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Quantitative Structure-Activity Correlation of Optical Isomers: a Molecular Basis for Pfeiffer's Rule

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SUMMARY

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The quantitative approach of Hansch and his co-workers to structure-activity relationships has been extended to optical isomers of a series of phenoxyproprionic acids acting as plant growth regulators. We have treated the physicochemical constants of the two chiral substituents as independent variables. Pfeiffer's rule, which states that the isomeric activity ratio of a more active compound is higher than that of a less active one, is explained in terms of different structural requirements for the substituents as measured by π and van der Waals volume. A positive dependence on the aromatic ring substituent constant σ suggests a drug-receptor interaction of electronic nature in addition to hydrophobic interactions.

INTRODUCTION

Since the pioneering work of Hansch and his co-workers (1-4), free energy-related parameters, coupled with the powerful tool of computerized multiple regression analysis, have found wide applications in correlating biological activities with various chemical structures in numerous systems (5-11). However, optical isomers are usually not included in quantitative structure-activity correlation studies, mainly because 1-octanol-water or other optically inactive solvent systems used in determining the partition coefficients cannot differentiate the partition behavior of enantiomorphs. So far most structure-activity relationship studies on stereoisomers have been either qualitative or semiquantitative in nature (12-18). Among the empirical generalizations reported, Pfeiffer's rule appears to be valid in many cases; i.e., the isomeric activity ratio of a more active compound is higher than that of a less active one, although there are some exceptions (19).

The main purpose of this paper is to report that by treating the physicochemical properties of the two chiral substituents at the optically active center (see Tables 1 and 2) as independent variables, the variation in the biological activities of many pairs of enantiomorphs can be quantitatively correlated with the molecular structures. Because of the availability of data on the inhibitory activity on flax root growth of a large number of optically active aryloxypropionic acid derivatives, these are used as an example in the regression analysis. Since all enzymes and/or

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receptor proteins are made of naturally occurring, optically active L-amino acids (except glycine), any drug-receptor interaction of high specificity should be considered in terms of a drug molecule occupying a chiral environment. Consequently the two substituents of a highly active *R* isomer should contribute quite differently to the binding energy compared with the enantiomorphic *S* isomer.

METHODS

The inhibitory activities toward flax root growth of 56 optically active aryloxypropionic acids and structurally related derivatives are taken from the compilations of Jonsson (20) and Åberg (21), where C_{50} is the concentration of the substance which reduces growth to 50% of control in the flax root test. Compounds without an oxygen or other heteroatom connecting the aromatic ring and the propionic acid moiety (e.g., indolepropionic acids) are not included in this study, in order to avoid too many structural variables for just a few additional compounds.

The π value of the Ph−O− in 1-octanol-water is calculated from log *P* of phenoxyacetic acid (1.26) and that of acetic acid (−0.31) (22), where *P* is the 1-octanol-water partition coefficient of the whole molecule and π is that of the substituent. The other π values and Hammett's σ constants are taken from the literature (23, 24). The van der Waals volume *V* (25) is used as a first approximation of the steric (bulk) effect. We elected to use log *V* instead of the volume term itself so that we would not have to specify the exponent associated with the *V* term (10) before the logarithmic function was taken, since the exponent of *V* is incorporated into the coefficient when the logarithmic function is used ($k \cdot \log V^n = nk \cdot \log V$). The physicochemical constants and biological data used are assembled in Table 1. The method of least squares was used in deriving the equations listed in Table 2, using an IBM 370/158 computer (9).

