70				
12	fenthion	−6.14	4.09	0	0.367	0.000	4.09				
13	tebufenozide	−4.80	4.25	0	0.449	0.132	4.25				

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Table 2. Continued

compd no.	compd name	log $P_{app\text{-}PAMPA}$ (measured)	log P	$|pK_a-7.3|$	SA_{HA}	SA_{HD}	log D_{app}	log $P_{app\text{-}PAMPA}$ (calcd)	CLOGP	$|(ACD/pK_a)-7.3|$	TPSA
14	acephate		−0.85					−5.05	−0.89	0	0.554
15	acetamiprid							−4.29	1.45	0	0.523
16	etoxazole							−2.63	6.56	0	0.308
17	etofenprox		7.05					−2.37	7.36	0	0.277
18	chlorfenapyr		4.83					−3.00	5.42	0	0.380
19	dinotefuran		-					−5.07	−0.93	0	0.915
20	tefluthrin		6.00					−2.77	6.14	0	0.263
21	fipronil		4.00					−3.37	4.29	0	0.847
22	benfuracarb		4.30					−3.30	4.52	0	0.683
23	fosthiazate							−4.13	1.95	0	0.466
24	methomyl		0.60					−4.59	0.54	0	0.507
25	clothianidin							−4.73	0.12	0	0.951
	herbicides										
1	atrazine	−4.53	2.61	0	0.547	0.295	2.61				
2	benthiocarb	−4.69	3.42	0	0.168	0.000	3.42				
3	butamifos	−6.40	4.62	0	0.597	0.136	4.62				
4	2,4-D		2.81					−5.07	2.73	4.32	0.465
5	bensulfuron-methyl							−3.94	2.58	0	1.458
6	dichlobenil		2.74					−3.87	2.74	0	0.238
7	diuron		2.68					−3.89	2.68	0	0.323
8	linuron		3.20					−3.79	3.00	0	0.416
9	bentazone		2.80					−4.95	2.80	3.96	0.665
10	bromacil		2.11					−3.89	2.69	0	0.549
11	sethoxydim		-					−3.85	2.81	0	0.554
12	trifluralin		5.07					−3.05	5.29	0	0.949
13	cyanazin		2.22					−4.32	1.39	0	0.865
14	oxaziclomefone							−2.88	5.80	0	0.295
15	dymron							−3.44	4.08	0	0.411
16	esprocarb		4.60					−3.45	4.03	0	0.203
17	asulam		−0.27					−5.59	−0.31	2.61	0.985
18	isouron		1.98					−4.29	1.47	0	0.584
19	alachlor		3.52					−3.73	3.19	0	0.295
20	karbutilate		1.66					−4.29	1.47	0	0.707

Log D_{app} is the apparent hydrophobicity; refer to our paper[14] for details.

On the basis of QSAR analyses of PAMPA permeability, we proposed an in silico prediction model of human oral absorption for mainly possibly transported compounds.[29] To simplify the analyses, the 71 relatively hydrophilic compounds in eq 7 were used and divided into 2 data sets, a training set with 60 compounds and a validated set with 11 compounds. QSAR eq 10 was formulated for the data of the 60 compounds in the training set using the experimentally determined log P and pK_a as well as polar surface areas (PSA) as a hydrogen-bonding descriptor calculated by Sybyl MOLPROP based on the 3D structures of compounds.

$$\log P_{app\text{-}PAMPA} = 0.43 \ (\pm 0.10) \log P - 0.29 \ (\pm 0.08)|pK_a - pH| - 1.06(\pm 0.29) \text{PSA} - 4.86 \ (\pm 0.31) \quad (10)$$

$$n = 60 \ \ s = 0.36 \ \ r^2 = 0.75 \ \ q^2 = 0.71$$

Equation 10 is identical to eq 7, but SA_{HA} and SA_{HD} were combined into PSA.

Log P, pK_a, and PSA were calculated by commercially available or freely accessible Web programs for in silico prediction. Finally, a good prediction of eq 11 for log $P_{app\text{-}PAMPA}$ values was obtained.

$$\log P_{app\text{-}PAMPA} = 0.33 \ (\pm 0.09) \text{ CLOGP} - 0.28 \ (\pm 0.09)|ACD/pK_a - pH| - 1.20 \ (\pm 0.36) \text{ TPSA} - 4.76 \ (\pm 0.33) \quad (11)$$

$$n = 60 \ \ s = 0.39 \ \ r^2 = 0.70 \ \ q^2 = 0.65$$

CLOGP, ACD/pK_a, and TPSA are the log P, pK_a, and PSA calculated by CLOGP,[30] ACD/pK_a,[31] and a free software.[32] Equation 11 was confirmed by the calculation of the log $P_{app\text{-}PAMPA}$ values of 11 compounds of the validation set.

