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Lipophilicity–Antifungal Activity Relationships for Some Isoflavonoid Phytoalexins

Anna Arnoldi* and Lucio Merlini

Dipartimento di Scienze Molecolari Agroalimentari, Sezione di Chimica, Università di Milano, Via Celoria 2, I-20133 Milano, Italy

The octanol/water partition coefficients of 18 isoflavonoid phytoalexins have been determined by reversed-phase HPLC and/or calculated by the use of Hansch hydrophobic parameters: The values obtained are in the range 1.5–4.2. From a study of the relationship between these data and the antifungal activity on *Aphanomyces euteiches* and *Fusarium solani* f.sp. *cucurbitae* reported by Van Etten, it appears that within groups of compounds of similar structure an increase in lipophilicity correlates positively with increased antifungal activity, whereas a general correlation for the whole class of isoflavonoid phytoalexins was not found. On the other hand, correlations with some other structural factors, such as the presence of a phenolic OH or benzylic hydrogen atoms, seem possible.

Phytoalexins are chemical compounds involved in the resistance of plants to diseases caused by fungi and bacteria.

Although a large number of studies have been published on this topic, the relationship between the molecular properties of isoflavonoid phytoalexins and their activity has not yet been clarified satisfactorily (Smith, 1982).

Lipophilicity seems, however, very important probably because it is indispensable for effective penetration of fungal membranes (Harborne and Ingham, 1978). Some lipophilic substituents seem particularly favorable for fungicidal activity: for example the dimethylchromene group in phaseollin and glyceollin (Van Etten, 1976) and the dimethylallyl in wighteone (Ingham et al., 1976) and kievitone (Smith, 1978).

Despite these qualitative indications, no systematic study of the possible correlation between partition coefficients of isoflavonoid phytoalexins and antifungal activity as

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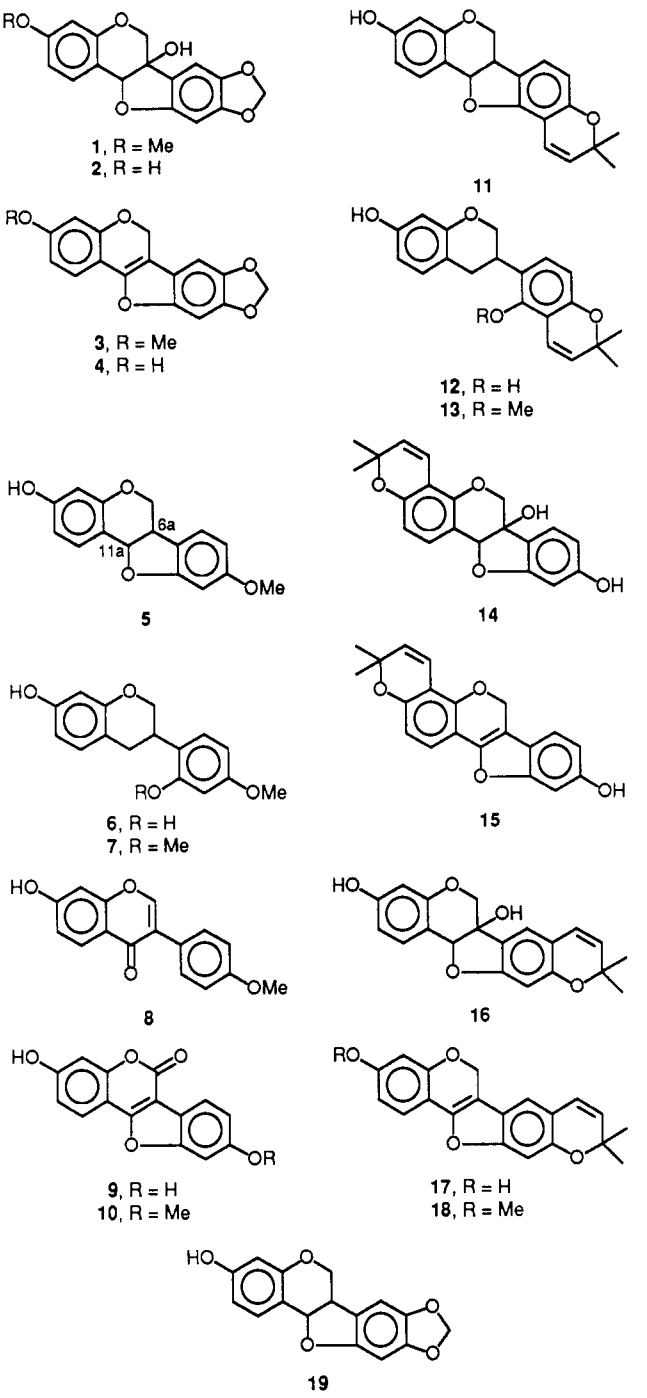
been reported. The only exceptions are the studies on synthetic 2-phenylbenzofurans (Carter et al., 1978) analogues of vignafuran, on synthetic 2-phenylcoumarins, structurally related to coumestans (Arnoldi et al., 1986), and on some natural isoflavonoids (Adesanya et al., 1986). In the latter paper the authors concluded that a high level of lipophilicity and the presence of at least one phenolic group are important, but they did not report the actual values of relative lipophilicities obtained by reversed-phase thin-layer chromatography (RP-18 plates, methanol/water mixtures). As far as we know, absolute partition coefficients have not yet been determined, although these data can be useful not only for possible correlation with fungitoxicity but also for a better understanding of the physicochemical properties linked to the possible mobility of phytoalexins in plant tissues. In fact, whereas many mechanisms of resistance to plant diseases may be activated, accumulation of phytoalexins occurs only in tissues adjacent to the invading fungus (Salt and Kuc, 1985).