RESULTS AND DISCUSSION

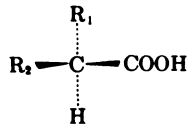
From Table 2, one can see that by using a quadratic equation of the π constant and log *V* terms for both R_1 and R_2 plus the σ constant of the aromatic ring, a correlation coefficient (*r*) of 0.80 is obtained for all the 56 compounds examined (Eq. 1). By stepwise elimination of the "outliers" (compounds with more than twice the standard deviation *s*), an acceptable *r* value of 0.902 is obtained for 47 compounds (Eq. 7). More than 81% ($r^2 > 0.81$) of the variance in the data can be accounted for by this equation, using five independent variables (eight terms). Further deletions of outliers give Eqs. 8–13. Although the standard deviation decreases from 0.48 to 0.33, the correlation coefficients remain around 0.92. This is primarily due to the fact that most of the potent compounds with activity (log 1/*C*) higher than 7.0 have higher deviations than the less potent compounds. When these compounds are eliminated, the spread in biological activity decreases and keeps the correlation coefficient from increasing even though the standard deviation of the regression (*s*) is diminishing. Therefore extreme care should be taken in eliminating the so-called outliers in order to improve the correlation.

Among the equations in Table 2, Eq. 7 is considered the most representative, since it has an *r* of 0.902 and an *s* of 0.48 for 47 compounds, including four compounds with activity higher than 7.0 and three compounds with activity below 4.0. The σ_{Ar} and log V_1 terms in Eq. 7 are statistically significant at the 99th and 90th percentiles, respectively, as indicated by an *F* test ($F_{1,39} = 8.5$ and 4.0, respectively). The ideal lipophilicity $(\pi_1)_0$ for maximum activity is 2.36, with a 95% confidence interval of 1.70–2.78, while the ideal $(\pi_2)_0$ is 3.43 (2.82–4.75), significantly higher than $(\pi_1)_0$. This strongly suggests that the hydrophobic nature of the receptor site for R_1 is different from that for R_2. This is also reflected by the different dependence on the log *V* for R_1 and R_2 (compare k_3 and k_7 in Table 2).

The positive dependence on σ_{Ar} in all the equations derived (see k_4 in Table 2) reflects the formation of a drug-receptor complex of the charge transfer (26) or dipole-dipole type. The concept of multiple-point or three-point attachment (27) ap-

TABLE 1

Physicochemical constants and biological data for aryloxypropionic acid derivatives inhibiting flax root growth



R_1 = aryloxy and R_2 = alkyl for the *R* (+) isomers, with the notable exceptions of 2-iodophenoxypropionic acid, α-naphthoxypropionic acid, and 1-naphthoxy-*n*-butyric acid: the (+) isomer belongs to the *S* series.