To examine the ability of our prediction model using in silico descriptors (eq 11), we attempted to predict the percent human oral absorption reported by Deconinck et al.[33] using calculated PAMPA permeability values. The percent human intestinal absorption values [HIA (%)] were transformed by the logit function (eq 12),[34] and logit (HIA) was used as the index of

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human oral absorption. When HIA = 100, logit (HIA) was tentatively taken as 2.5.

$$\text{logit (HIA)} = \log\left[\text{HIA}/(100 - \text{HIA})\right] \quad (12)$$

The relationship between the predicted PAMPA permeability coefficient and logit (HIA) is shown in Figure 3. For most compounds the correlation of both permeabilities was good, but several compounds were underestimated (above the correlation line) and one compound was overestimated (below the correlation line). In general, compounds could be classified into three groups according to their absorption pathways (passively transported compounds, actively transported compounds, and compounds excreted by efflux systems).[13, 14] The underestimated compounds are considered to be actively transported. Although the reasons for the overestimation of a compound are not clear, some transporters for excretion may be involved in the transport of the compound. For 66 compounds excluding underestimated and overestimated compounds, a correlation equation between logit [HIA] and predicted $\log P_{\text{app-PAMPA}}$ was derived as follows.

$$\text{logit (HIA)} = 0.88\,(\pm 0.16)\,\log P_{\text{app-PAMPA}} + 5.80\,(\pm 1.01) \quad (13)$$

$$n = 66 \quad s = 0.70 \quad r^2 = 0.64 \quad q^2 = 0.62$$

Therefore, human oral absorption for passively transported compounds can be directly predicted from eq 13 and PAMPA permeability calculated with in silico descriptors.

Bioavailability of Pesticides. Lipinski's rule of 5 for drug absorption[35] is well-known. According to his rule, drug candidates should have molecular mass of ≤500, CLOGP ≤ 5 (mlog P ≤ 4.15), number of hydrogen-bond donors ≤5, and number of hydrogen-bond acceptors ≤10. The mlog P is log P calculated by Moriguchi's method.[36] Tice examined the distribution of these parameters for 136 postemergence herbicides and 243 insecticides, miticides, and acaricides[37] to confirm whether Lipinski's rule can be applied to the bioavailability of pesticides. On the basis of his examination, the molecular mass of postemergence herbicides and insecticides is the same as pharmaceuticals. The mlog P values are larger for insecticides (mlog P ≤ 5.0) but smaller for herbicides (mlog P ≤ 3.5). Significant differences in the number of hydrogen-bond donors and acceptors between pharmaceuticals and pesticides were also identified. For insecticides a smaller number of hydrogen-bond donors and acceptors (≤2 and ≤8, respectively) is allowed, but a smaller number of donors (≤3) and larger number of acceptors (≤12) for herbicides are permitted.