In order to gain further insight in the possible correlation between lipophilicity and antifungal activity, we needed a consistent set of activity data. We did not have at our disposal a sufficient number or amount of compounds to measure their activity. A perusal of the literature showed that Van Etten (1976) had studied the antifungal activity of a large group of isoflavonoid phytoalexins against *Fusarium solani* f.sp. *cucurbitae* and *Aphanomyces euteiches* in radial growth tests. Therefore, we determined the lipophilicity (expressed as partition coefficient between 1-octanol and water, log P) of these phytoalexins (Chart I) and used Van Etten's data to study the correlation.

Direct determination of log P by the shaking-flask method (Martin, 1978) is certainly the most direct method but is very tedious, requires a large amount of very pure compound, and is therefore impracticable for compounds available only in small amounts. For these reasons, methods involving thin-layer chromatography (Tomlinson, 1975) and high-performance liquid chromatography (HPLC) (Braumann, 1986; Koopmans and Rekker, 1984) have developed in the last decade. They require small amounts of compound, and impurities do not interfere because they are separated during the chromatographic process. Thin-layer chromatography is faster, and the log P values of more than 20 compounds can be determined at the same time, but HPLC is more accurate and reproducible.

With this method, we could obtain the log P of nine phytoalexins; however, we were interested in obtaining data on a larger number of phytoalexins. We calculated the other values by Hansch and Leo's hydrophobic fragment constants and π values (Hansch and Leo, 1979).