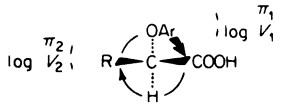
log $1/C_{50}$		log V_{R_1}	π_{R_1}	π_{R_2}	log V_{R_2}	σ_{Ar}	Configuration			No.
Observed[a]	Calculated[b]							R_1	R_2	
5.89	6.22	1.69	1.57	0.56	1.14	0.00	*R* (+)	Ph—O—	Me—	1
3.96	4.18	1.14	0.56	1.57	1.69	0.00	*S* (−)	Me—	Ph—O—	1′
7.48	6.49	1.82	3.03	0.56	1.14	0.45	*R* (+)	2,4-DiCl—Ph—O—	Me—	2
4.89	4.99	1.14	0.56	3.03	1.82	0.46	*S* (−)	Me—	2,4-DiCl—Ph—O—	2′
7.55	6.65	1.82	3.03	0.56	1.14	0.60	*R* (+)	3,4-DiCl—Ph—O—	Me—	3
5.46	5.15	1.14	0.56	3.03	1.82	0.60	*S* (−)	Me—	3,4-DiCl—Ph—O—	3′
5.00	5.09	1.14	0.56	3.79	1.87	0.83	*S* (−)	Me—	2,4,5-TriCl—Ph—O—	4
7.68	(5.94)[c]	1.83	3.11	0.56	1.14	0.06	*R* (+)	4-Cl-2-Me—Ph—O—	Me—	5
4.74	4.48	1.14	0.56	3.11	1.83	0.06	*S* (−)	Me—	4-Cl-2-Me—Ph—O—	5′
5.85	5.43	1.69	1.57	1.02	1.38	0.00	*R* (+)	Ph—O—	Et—	6
4.05	4.32	1.38	1.02	1.57	1.69	0.00	*S* (−)	Et—	Ph—O—	6′
7.55	(6.03)[c]	1.82	3.03	1.02	1.38	0.46	*R* (+)	2,4-DiCl—Ph—O—	Et—	7
4.85	5.13	1.38	1.02	3.03	1.82	0.46	*S* (−)	Et—	2,4-DiCl—Ph—O—	7′
7.49	(5.93)[c]	1.87	3.79	0.56	1.14	0.83	*R* (+)	2,4,5-TriCl—Ph—O—	Me—	8
3.52	(5.21)[c]	1.69	1.57	2.04	1.65	0.00	*R* (+)	Ph—O—	*n*-Bu—	9
3.52	4.51	1.65	2.04	1.57	1.69	0.00	*S* (−)	*n*-Bu—	Ph—O—	9′
7.70	(5.99)[c]	1.87	2.84	0.56	1.14	0.04	*R* (+)	2-Naph—O—	Me—	10
4.09	4.10	1.14	0.56	2.84	1.87	0.04	*S* (−)	Me—	2-Naph—O—	10′
4.84	(5.99)[c]	1.87	2.84	0.56	1.14	0.04	*R* (−)	1-Naph—O—	Me—	11
4.64	4.10	1.14	0.56	2.84	1.87	0.04	*S* (+)	Me—	1-Naph—O—	11′
4.33	4.24	1.38	1.02	2.84	1.87	0.04	*S* (+)	Et—	1-Naph—O—	12
7.00	(5.11)[c]	1.87	2.84	1.02	1.38	0.04	*R* (+)	2-Naph—O—	Et—	13
4.14	4.24	1.38	1.02	2.84	1.87	0.04	*S* (−)	Et—	2-Naph—O—	13′
4.92	5.43	1.92	3.60	0.56	1.14	0.27	*R* (+)	1-Cl-2-Naph—O—	Me—	14
4.21	4.13	1.14	0.56	3.60	1.92	0.27	*S* (−)	Me	1-Cl-2-Naph—O—	14′

