the reaction mixture to ice water, the aq layer was extd with $CHCl_3$, washed with 8% $NaHCO_3$ soln, and dried ($MgSO_4$). Removal of solvent afforded a brown oil which after drying *in vacuo* was redissolved in $CHCl_3$ and decolorized. Addn of dry HCl followed by evapn of solvent resulted in an oily residue which solidified when triturated with Et_2O. The yield of cryst (MeOH–Et_2O) product, mp 198–200° dec, was 0.26 g (55%). *Anal.* ($C_{26}H_{28}N_2O_4 \cdot HCl$) C, H, N.

p-(4-Ethoxycarbonyl-4-phenyl-1-piperidinoethyl)maleanilic Acid (7a).—This was obtained in 89% yield following the procedure of Cava[11] for the prepn of maleanilic acid; recrystd from THF–Et_2O, mp 236–238 dec. *Anal.* ($C_{26}H_{30}N_2O_5$) C, H, N.

Acetic N-(p-Ethoxycarbonyl-4-phenyl-1-piperidinophenethyl)-maleamic Anhydride·HCl (7).—When **7a** was treated with Ac_2O and NaOAc as per the procedure of Cava[11] described for maleimide, an oily residue was obtd which was purified on column (silica gel) using EtOAc. It was dissolved in $CHCl_3$ and treated with dry HCl. Evapn of the solvent left an oily residue which solidified on washing with Et_2O. Two recrystns (MeOH–Et_2O) gave 0.31 g (63%) of the product as hydrochloride, mp 222–223°. *Anal.* ($C_{28}H_{32}N_2O_6 \cdot HCl$) C, H, N.

Ethyl 1-(p-propionamidophenethyl)-4-phenyl-4-piperidinecarboxylate·HCl (8) was prepared in 79% yield by treating anileridine·HCl with $EtCO_2H$ as described for **3**; recrystd (MeOH–Et_2O) mp 191–192°. *Anal.* ($C_{25}H_{32}N_2O_3 \cdot HCl$) C, H, N.

Ethyl p-(4-Ethoxycarbonyl-4-phenyl-1-piperidinoethyl)succinanilate·HCl (9).—Succinyl chloride monoethyl ester was treated with **1** according to the procedure described for **5** with the exception that the reaction mixture was heated for 4 hr. Two recrystns (MeOH–Et_2O) yielded **9** (78%), mp 176–177°. *Anal.* ($C_{28}H_{36}N_2O_5 \cdot HCl$) C, H, N.

Ethyl 1-(p-succinimidophenethyl)-4-phenyl-4-piperidinecarboxylate·HCl (10) was obtained in 75% yield following the procedure of Fieser.[19] The product melted at 239–240°. *Anal.* ($C_{26}H_{30}N_2O_5 \cdot HCl$) C, H, N.

Acknowledgments.—We thank Dr. A. A. Patchett, Research Laboratories, Merck and Co., Rahway, N. J., for the generous supply of anileridine and Dr. Ralph Jacobsen, Endo Laboratories, Garden City, N. Y., for the suply of naloxone used in these studies.

(19) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Company, Boston, Mass., 1955, pp 105–106.

Structure–Activity Study of Phenethylamines as Substrates of Biosynthetic Enzymes of Sympathetic Transmitters[1]

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Regression analyses by a modification of the Free–Wilson technique were applied to the phenethylamines as substrates of enzymes associated with the biosynthetic pathway of sympathetic transmitters, such as dopamine β-hydroxylase and phenylethanolamine *N*-methyltransferase. The mathematical contribution of substituents to the activity of unsubstituted phenethylamine was found to be additive with the use of logarithmic activity data. It was also shown that the contribution values can be related to more fundamental physicochemical substituent parameters such as the Hammett σ and the hydrophobic constant, π, in certain cases.

