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Quantitative Structure-activity Relations in Pyrazolylpyrimidine Derivatives for Their Analgesic Activities

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Statistically significant correlations have been demonstrated between analgesic activities of a series of pyrazolylpyrimidine derivatives and molecular properties. The structural parameters are partition coefficients, molar refractivities, an indicator variable, and MO indices obtained from the CNDO/2 method. The influence of the torsional angle between the pyrazole and pyrimidine rings on the electronic state was examined. The correlations indicate that transport and partition processes and electronic factors play a major part in determining the analgesic activity. In particular, of electronic parameters MO indices on the pyrazole ring are significant. These structure-activity relationships can be used to estimate the analgesic activities with some degree of confidence.

It is known that non-narcotic analgesics, including the derivatives of pyrazole, salicylic acid and acetanilide, have antipyretic and antiinflammatory properties. The most popular pyrazole compounds are antipyrine and aminopyrine.

Many attempts[1,2] have been carried out to develop new drugs by modification of existing pyrazole compounds, *e.g.*, antipyrine as a lead compound. The Hansch analysis has been applied to the studies of quantitative structure-activity relationships (QSAR) of antipyrine derivatives.[3] These studies revealed that pyrazoles having an alicyclic or heterocyclic group instead of a phenyl ring in antipyrine are potentially active.

Naito *et al.*, therefore, synthesized pyrazolylpyrimidine derivatives to find a highly potent drugs.[4,5] As a result it has been found that 4-methoxy-2-(5-methoxy-3-methyl-1*H*-pyrazol-1-yl)-6-methylpyrimidine (mepirizole) is the most potent compounds having an analgesic effect. In the QSAR studies it is important to ascertain if metabolites of the drug are not potent. It has been found that the metabolites of mepirizole have little effect.[6,7]

In an attempt to further investigate analgesic activities of pyrazole compounds, correlation between the activities of pyrazolylpyrimidine derivatives and the molecular structure is studied using the QSAR techniques in this paper. The structural parameters to establish QSAR are hydrophobic parameters, molar refractivities, an indicator variable and a variety of MO indices obtained from the CNDO/2 method.

Experimental

Data Set. The data used in this study were taken from the studies on a series of 44 pyrazolylpyrimidine compounds.[5] The analgesic activities are expressed as $\log A$, where A is relative potency compared with equimolar amounts of aminopyrine measured by the pressure method in mice. These values are given in Table 1. The fragments involving pyrazole R_i and pyrimidine P_j are shown in Fig. 1 to represent the compounds in Table 1.
The forty-four compounds are divided into two groups, (N^1 and N^2). Groups N^1 and N^2 contain subgroups A, B and C, D, respectively. Subgroups A and B contain series

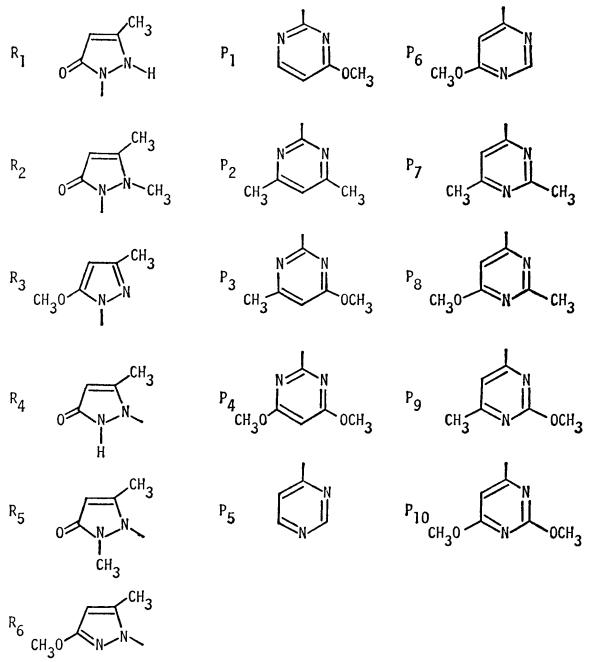

Fig. 1. The chemical structures of pyrazole R_i and pyrimidine P_j fragments.