5.55	4.73	1.87	2.84	2.04	1.65	0.04	*R* (+)	2-Naph—O—	*n*-Bu—	15
4.30	4.43	1.65	2.04	2.84	1.87	0.04	*S* (−)	*n*-Bu—	2-Naph—O—	15′
5.66	5.43	1.73	0.98	0.56	1.14	0.00	*R* (+)	Ph—NH—	Me—	16
3.52	3.00	1.14	0.56	0.98	1.73	0.00	*S* (−)	Me—	Ph—NH—	16′
6.74	(5.78)[c]	1.91	3.56	0.56	1.14	0.04	*R* (+)	2-Naph—S—	Me—	17
4.30	3.94	1.14	0.56	3.56	1.91	0.04	*S* (−)	Me—	2-Naph—S—	17′
6.0[d]	6.35	1.71	1.72	0.56	1.14	0.06	*R* (+)	4-F—Ph—O—	Me—	18
4.0[d]	4.30	1.14	0.56	1.72	1.71	0.06	*S* (−)	Me—	4-F—Ph—O—	18′
6.5[d]	6.62	1.76	2.27	0.56	1.14	0.23	*R* (+)	4-Cl—Ph—O—	Me—	19
4.4[d]	4.72	1.14	0.56	2.27	1.76	0.23	*S* (−)	Me—	4-Cl—Ph—O—	19′
6.6[d]	6.55	1.78	2.59	0.56	1.14	0.23	*R* (+)	4-Br—Ph—O—	Me—	20
4.5[d]	4.81	1.14	0.56	2.59	1.78	0.23	*S* (−)	Me—	4-Br—Ph—O—	20′
7.4[d]	6.56	1.81	2.72	0.56	1.14	0.35	*R* (+)	3-I—Ph—O—	Me—	21
5.1[d]	4.81	1.14	0.56	2.72	1.81	0.35	*S* (−)	Me—	3-I—Ph—O—	21′
6.2[d]	6.32	1.81	2.83	0.56	1.14	0.18	*R* (+)	4-I—Ph—O—	Me—	22
5.9[d]	6.10	1.77	2.09	0.56	1.14	−0.17	*R* (+)	4-Me—Ph—O—	Me—	23
7.3[d]	6.61	1.82	3.09	0.56	1.14	0.60	*R* (+)	2,5-DiCl—Ph—O—	Me—	24
5.0[d]	5.17	1.14	0.56	3.09	1.82	0.60	*S* (−)	Me—	2,5-DiCl—Ph—O—	24′
6.5[d]	6.61	1.82	3.09	0.56	1.14	0.60	*R* (+)	2,3-DiCl—Ph—O—	Me—	25
5.0[d]	5.17	1.14	0.56	3.09	1.82	0.60	*S* (−)	Me—	2,3-DiCl—Ph—O—	25′
5.4[d]	5.01	1.14	0.56	3.09	1.82	0.46	*S* (−)	Me—	2,6-DiCl—Ph—O—	26
5.4[d]	(6.77)[c]	1.82	3.09	0.56	1.14	0.74	*R* (+)	3,5-DiCl—Ph—O—	Me—	27
4.8[d]	5.33	1.14	0.56	3.09	1.82	0.74	*S* (−)	Me—	3,5-DiCl—Ph—O—	27′
5.1[d]	5.77	1.87	3.79	0.56	1.14	0.69	*R* (+)	2,4,6-TriCl—Ph—O—	Me—	28
4.6[d]	4.93	1.14	0.56	3.79	1.87	0.69	*S* (−)	Me—	2,4,6-TriCl—Ph—O—	28′
4.7[d]	4.59	1.92	4.55	0.56	1.14	1.06	*R* (+)	2,4,5,6-TetraCl—Ph—O—	Me—	29
4.6[d]	4.61	1.14	0.56	4.55	1.92	1.06	*S* (−)	Me—	2,4,5,6-TetraCl—Ph—O—	29′
6.0[d]	6.43	1.81	2.49	0.56	1.14	0.18	*R* (−)	2-I—Ph—O—	Me—	30
5.0[d]	4.48	1.14	0.56	2.49	1.81	0.18	*S* (+)	Me—	2-I—Ph—O—	30′
5.6[d]	6.45	1.82	3.09	0.56	1.14	0.46	*R* (+)	2,6-DiCl—Ph—O—	Me—	31
4.3	4.45	1.99	3.93	0.56	1.14	0.01	*R* (+)	2-*i*—Pr-4-Cl-5-Me—Ph—O—	Me—	32

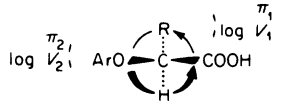
[a] From ref. 20 unless stated otherwise.
[b] Calculated from Eq. 7.
[c] Not included in the derivation of Eq. 7.
[d] From ref. 21.

TABLE 2

Equations correlating auxin activity with physicochemical constants of optical isomers of phenoxypropionic acid derivatives



(+) isomer = *R* configuration



(-) isomer = *S* configuration

$$\log 1/C_{50} = -k_1(\pi_1)^2 + k_2\pi_1 + k_3 \log V_1 + K_4\sigma_{Ar} - k_5(\pi_2)^2 + k_6\pi_2 + k_7 \log V_2 + k_8$$

Eq.	k_1	k_2	k_3	k_4	k_5	k_6	k_7	k_8	n	r	s
1	0.569	3.224	−4.260	0.583	0.289	2.190	−6.858	16.365	56	0.802	0.767
2	0.567	3.423	−5.085		0.273	2.306	−7.543	18.186	56	0.796	0.769
3	0.586	3.342	−5.074	0.496	0.286	2.324	−8.026	19.004	52	0.864	0.642
4	0.585	3.270	−4.965	0.439	0.288	2.343	−7.994	18.846	50	0.874	0.585
5	0.581	3.381	−5.506		0.275	2.428	−8.516	20.155	50	0.870	0.585
6	0.549	2.932	−4.210	0.688	0.295	2.278	−7.529	17.469	49	0.878	0.552
7	0.534	2.514	−2.619	1.151	0.356	2.442	−6.886	14.606	47[a]	0.902	0.484
8	0.493	3.082	−5.132	0.196	0.271	2.338	−8.200	19.440	46	0.912	0.514
9	0.482	3.088	−5.306		0.265	2.370	−8.410	19.933	46	0.911	0.509
10	0.538	2.458	−1.941	1.229	0.326	2.127	−5.682	12.281	45	0.913	0.430
11	0.438	1.650		1.485	0.321	1.992	−4.858	9.210	45	0.906	0.440
12	0.451	1.973	−1.401	1.033	0.323	2.161	−5.637	11.777	43	0.917	0.370
13	0.395	1.648	−1.027	0.866	0.319	2.189	−5.667	11.512	42	0.924	0.328