Recently, we have reported an example of analyses of structure–activity relationship of a series of sympathomimetic amines using the Free–Wilson technique.[2,3] The inhibitory effect of the amines of variously modified structures on the norepinephrine uptake into isolated rat heart has been nicely correlated with the mathematical sum of contributions of structural fragments to the total activity of the molecule [3]

In this paper we wish to extend this mathematical method to the structure–activity analysis of phenethylamines as substrates of enzymes associated with the biosynthetic pathway of sympathetic transmitters such as dopamine β-hydroxylase and phenylethanolamine *N*-methyltransferase.

Method

The method used in this paper is a modification of the Free–Wilson technique. In the same manner as in our previous analysis, we have used the log of activity data, since the log of activity is considered to be a free energy related parameter which is additive. Assuming that the effect of a certain substituent at a certain position on the activity of the phenethylamine molecule is constant and additive, we can derive a linear equation for each compound in the form of eq 1, where A and A_0 represent the

$$\log \frac{A}{A_0} = \Sigma G_i X_i \qquad (1)$$

magnitude of the activity of substituted and unsubstituted phenethylamine, respectively, G_i is the log activity contribution or the log activity enhancement factor of the ith substituent relative to that of H and X_i is a parameter which takes a value of 1 or 0 according to the presence or absence of the ith substituent.

For a set of structure–activity analysis, $\log A_0$ is a constant. Thus, eq 1 is modified to eq 2, where c is a constant. Substitution of the values of X_i, for substituents at various positions, into eq 2 yields simultaneous equations, the number of which is equal

$$\log A = \Sigma G_i X_i + c \qquad (2)$$

to the number of compounds in the set. The activities of the compounds, for example, are given as shown in eq 3–6, where the notations in parenthesis represent the substituent and its position.

$$\text{phenethylamine: } \log A = c \qquad (3)$$

$$\text{dopamine: } \log A = G(p\text{-OH}) + G(m\text{-OH}) + c \qquad (4)$$

$$\text{3,5-dimethoxy-}p\text{-tyramine: } \log A = G(p\text{-OH}) + G(m\text{-OCH}_3) + G(m'\text{-OCH}_3) + c \qquad (5)$$

* To whom correspondence should be addressed.

(1) Studies on Structure–Activity Relationship. 3.

(2) S. H. Free, Jr. and J. W. Wilson, *J. Med. Chem.*, **7**, 395 (1964).

(3) (a) T. Ban and T. Fujita, *ibid.*, **12**, 353 (1969). (b) A. S. V. Burgen and L. L. Iversen, *Brit. J. Pharmacol.*, **25**, 34 (1965).

$$N\text{-methyldopamine: } \log A = G(p\text{-OH}) + G(m\text{-OH}) + G(\text{NCH}_3) + c \quad (6)$$

A substituent at an asymmetric C is expected to contribute to the total activity differently according to the absolute configuration. The activity of the (+) and (−) isomers of norepinephrine is expressed by eq 7 and 8, respectively.

$$(+)\text{-norepinephrine: } \log A = G(p\text{-OH}) + G(m\text{-OH}) + G(\text{S-}\beta\text{-OH}) + c \quad (7)$$

$$(-)\text{-norepinephrine: } \log A = G(p\text{-OH}) + G(m\text{-OH}) + G(\text{R-}\beta\text{-OH}) + c \quad (8)$$

For racemic compounds, half the number of molecules have the R and the other half have the S configuration around an asymmetric C so that the value of 0.5 is assigned to X for a substituent of different configurations. Examples are shown in eq 9 and 10.

$$(\pm)\text{-}\alpha\text{-methyldopamine: } \log A = G(p\text{-OH}) + G(m\text{-OH}) + 0.5G(\text{R-}\alpha\text{-CH}_3) + 0.5G(\text{S-}\alpha\text{-CH}_3) + c \quad (9)$$

$$(\pm)\text{-}p\text{-hydroxynorephedrine: } \log A = G(p\text{-OH}) + 0.5G(\text{R-}\beta\text{-OH}) + 0.5G(\text{S-}\beta\text{-OH}) + 0.5G(\text{R-}\alpha\text{-CH}_3) + 0.5G(\text{S-}\alpha\text{-CH}_3) + c \quad (10)$$

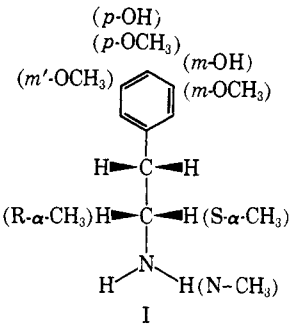
If the number of compounds in a set, n, is sufficiently large, the G value of various substituents and the constant, c, can be obtained by solving n simultaneous equations with the use of the least-squares method.