R_1, R_2, and R_3 and subgroups C and D contain series R_4, R_5, and R_6, respectively. The numbers of active compounds in each group and series are shown in Table 2.

Structural Parameters of Pyrazoles. The hydrophobic parameters are determined experimentally or estimated using the observed data. 1-Octanol/water partition coefficients P for 23 compounds were measured at pH 7 and at room temperature by the flask shaking method. Table 1 shows the observed log P values. The fragment addition model, which is a similar procedure to the Free-Wilson method, is used to calculate the log P values for the remaining 15 compounds. This model is given by the following equation:

$$\log P = \sum_i R_i X_i + \sum_j P_j Y_j + \mu, \quad (1)$$

where R_i is the fragment contribution of a pyrazole ring, P_j is that of a pyrimidine ring, and μ is the overall average of the observed log P values ($X_i=1$ if the pyrazole ring is the i-th fragment, otherwise $X_i=0$, $Y_j=1$ if the pyrimidine ring is the j-th fragment, otherwise $Y_j=0$). Further the

Table 1. Analgesic activities, log P and MR values for pyrazolylpyrimidine derivatives

No.	Structure R_i	Structure P_j	log A	log P Obsd[a]	log P Calcd	MR
1	R_1	P_1	−0.18	—	0.645	52.83
2	R_1	P_2	−0.48	0.720	0.497	55.70
3	R_1	P_3	0.15	—	0.898	57.48
4	R_1	P_4	−0.48	1.158	1.158	59.26
5	R_1	P_5	−0.50	—	0.414	46.40
6	R_1	P_6	−0.59	0.987	0.992	52.83
7	R_1	P_7	−0.15	0.894	0.883	55.70
8	R_1	P_8	0.30	0.718	0.947	57.48
9	R_1	P_9	−0.46	1.030	1.030	57.48
10	R_1	P_{10}	−0.37	—	1.500	59.26
11	R_2	P_1	Inactive	—	0.119	57.67
12	R_2	P_2	−1.37	—	−0.028	60.53
13	R_2	P_3	−1.16	—	0.372	62.32
14	R_2	P_4	−0.57	—	0.632	64.10
15	R_2	P_5	Inactive	—	−0.112	51.24
16	R_2	P_6	−0.38	0.297	0.466	57.67
17	R_2	P_7	−0.61	0.244	0.357	60.53
18	R_2	P_8	−0.21	0.704	0.421	62.32
19	R_2	P_9	−0.54	—	0.504	62.32
20	R_2	P_{10}	−0.09	—	0.974	64.10
21	R_3	P_1	−0.12	1.007	1.007	58.05
22	R_3	P_2	−0.04	0.730	0.860	60.91
23	R_3	P_3	0.33	1.260	1.260	62.70
24	R_3	P_4	0.19	—	1.520	64.48
25	R_3	P_5	0.19	0.497	0.776	51.62
26	R_3	P_6	0.17	1.528	1.354	58.05
27	R_3	P_7	−0.12	—	1.245	60.91
28	R_3	P_8	0.10	1.544	1.309	62.70
29	R_3	P_9	0.04	—	1.392	62.70
30	R_3	P_{10}	−0.11	1.862	1.862	64.48
31	R_4	P_2	−0.03	1.291	1.387	55.70
32	R_4	P_3	−0.11	—	1.788	57.48
33	R_4	P_5	−1.18	1.400	1.304	46.40
34	R_4	P_7	Inactive	—	1.770	55.70
35	R_4	P_8	Inactive	—	1.837	57.48
36	R_5	P_2	−0.59	0.510	0.221	60.53
37	R_5	P_3	Inactive	—	0.622	62.32
38	R_5	P_7	Inactive	—	0.607	60.53
39	R_5	P_8	−0.46	0.382	0.671	62.32
40	R_6	P_2	−0.41	1.822	2.107	60.91
41	R_6	P_3	−0.21	—	2.507	62.70
42	R_6	P_5	−0.40	2.206	2.023	51.62
43	R_6	P_7	−0.42	2.595	2.493	60.91
44	R_6	P_8	−0.51	—	2.556	62.70

a) A dash indicates no data.