[a] The most representative equation.

pears to be more attractive than the two-point attachment hypothesis (26, 27). The finding that not all the *ortho*-substituted compounds are less active than predicted from Eq. 7 tends to exclude the possibility of nucleophilic attack by the receptor at the *ortho* position (2).

In most of the compounds examined the *R* isomers are more active than the corresponding *S* isomers. A few exceptions are noteworthy; both the *R* and *S* isomers of α-phenoxy-*n*-caproic acids have the same activity although the calculated value of the *R* isomer (R_1 = Ph−O−, R_2 = *n*-Bu−) is about 0.70 log unit higher than the *S* isomer (compounds 9 and 9′). The *S* isomer of indolepropionic acid, not included in this study, has been shown to have a slightly higher activity than the *R* isomer (21). Whether this is due to the difference in transport (27) or a different mechanism of action remains to be investigated. It is interesting that different growth-regulating properties have also been observed for the *cis-trans* isomers of many cinnamic acids and related compounds, and the difference between the geometric isomers seems to be least pronounced in certain 3-indolyl compounds (27).

The validity of our approach, treating R_1 and R_2 as independent variables, is confirmed by the $(\pi_1)_0$ and $(\pi_2)_0$ values obtained for the *R* and *S* isomers as separate groups. For *S* isomers alone:

$$\log\frac{1}{C_{50}} = -0.333(\pi_2)^2 + 1.878\pi_2 - 0.641 \log V_2 - 0.236 \log V_1 + 1.048\sigma_{Ar} + 3.112, \quad (14)$$
$$n = 27, r = 0.886, s = 0.261$$
$$(\pi_2)_0 = 2.82 \text{ (2.06–3.76)}$$

For *R* isomers alone:

$$\log\frac{1}{C_{50}} = -0.684(\pi_1)^2 + 3.434\pi_1 + 0.067 \log V_1 - 0.882\pi_2 + 0.885\sigma_{Ar} + 2.603, \quad (15)$$
$$n = 29, r = 0.617, s = 0.993$$
$$(\pi_1)_0 = 2.51 \text{ (0.91–4.51)}$$

The $(\pi_2)_0$ of 2.82 is not too different from that obtained from Eq. 7 (3.43), and the

$(\pi_1)_0$ of 2.5 is almost the same as that from Eq. 7 (2.36). The correlation coefficient (r) of Eq. 15 is low, since most of the outliers belong to the R series.

The finding that five out of the nine outliers have activities above 7.0 and none of the values calculated from Eq. 7 is above 7.0 is due partly to the inherent nature of the method of least squares and partly to some subtle drug-receptor interactions not adequately represented by the parameters used. For example, $R(+)$-2-naphthoxypropionic acid (compound 10) has an inhibitory activity of 7.70, while $R(-)$-1-naphthoxypropionic acid (compound 11), a position isomer, has an inhibitory activity of only 4.84. Whether this is due to a steric or electronic factor remains to be investigated. Furthermore, a curve embracing the least sum of squares will usually have highly active compounds lying above and poorly active ones below it.