The above method differs from the original Free–Wilson method in two respects. First, in the Free–Wilson method, the activity contributions of substituents including H have to be considered and restriction equations, where the group contributions at each position are summed up over a whole set of compounds and set to zero, must be applied. In our method, the activity contribution of a substituent is relative to that of H at each position, and restriction equations are not required. Secondly, the constant term in the linear equation in the Free–Wilson model should be equal to the overall average of the activity values for a set of compounds although defined as the activity contribution from the parent "skeleton." In our model, the constant term obtained by the least-squares method is a theoretically predicted activity value of the unsubstituted compound itself. The calculation procedure is much simpler than that of the Free–Wilson model especially when the activity of the unsubstituted compound is known.

The calculations were carried out by a FACOM 230/60 computor of the Data Processing Center of this University.

Results and Discussion

(1) Activity of Phenethylamines as Substrates of Dopamine β-Hydroxylase.—The enzyme has been shown to catalyze the β-hydroxylation not only of dopamine to norepinephrine but also of a large number of related amines with a phenethylamine structure.[4] The data shown in Table I are taken from the work of van der Schoot and Creveling.[4] They have measured the rate of formation of a β-hydroxylated product by a purified enzyme preparation from fresh bovine adrenal glands and expressed the substrated activity of compounds relative to that of the most active 4-hydroxyphenethylamine as $A = 100$. Of 23 compounds studied by the original authors, 16 compounds of closely related structure, as shown in Table I, are used for the regression analysis. The set of compounds comprises those substituted by various combinations of 8 substituents indicated in structure I.



I

Since the compounds are either optically inactive or racemic, the individual G values for the α-Me of R and S configurations cannot be assigned, but the sum of the two can. The terms, $G(R\text{-}\alpha\text{-CH}_3)$ and $G(S\text{-}\alpha\text{-CH}_3)$ appear in a linear equations always as a pair so that we can combine the two as in eq 11. The activity of racemic compounds in this set is expressed as in eq 12 and 13.

$$G(\alpha\text{-CH}_3) = 0.5[G(R\text{-}\alpha\text{-CH}_3) + G(S\text{-}\alpha\text{-CH}_3)] \quad (11)$$

$$(\pm)\text{-}\alpha\text{-methyl-}p\text{-tyramine: } \log A = G(p\text{-OH}) + G(\alpha\text{-CH}_3) + c \quad (12)$$

$$(\pm)\text{-}\alpha\text{-methylnorepinephrine: } \log A = G(p\text{-OH}) + G(m\text{-OH}) + G(\alpha\text{-CH}_3) + c \quad (13)$$

Thus, the number of unknowns is reduced from 9 including c to 8 by the combination for the α-Me. The 16 simultaneous equations with 8 unknowns are solved to yield activity contribution values which are shown in Table II. The correlation between observed and calculated activities is very good as judged from multiple correlation coefficient ($r = 0.962$) and standard deviation ($s = 0.238$). The F ratio between variance of calculated activity and that of observed activity is significant at the 99.5% level.