Table 2. Groups and series of pyrimidine compounds

Group	$N^1(28)$[a]			$N^2(10)$		
Subgroup	A(18)		B(10)	C(5)		D(5)
Series	$R_1(10)$	$R_2(8)$	$R_3(10)$	$R_4(3)$	$R_5(2)$	$R_6(5)$

a) Values in parentheses are the numbers of active compounds in the groups or series.

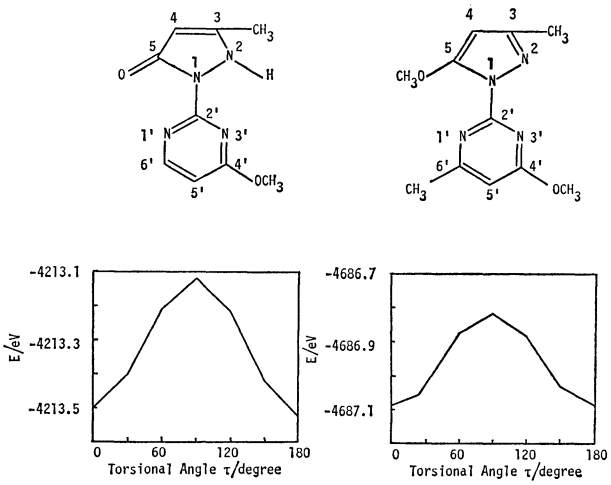

Fig. 2. Pyrazole numbering system (τ=0°) and total energies of compound **1** (left) and mepirizole *vs.* rotation around N^1–$C^{2'}$ bond.

symmetry relations are given by the following equations:

$$\sum_i n_i R_i = 0, \qquad \sum_j n_j P_j = 0, \tag{2}$$

where n_i is the number of i-th pyrazole rings and n_j is that of the j-th pyrimidine rings for 23 compounds.

Combining Eqs. 1 and 2, the symmetry constraints vanish. The resulting simultaneous equations are solved by the least squares method to obtain the fragment contributions. The regression equation is

$$\begin{aligned}\log P = &-0.305X_1 - 0.831X_2 + 0.057X_3 + 0.585X_4 \\ &- 0.581X_5 + 1.305X_6 - 0.154Y_1 - 0.301Y_2 \\ &+ 0.099Y_3 + 0.359Y_4 - 0.385Y_5 + 0.193Y_6 \\ &+ 0.084Y_7 + 0.148Y_8 + 0.231Y_9 + 0.701Y_{10} \\ &+ 1.104 \end{aligned} \tag{3}$$

The correlation coefficient between observed and calculated log P values for 23 compounds is 0.965. The log P values for other compounds were calculated by this equation. These log P values are shown in Table 1.

In order to represent the steric feature, molar refractivities MR were calculated from bond refractivites.[8] The values are shown in Table 1. Seventeen varieties of MR values exist for all compounds.

Quantum mechanical indices were determined from the CNDO/2 method to explain electronic aspects of drug-acceptor interactions. They are energies of the highest occupied molecular orbital HOMO, the lowest unoccupied molecular orbital LUMO, the energy difference GAP between LUMO and HOMO, and total electron densities associated with the atoms on pyrazole ring (q_1—q_5). The numbering system for pyrimidine derivatives is shown in Fig. 2.