The negative dependence on log V_1 and log V_2 (see k_3 and k_7 in Table 2) strongly suggests that a highly bulky group at either R_1 or R_2 is incompatible with high inhibitory activity. The lower absolute k_3 than absolute k_7 value indicates that the bulk tolerance at R_1 is greater than at R_2. This is in agreement with the general observation that R isomers, which have the bulkier aryloxy group at the R_1 position, are usually more active than S isomers. Although eight terms are included in Eq. 7 for a total of 47 data points, only five independent variables are used. In general it is necessary to have a sufficient number of data points for every variable used, to avoid chance correlations (28). In our case 47 data points for five independent variables are considered quite sufficient, and the possibility of having chance correlations is negligible.

A plot of isomeric ratio (Δ log $1/C_{50}$) vs. the inhibitory activity of the more active R isomer is shown in Fig. 1. A plot of the observed log $1/C_{50}$ vs. the log $1/C_{50}$ calculated from Eq. 7 is given in Fig. 2.

It is not uncommon to have a series of drugs ranging from agonists to partial agonists and then to antagonists (29–31). The same phenomenon is also observed in the plant growth regulators, many of which

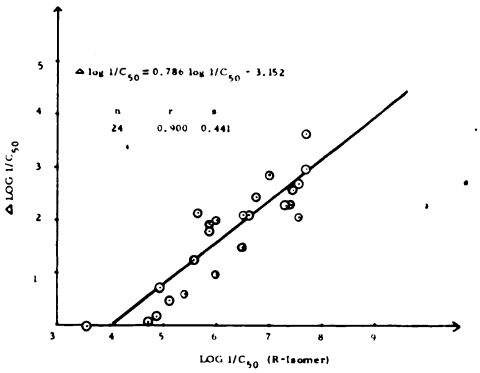


FIG. 1. *Pfeiffer plot of isomeric ratio vs. inhibitory activity of the more active R isomer*

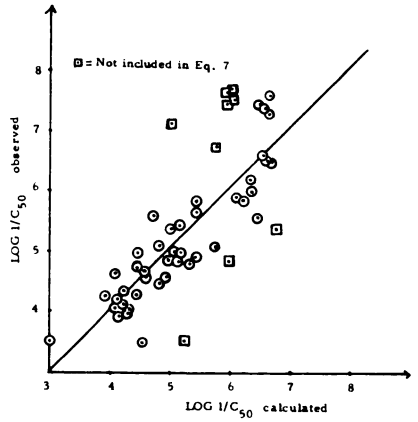


FIG. 2. *Plot of observed vs. calculated inhibitory activity, using Eq. 7*

have been shown to have both auxin and antiauxin activities (21). The approach we used in analyzing the quantitative structure-inhibitory activity relationships of inhibitors of plant growth may also be applied to the optical isomers of series of pharmacological agents acting in animals. We have also used the same approach in the quantitative structure-activity correlation of geometric isomers acting as antihistamines.[2]

From consideration of the structural requirements one would expect that the discriminatory effect for the two substituents by a receptor might not be so critical if the chiral center were not adjacent or close to the critical binding site. Indeed, this has been observed in the case of cholinesters of

[2] E. J. Lien, J. F. Rodrigues de Miranda, and E. J. Ariëns, unpublished observations.

phenylcyclohexylglycolic acid acting as anticholinergic drugs, where Pfeiffer's rule holds for the asymmetry center in the acyl moiety but not for the asymmetry center in the amino alcohol moiety (32).