Although this result indicates that the substituents contribute to the total activity almost independently and additively, a possibility still exists of improving the correlation statistically by using a model where interactions between substituents are considered. We have considered here possible interactions between substituents on the benzene ring. For the contributions from mutually interacting groups 1 and 2, eq 14 can be derived where suffixes represent the groups, and an asterisk indicates parameters due to the interaction. When both groups are present, *i.e.*, $X_1 = X_2 = X^* = 1$, contribution to the total activity becomes $G_1 + G_2 + G^*$. If only one of these two is placed on the ring, *i.e.*, if either X_1 or X_2 is zero, the contribution to the activity from this part of the molecule is either G_1 or G_2. The contribution due to interaction, G^*, can be regarded to play a role in correcting the sum of otherwise independent group contributions.

$$\Sigma \text{ contribution} = X_1G_1 + X_2G_2 + X^*G^* = X_1G_1 + X_2G_2 + X_1X_2G^* \quad (14)$$

For the m,p-dihydroxy compounds, the interaction term, $G^*(\text{OH:OH})$, can be added to the linear equation. For the m-hydroxy-p-methoxy compounds, it is

(4) (a) J. B. van der Schoot and C. R. Creveling, *Advan. Drug Res.*, **2**, 47 (1965). (b) C. R. Creveling, J. W. Daly, B. Witkop, and S. Udenfriend, *Biochim. Biophys. Acta*, **64**, 125 (1962).

TABLE I

OBSERVED AND CALCULATED ACTIVITY OF SUBSTRATES OF DOPAMINE β-HYDROXYLASE

Compd	Group								log A	
	X(p-OH)	X(p-OCH3)	X(m-OH)	X(m-OCH3)	X(α-CH3)	X(N-CH3)	X(m'-OCH3)	X*(OH:OCH3)	Obsd	Calcd[a]
Phenethylamine									1.80	1.87
4-OH	1								2.00	2.02
3-OH			1						1.89	1.93
4-OCH3		1							0.48	0.54
4-OH, N-CH3	1					1			1.40	1.37
4-OH, α-CH3	1				1				1.81	1.68
3-OH, α-CH3			1		1				1.70	1.59
3,4-(OH)2	1		1						1.97	2.08
4-OH, 3-OCH3	1			1				1	1.85	1.52
3-OH, 4-OCH3		1	1					1	0.30	0.27
3,4-(OCH3)2		1		1					0.30	0.36
3,4-(OH)2, N-CH3	1		1			1			1.40	1.43
3,4-(OH)2, α-CH3	1		1		1				1.76	1.73
4-OH, 3-OCH3, α-CH3	1			1	1			1	0.90	1.17
4-OH, 3,5-(OCH3)2	1			1			1	1	1.45	1.54
3,4,5-(OCH3)3		1		1			1		0.48	0.39

[a] Calcd from *G* values obtained by solving simultaneous equations similar to eq 16 which are shown in Table II.

TABLE II

CALCULATED GROUP CONTRIBUTIONS OF SUBSTRATES OF DOPAMINE β-HYDROXYLASE

Group	*G* values calcd from simultaneous equations similar to: eq 16	eq 2
p-OH	0.147	0.054
p-OCH3	−1.334	−1.345
m-OH	0.054	−0.012
m-OCH3	−0.180	−0.376
α-CH3	−0.343	−0.305
N-CH3	−0.649	−0.555
m'-OCH3	0.026	−0.080
OH:OCH3[a]	−0.326	
c(phenethylamine)	1.875	1.906

[a] *G**(OH:OCH3), interaction term between OH and OCH3.

assumed that the same interaction term, *G**(OH:OCH3), can be used as for the *p*-hydroxy-*m*-methoxy compounds. Whether or not the addition of interaction term(s) is of significance in improving the correlation is examined by three sets of calculations to solve 16 simultaneous equations with the *G**(OH:OH) term (eq 15), with the *G**(OH:OCH3) term (eq 16), and with both terms (eq 17). The correlation is improved when only

$$\log A = \Sigma X_i G_i + X^*(\mathrm{OH{:}OH})G^*(\mathrm{OH{:}OH}) + c \quad (15)$$

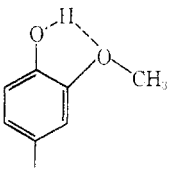
$$\log A = \Sigma X_i G_i + X^*(\mathrm{OH{:}OCH_3})G^*(\mathrm{OH{:}OCH_3}) + c \quad (16)$$

$$\log A = \Sigma X_i G_i + \Sigma X^* G^* + c \quad (17)$$

the *G**(OH:OCH3) term is added. The multiple correlation coefficient is 0.978 and the standard deviation is 0.194. An *F* test shows that the addition of the interaction term is significant at better than the 0.95 confidence level ($F_{1,8} = 5.80$; $F_{1,8,0.05} = 5.31$). The *G* values thus obtained are shown in Table II. The calculated activity of the compounds is shown in Table I obtained by summing up the values including that of the interaction term.