Molecular geometries are determined from the X-ray crystallographic data for pyrazole,[9] pyrimidine[10] and antipyrine.[11] The torsional angle τ between the pyrazole and pyrimidine rings in mepirizole(compound **23**) was determined as 20.5° from X-ray crystallographical data. The details of the characteristic feature of the geometry of pirizole will be published in the near future, and not demescribed in the present paper. The torsion of pyrimidine ring toward the pyrazole ring is most likely to have the most influence on the electronic state. In order to investigate

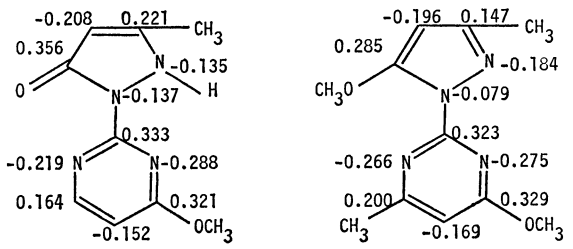

Fig. 3. Charge distribution of compound **1** (left) and mepirizole.

the effect of conformational alternations on the electronic states of these compounds, the rotation around the N^1–$C^{2'}$ bond were carried out with 30° increments for the typical compounds, compound **1** and mepirizole.

Conformation and Electronic State. The total energies of compound **1** and mepirizole vary in accordance with increment of the torsional angle (Fig. 2). The lowest energies are obtained at $\tau=0°$ and 180°, where pyrazole and pyrimidine situate on the same plane and electronic delocalization may occur over two rings. The highest energy is obtained at $\tau=90°$ for both compounds. The energy at 20.5° is a little higher than the lowest energy. The value is 0.04 eV which is near to the thermal energy and the torsion of that extent may easily occur. On the other hand, that the difference between the highest and lowest energy is more than 0.3 eV indicates the presence of the high energy barrier for the free rotation around the N^1–$C^{2'}$ bond. HOMO, LUMO, and GAP of the two compounds at 20.5° are slightly higher than the corresponding lowest energies.

Total electron densities on the pyrazole ring indicate the slight change in charge distribution for both compounds at 20.5° and 0°. The patterns of charge distribution at 20.5° are similar for both compounds (Fig. 3). All the pyrazole derivatives used in this study have similar patterns of charge distribution when the torsional angle is 20.5°. The rotational angles for all compounds are fixed at 20.5° to calculate the MO indices since the electronic state at 20.5° of torsional angle resembles that of the lowest energy.

Results and Discussion

By expressing the analgesic activity as the logarithm of relative potency log A, a systematic search of various parameters for pyrazole derivatives revealed statistically significant relationships. Linear regression analysis for 18 compounds in subgroup A yielded the following equations:

$$\log A = -0.906(\log P)^2 + 1.548(\log P) - 0.700\mathrm{HOMO} - 8.159, \quad (4)$$
$$n = 18,\ r = 0.798,\ s = 0.633,\ F = 8.21,$$

$$\log A = -0.608(\log P)^2 + 1.204(\log P) + 51.949Q_1 - 34.503Q_3 + 13.484, \quad (5)$$
$$n = 18,\ r=0.892,\ s=0.516,\ F=12.71.$$

In this report n represents the number of data points upon which the equation is based, s is the standard deviation, and F is the F ratio. Q_k is the net charge associated with the atom k on the pyrazole ring. These correlations, involving partition coefficients and MO parameters, indicate the importance of transport and electronic properties. By combining net charges on the pyrazole ring with hydrophobic parameters, 80% of the variation in the observed analgesic activities can be explained. Since Q_3 and Q_4 have a high negative correlation coefficient of −0.81, it seems that the substituents would have a similar effect on the net charges on these atom positions, which might play an important role for the analgesic activity.