REFERENCES

1. Hansch, C., Maloney, P. P., Fujita, T. & Muir, R. M. (1962) *Nature*, 194, 178–180.
2. Hansch, C., Muir, R. M., Fujita, T., Maloney, P. P., Geiger F. & Straich, S. (1963) *J. Am. Chem. Soc.*, 85, 2817–2824.
3. Fujita, T., Iwasa, J. & Hansch, C. (1964) *J. Am. Chem. Soc.*, 86, 5175–5180.
4. Iwasa, J., Fujita, T. & Hansch, C. (1965) *J. Med. Chem.*, 8, 150–153.
5. Hansch, C. (1971) in *Drug Design* (Ariëns, E. J., ed.) Vol. 1, pp. 271–342, Academic Press, New York.
6. Verloop, A. (1972) in *Drug Design* (Ariëns, E. J., ed.), Vol. 3, pp. 133–187, Academic Press, New York.
7. Gould, R. (1972) *Adv. Chem. Ser.*, 114, 1–304.
8. Purcell, W. P., Bass, G. E. & Clayton, J. M. (1973) *Strategy of Drug Design, a Guide to Biological Activity*, pp. 1–193, Wiley, New York.
9. Hansch, C. (1973) in *International Encyclopedia of Pharmacological Therapeutics*, Sect. 5, Vol. 1 (Cavallito, C. J., ed.), pp. 75–166, Pergamon Press, New York.
10. Lien, E. J. (1974) in *Medicinal Chemistry IV, Proceedings of the 4th International Symposium on Medicinal Chemistry (Noordwijkerhout, Netherlands)*, pp. 319–342, Elsevier, Amsterdam.
11. Lien, E. J. (1975) in *Drug Design* (Ariëns, E. J., ed.), Vol. 5, pp. 81–132, Academic Press, New York.
12. Pfeiffer, C. C. (1956) *Science*, 124, 29–31.
13. Ellenbroek, B. W. J. (1964) Stereoisomerie en Biologische aktiviteit Ph.D. thesis, University of Nijmegen, The Netherlands.
14. Ellenbroek, B. W. J. (1966) *Acta Physiol. Pharmacol. Neerl.*, 14, 53–54.
15. Ellenbroek, B. W. J., Nivard, R. J. F., van Rossum, J. M. & Ariëns, E. J. (1965) *J. Pharm. Pharmacol.*, 17, 393–404.
16. Ellenbroek, B. W. J. & van Rossum, J. M. (1960) *Arch. Int. Pharmacodyn.*, 125, 216–220.
17. Keijer, J. H. & Wolring, G. Z. (1969) *Biochim. Biophys. Acta*, 185, 465.
18. Barlow, R. B., Franks, F. M., Pearson, J. D. M. & Butt, A. A. (1972) *Br. J. Pharmacol.*, 46, 300–314.
19. Ariëns, E. J. (1971) in *Drug Design* (Ariëns, E. J., ed.), Vol. 1, pp. 149–193, Academic Press, New York.
20. Jonsson, A. (1961) in *Handbuch der Pflanzenphysiologie*, Vol. 14 (Ruhland, W., ed.), pp. 959–1001, Springer, Heidelberg.
21. Åberg, B. (1961) in *4th International Conference on Plant Growth Regulation* Ames Iowa State University Press (*Yonkers, N.Y.*), pp. 219–232.
22. Leo, A., Hansch, C. & Elkins, D. (1971) *Chem. Rev.*, 71, 525–616.
23. Hansch, C., Leo, A., Unger, S. H., Kim, K. H., Nikaitani, D. & Lien, E. J. (1973) *J. Med. Chem.*, 16, 1207–1216.
24. Fujita, T., Kamoshita, K., Nishioka, T. & Nakajima, M. (1974) *Agric. Biol. Chem.*, 38, 1521–1528.
25. Bondi, A. (1964) *J. Phys. Chem.*, 68, 441–451.
26. Koshimizu, K., Fujita, T. & Mitsui, T. (1960) *J. Am. Chem. Soc.*, 82, 4041–4044.
27. Topliss, J. G. & Costello, R. J. (1972) *J. Med. Chem.*, 15, 1066–1068.
28. Fredga, A. & Åberg, B. (1965) *Annu. Rev. Plant Physiol.*, 16, 53–72.
29. Ariëns, E. J., Simonis, A. M. & van Rossum, J. M. (1964) in *Molecular Pharmacology* (Ariëns, E. J., ed.), Vol. 1, pp. 119–286, Academic Press, New York.
30. Laycock, G. M. & Shulman, A. (1963) *Nature*, 200, 849–851.
31. Shulman, A., Laycock, G. M. & Henry, J. A. (1965) *Nature*, 208, 568–571.
32. Ariëns, E. J. (1971) in *Drug Design* (Ariëns, E. J., ed.), Vol. 1, pp. 182–184, Academic Press, New York.