Comparing the *G* values, the most significant activity enhancement group over phenethylamine is found to be the *p*-OH which increases the activity by a factor of about 1.4(log^{-1} 0.15), and the most powerful activity-lowering group seems the *p*-OMe which affects the activity by a factor of about 0.05(log^{-1} −1.33). The meta substituents do not seem to play such significant roles as the para substituents. The difference in *G* values between *p*-OH and *p*-OMe might be ascribed not only to the H bond formation with the enzyme but perhaps also to other factors such as hydrophobic and steric. Both the *N*-Me and α-Me groups reduce the activity of phenethylamine molecule.

That the activity is reduced when OH and OMe are placed vicinally may be due to either a capture of the OH adjacent to the MeO by an intramolecular H bond



II

(II) or a steric hindrance presented by the MeO group as has been suggested for the α and β activities of phenethylamine derivatives.[5] The lack of significance of interaction between two vicinal OH groups may suggest that the interaction of each OH group with receptor site(s) is stronger than the intramolecular H bond formation. The absolute value of *G**(OH:OMe) is comparable to that of *G*(*p*-OH) so that the interaction between OH and OMe might cancel out the effect of *p*-OH on the receptor.

The analysis is further substantiated by application to another series of experimental data obtained by Goldstein and Contrera.[6] Shown in Table III is the inhibitory activity of the same class of compounds as competitive substrates on conversion of dopamine to norepinephrine by the enzyme similarly prepared from fresh bovine adrenal glands. The data are recalculated from the original ones by averaging those obtained at 2 different inhibitor concentrations and by taking the activity relative to that of 4-hydroxyphenethylamine as 100

(5) (a) P. Pratesi and E. Grana, *Advan. Drug Res.*, **2**, 134 (1965). (b) P. Pratesi, A. La Manna, L. Villa, E. Grana and L. Lilla, *Farmaco. Ed. Sci.*, **18**, 932 (1963).

(6) M. Goldstein and J. F. Contrera, *J. Biol. Chem.*, **237**, 1898 (1962).

TABLE III
OBSERVED AND CALCULATED ACTIVITY OF COMPETITIVE SUBSTRATES OF DOPAMINE β-HYDROXYLASE

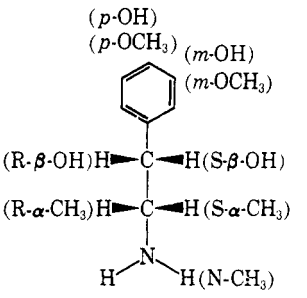
Compd	log A Obsd	log A Calcd
Phenethylamine	1.72	1.87
p-Tyramine	2.00	2.02
(±)-*p*-Hydroxyamphetamine	1.76	1.68
Epinine	1.24	1.42
Mescaline	Inactive	0.39
(±)-α-Methyldopamine	1.78	1.74
(±)-Amphetamine	1.55	1.53
(±)-Deoxyephedrine	0.67	0.88
m-*O*-Methyldopamine	1.35	1.51

in order to make the standard the same as that of the substrate study.

Since the inhibitory potency of a competitive substrate can be regarded as a first approximation to be proportional to the degree of the Michaelis complex formation, the inhibitory data would be elucidated by the sum of the group contribution values obtained from the substrate activity. As expected, the relative inhibitory activity data calculated with G values obtained from simultaneous equations similar to eq 16 in Table II agree fairly well with the observed values as shown in Table III. The simple correlation coefficient and level of significance of F ratio calculated for 8 compounds (except mescaline) are 0.997 and 99.5%, respectively.

activity relative to that of (−)-normetanephrine as 100. Of 17 compounds which the original author studied, 12 have appreciable activity, while the others including unsubstituted phenethylamine are inactive. Here, we have chosen arbitrarily a value of zero as the logarithmic activity of phenethylamine.