Using similar approach, more extended relationships which include the entire members of group N^1 (subgroup A, B) were developed. The following equations are generated,

$$\log A = -0.532(\log P)^2 + 1.044(\log P) - 0.797\mathrm{HOMO} - 9.029, \quad (6)$$
$$n = 28,\ r = 0.842,\ s = 0.572,\ F = 19.51,$$

$$\log A = -0.666(\log P)^2 + 1.450(\log P) - 15.329Q_4 + 2.020, \quad (7)$$
$$n = 28,\ r = 0.835,\ s = 0.584,\ F = 18.40.$$

The hydrophobic parameters and HOMO or Q_4 correlated well with the activities of these derivatives as well as only with that of the subgroup B derivatives. This suggests that the mechanism of action of the subgroup B derivatives seems to be similar to that of the subgroup A derivatives.

The parabolic relationships of hydrophobic parameters in Eqs. 4—7 indicate that the optimal log P value for activity is about one. The log P values for the compounds having higher activity (compounds **3**, **8**, **23**) are close to this value, on the other hand, that for the compounds having low activities (**12**, **13**) and inactive compounds are far from this value. However, the electronic factor is also important. Since the correlation between Q_3 and Q_4 is high in group N^1, Eq. 5 is closely related to Eq. 7. Therefore these positions of the pyrazole ring are considered to be fairly important for the group N^1 derivatives. No improvement is obtained by adding other parameters because MO parameters are relatively well correlated with each other.

The negative sign of the coefficients associated with HOMO in Eqs. 4 and 6 indicates that the more electron-donating ability, the lower activity becomes. In contrast with this result, Neely *et al.*[12] reported the positive sign of the coefficient with HOMO in the studies of a series of imidazole derivatives, that leads to a charge transfer complex model. Neither *MR* nor total electron density on the atom of the pyrimidine ring were of significant value in correlating the activity.

An analysis of the analgesic activities of 10 compounds in group N^2 revealed that *MR*, LUMO and GAP are significant parameters.

$$\log A = -0.009MR^2 + 1.051MR - 29.963, \quad (8)$$
$$n = 10,\ r = 0.879,\ s=0.542,\ F = 11.84,$$

$$\log A = 0.690\mathrm{LUMO} - 0.144\mathrm{IV} - 2.33, \quad (9)$$
$$n = 10,\ r = 0.842,\ s=0.612,\ F = 8.54,$$

$$\log A = 0.867\mathrm{GAP} - 0.907\mathrm{IV} - 11.535, \quad (10)$$
$$n = 10,\ r = 0.954,\ s = 0.341,\ F = 35.09,$$

where IV is an indicator variable with a value of

Table 3. Predicted log A values for Inactive compounds

No.	Predicted				No.	Predicted		
	Eq. 4	Eq. 5	Eq. 6	Eq. 7		Eq. 8	Eq. 9	Eq. 10
11	−0.95	−1.22	−0.90	−0.94	**34**	−0.17	−1.05	−1.14
15	−1.25	−0.98	−1.08	−1.23	**35**	−0.17	−1.10	−1.11
					37	−0.46	−0.31	−0.63
					38	−0.30	−0.40	−0.43

1 for the subgroup C derivatives and 0 for the subgroup D derivatives. The introduction of hydrophobic parameters into each regression in no case produced a significant improvement.

Equation 8 indicates that there exists an optimal MR value; a proper steric feature would be required for drug-acceptor interactions. The positive coefficient with LUMO in Eq. 9 indicates that the activity increases with the stability of electronic state. The indicator variable IV highly correslates with the net charges on the atoms of the pyrazole ring and reflects these electronic features. GAP, concerning with the transition energy, also correlates well with activity. Another regression analysis combining the other series compounds $R_i(i=1, 2,\cdots 6)$ in no case produced a significant correlation.

In order to examine the reliability of the results obtained above, the activities were predicted from Eqs.. 4—10 for those compounds which are found to be inactive. The predicted activities are shown in Table 3. The analgesic activities for the group N^1 compounds were successfully predicted to be inactive from Eqs. 4—7. On the other hand, the group N^2 compounds were predicted to be not inactive from Eq. 8. This failure may be due to some unexplained factors. However, it is expected that observed relationships aid the development of understanding of the analgesic activities for these compounds.

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