In the previous section, we showed the usefulness of PAMPA permeability to predict the human oral absorption of diverse compounds. Because log P, pKₐ, and hydrogen-bond ability contribute to PAMPA permeability, it may also be a good index by itself to evaluate the bioavailability of pesticides against pests. We calculated $\log P_{\text{app-PAMPA}}$ values of insecticides and herbicides and examined their distribution of the values. The $\log P_{\text{app-PAMPA}}$ values of pesticides were calculated by eq 11 using in silico descriptors. The calculated values are shown in Table 2 with the experimentally measured values of pesticides and drugs.[14] The distribution of the log $P_{\text{app-PAMPA}}$ values of 38 drugs, 25 insecticides, and 20 herbicides is plotted in Figure 4 by combining measured and calculated values. The distribution pattern was similar for all groups, but compounds with higher PAMPA permeability seem to be more preferable for pesticides than for drugs. In addition, a broader range of compounds is
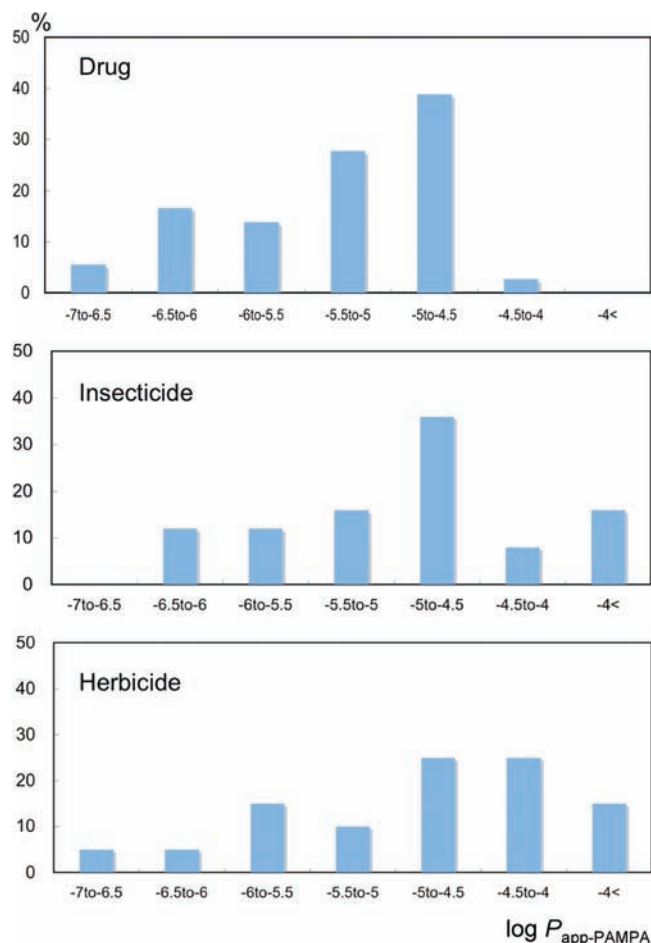

Figure 4. Distribution of PAMPA permeability coefficients of drugs and pesticides.

acceptable for herbicides. It should be noted that compounds with calculated log $P_{\text{app-PAMPA}}$ > −4.5 accumulate in membranes and their actual permeability decreases as the apparent hydrophobicity log D_{app} increases as shown in eq 9[14]. For drugs and insecticides, almost 40% of compounds had log $P_{\text{app-PAMPA}}$ = −5 to −4.5. An important difference between drugs and pesticides (insecticides and herbicides) is that the rate of compounds for which log $P_{\text{app-PAMPA}}$ values were more than −4.5 and accumulated in membranes was 24% (6 compounds) in insecticides and 40% (8 compounds) in herbicides, but only 3% (1 compound) in drugs, supporting the idea that more hydrophobic compounds are more favorable for pesticides. The highest log $P_{\text{app-PAMPA}}$ values are −4.41 (measured, phenytoin) for drugs, −2.70 (calculated, etofenprox) for insecticides, and −3.23 (calculated, oxaziclomefone) for herbicides, whereas the lowest log $P_{\text{app-PAMPA}}$ values are −6.71 (measured, norfloxacin) for drugs, −6.24 (calculated, phenthoate) for insecticides, and −6.76 (calculated, asulam) for herbicides. Table 2 shows that compounds with log $P_{\text{app-PAMPA}}$ = −5.5 to −4.5, −5 to −4.5, and −5 to −4 are recommended for candidates of drugs, insecticides, and herbicides, respectively, although it should be considered whether the administration of pesticides is topical or oral.

■ CONCLUDING REMARKS

We have described the importance of the physicochemical properties for QSAR and the bioavailability of pesticides. In recent years, the evaluation of drug absorption in the early stage

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of drug discovery has been applied as a filtering method. We showed that the PAMPA permeability coefficient is an excellent descriptor to predict human oral absorption. Although it is also useful to find a good parameter that quantitatively represents penetration ability of chemicals into insects or weeds and analyze the relationship between the penetration parameter and PAMPA permeability, we believe that it could be applied to filter new pesticide candidates. The second index evaluated by PAMPA, an artificial membrane accumulation index, was useful to estimate the bioconcentration factor of organophosphorus pesticides in our previous paper.[38] This may be another effective descriptor in pesticide design.

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■ ABBREVIATIONS USED

QSAR, quantitative structure—activity relationships; CoMFA, comparative molecular field analysis; PAMPA, parallel artificial membrane permeation assay; nAChRs, nicotinic acetylcholine receptors; BC, neuroblocking concentration; MLD, minimum lethal dose; PSA, polar surface areas.

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