Substituents of this series are shown in III. There are 9 substituents and the parent compound for which contribution values must be calculated. The 13 simultaneous equations including the one for phenethylamine (those for **1–13** in Table IV) with 10 unknowns



III

are solved in this case. The calculated activity contribution values, G and c, are shown in Table V. The total calculated activity of each compound is shown in Table IV. The correlation between observed and calculated activities is very good, judged from the correlation coefficient, $r = 0.998$, and standard deviation,

TABLE IV
OBSERVED AND CALCULATED ACTIVITY OF SUBSTRATES OF PHENYLETHANOLAMINE *N*-METHYLTRANSFERASE

	Compd	Group X(*p*-OH)	X(*p*-OCH3)	X(*m*-OH)	X(*m*-OCH3)	X(R-β-OH)	X(S-β-OH)	X(R-α-CH3)	X(S-α-CH3)	X(NCH3)	log A Obsd	log A Calcd
1	(−)-Normetanephrine	1			1	1					2.00	2.00
2	(±)-Norparanephrine		1	1		0.5	0.5				2.00	2.00
3	(±)-Phenylethanolamine					0.5	0.5				1.86	1.86
4	(±)-Octopamine	1				0.5	0.5				1.26	1.25
5	(±)-*m*-Hydroxyphenylethanolamine			1		0.5	0.5				1.78	1.84
6	(−)-Norepinephrine	1		1		1					1.32	1.26
7	(+)-Norepinephrine	1		1			1				1.18	1.19
8	(−)-Epinephrine	1		1		1				1	0.60	0.66
9	(±)-Neosynephrine			1		0.5	0.5			1	1.30	1.24
10	(−)-Norephedrine					1			1		1.15	1.15
11	(±)-*p*-Hydroxynorephedrine	1				0.5	0.5	0.5	0.5		1.26	1.27
12	(±)-3,4-Dihydroxynorephedrine	1		1		0.5	0.5	0.5	0.5		1.26	1.25
13	Phenethylamine										0.00[a]	0.00[a]
14	3-Methoxytyramine	1			1						Inactive	0.10[a]
15	Tyramine	1									Inactive	−0.61[a]
16	Dopamine	1		1							Inactive	−0.63[a]
17	(±)-Amphetamine							0.5	0.5		Inactive	0.02[a]

[a] If log A(obsd) of phenethylamine is taken as −1.00, the values of log A(calcd) are reduced to −1.00, −0.90, −1.61, −1.63, and −0.98, resp.

(2) Activity of Phenethylamines as Substrates of Phenylethanolamine *N*-Methyltransferase.—Axelrod has shown that an enzyme preparation from monkey adrenal glands, phenylethanolamine *N*-methyltransferase, catalyzes the *N*-methylation of norepinephrine to epinephrine as well as of a number of related compounds.[7] He has measured the rate of formation of N-methylated compound and expressed the substrate

$s = 0.070$. The level of significance of F ratio between the variance of the observed activity and that of the estimated activity is 99.5%. It should be noticed that the observed and calculated activity values are identical for several compounds. This is necessarily so for (−)-normetanephrine and (±)-norparanephrine, because

(7) (a) J. Axelrod, *J. Biol. Chem.*, **237**, 1657 (1962). (b) J. Axelrod, *Pharmacol. Rev.*, **18**, 95 (1966).

TABLE V

CALCULATED GROUP CONTRIBUTIONS OF SUBSTRATES OF PHENYLETHANOLAMINE *N*-METHYLTRANSFERASE

Group	*G*
p-OH	−0.615
p-OCH_3	0.160
m-OH	−0.022
m-OCH_3	0.714
R-β-OH	1.901
	(2.901)[a]
S-β-OH	1.823
	(2.823)[a]
R-α-CH_3	0.798
S-α-CH_3	−0.751
NCH_3	−0.602
c(phenethylamine)	0.00
	(−1.000)[a]

[a] The values which are obtained when the logarithmic activity of inactive phenethylamine is taken as −1.000.

these compounds have a substituent which is only observed once. In this example, the addition of interaction term(s) between ring substituents does not improve the correlation.

Although the calculation is based on the data including arbitrarily chosen activity value for the inactive parent compound, the summation of *G* values predicts other inactive compounds as well. Even if we choose a value of −1.000 for the logarithmic activity of phenethylamine, the correlation is not varied at all. The contribution values, however, are changed so that $c = -1.000$ and both the *G* values for β-OH of different configurations are increased by the amount of +1.000. Thus, the calculated activity values are not varied except for phenethylamine (−1.000). The summation of *G* values now predicts the "activity" value for inactive compounds to be 1.000 log unit less than those shown in Table IV.

Although individual *G* values of β-OH of different configurations cannot be derived definitely since the activity value is arbitrarily chosen for the inactive parent compound, it is certain that they are similar in magnitude to each other. This may suggest that the interaction between β-OH and receptor is necessary for the substrate but is not stereospecific. The absolute configuration of the molecule around the α-C, however, affects the activity markedly. The α-Me of *R* configuration enhances the activity by a factor of 40 over that of *S* configuration. It would be reasonable to assume that the more closely situated an asymmetric C to the position of N-methylation, the more pronounced is the steric effect of substituent according to the absolute configuration.

The effect of ring substituents is certainly not one of enhancing the activity by H bond formation with receptor, since the values of *m*- and *p*-OH contributions are negative. Since the ring substituents contribute to the activity additively, we have tried to analyze their *G* values by linear free energy substituent parameters such as the Hammett σ and the hydrophobic constant, π.[8,9] Using the values shown in Table VI, we have obtained eq 18 and 19 by the method of least squares, where *s* is standard deviation and *r* is multiple correlation coefficient.

TABLE VI

LINEAR FREE ENERGY PARAMETERS AND GROUP CONTRIBUTIONS OF THE RING SUBSTITUENT

Ring substituents	π	σ_1	σ_2	*G* value: Original	*G* value: Calcd from eq 19
p-OH	−0.85	−0.37	0.12	−0.615	−0.677
p-OCH_3	0.00	−0.27	0.12	0.160	0.091
m-OH	−0.61	0.12	−0.37	−0.022	0.045
m-OCH_3	0.08	0.12	−0.27	0.714	0.565
H	0.00	0.00	0.00	0.000	0.214

$$G = 0.323 + 0.743\pi + 0.881\sigma_1 \quad n = 5 \quad s = 0.284 \quad r = 0.906 \quad (18)$$

$$G = 0.214 + 0.903\pi - 1.030\sigma_2 \quad 5 \quad 0.202 \quad 0.954 \quad (19)$$

In eq 19, σ_2 is the estimate of the electronic effect of substituent on the ortho position of the side chain. The correlation with σ_1, the electronic effect on the side-chain position, is poorer as shown in eq 18. Although the points of data used in the regression, *n*, is so small that the result may not be highly reliable, eq 19 would indicate that the higher the hydrophobicity of the ring system and the electron density at the ortho position, the stronger is the receptor–substrate interaction. It would be interesting to test this hypothesis with compounds which have hydrophobic and electron-donating groups such as *i*-Pr or *i*-Bu on the benzene ring.

The above results would illustrate additional examples of successful applications of mathematical models on structure–activity studies. When structural modifications are made at various positions in a molecule at the same time, the analysis with this model could be a powerful tool. Since the analysis is based on the logarithmic activity data and the group contribution for an H substituent at any position is assigned a value of zero, the calculated group contribution values can be further analyzed in terms of the linear free energy substituent effect parameters such as σ and π so that we could elucidate their physicochemical meanings in certain cases.

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(9) T. Fujita, J. Iwasa, and C. Hansch, *ibid.*, **86**, 5175 (1964).