Chart I



MATERIALS AND METHODS

Determination of Partition Coefficients by HPLC. The octanol/water partition coefficients, log P (eq 1), were determined by HPLC by comparison with those of six reference compounds whose log P values are known (Nys and Rekker, 1974). The references were chosen in order to cover the range of our phytoalexin retention times at intervals of 0.4–0.5 log P.

$$\log P = [S]_{octanol}/[S]_{water} \quad S = \text{substrate} \qquad (1)$$

Retention times (t_R) were determined on a Waters HPLC apparatus equipped with an U6K injector and a Waters Model 481 UV absorbance detector (254 nm). The column was a Merck RP-18 (5-μm particle size, 250 × 4 mm), the solvent methanol/water (HPLC grade, Carlo Erba; 67/33, v/v), and the flow rate 0.6 mL/min. Each compound was injected three times and mean log k' values were calculated from eq 2, where t_0 represents the elution time of an unretained peak.

$$\log k' = \log [(t_R - t_0)/t_0] \qquad (2)$$

The dependence of log P on log k' was calculated by regression analysis for the six reference compounds as

$$\log P = 2.18 + 1.79 \log k' \; (n = 6, r^2 = 0.986) \qquad (3)$$

Calculated values are reported in Table I. Differences between experimental and calculated values (Δ log P) are in the range 1.5–8.4%. Equation 3 was used to calculate log P values for the nine phytoalexins reported in Table I.

RESULTS AND DISCUSSION

Table I reports the absolute log P values of the nine phytoalexins we had on hand. In fact, reversed-phase

Table I. Computation of log *P* Values by Reversed-Phase HPLC

compound	log P_{exptl}	log k'	σ(log k')	log P_{calcd}	Δ log P^a
		Standards			
phenol	1.49	−0.362	0.003	1.53	0.04
2-methylphenol	1.95	−0.112	0.001	1.98	0.03
4-chlorophenol	2.39	0.005	0.001	2.19	0.20
bromobenzene	2.99	0.568	0.001	3.20	0.21
naphthalene	3.37	0.711	0.002	3.45	0.08
biphenyl	4.04	0.947	0.002	3.87	0.17
		Phytoalexins			
vestitol (**6**)		0.146	0.001	2.44	
(+)-pisatin (**1**)		0.223	0.001	2.58	
formononetin (**8**)		0.224	0.001	2.58	
maackiain (**19**)		0.241	0.000	2.61	
coumestrol (**9**)		0.282	0.001	2.69	
sativan (**7**)		0.569	0.001	3.21	
phaseollin (**11**)		0.768	0.006	3.58	
tuberosin (**16**)		0.246	0.009	2.62	
3-*O*-methyldihydrotuberosin (**18**)		0.551	0.002	3.18	

[a] Δ log P = [log P_{exptl} − log P_{calcd}].

Table II. log *P* Values and Effect of 0.1 mM Solutions of Isoflavonoid Phytoalexins on Radial Growth of *A. euteiches* and *Fusarium solani* f.sp. *cucurbitae*

			% inhibition[a]	
no.	phytoalexin	log P	*A. euteiches*	*F. solani*
1	pisatin	2.58	19.7	52.0
2	3,6a-dihydroxy-8,9-(methylenedioxy)pterocarpan	1.93	5.5	2.8
3	6a,11a-dehydropisatin	2.21	2.3	0.5
4	3-hydroxy-8,9-(methylenedioxy)-6a,11a-dehydropterocarpan	1.56	46.1	38.0
(±)-**5**	(±)-3-hydroxy-9-methoxypterocarpan	2.64	25.5	78.1
(+)-**5**	(+)-3-hydroxy-9-methoxypterocarpan	2.64	30.3	64.4
(−)-**5**	(−)-3-hydroxy-9-methoxypterocarpan	2.64	30.9	68.7
6	vestitol	2.43		25.0
7	sativan	3.21	39.8	54.3
8	formononetin	2.58	16.7	18.1
9	coumestrol	2.69	3.8	4.2
10	4′-*O*-methylcoumestrol	3.34	0.5	4.3
11	phaseollin	3.58	85.8	85.6
12	phaseollinisoflavan	3.37	96.9	86.7
13	2′-methoxyphaseollinisoflavan	4.15	88.5	79.9
14	glyceollin	2.62	77.3	75.4
15	6a,11a-dehydroglyceollin	2.53	18.4	35.6
16	tuberosin	2.62	96.9	55.0
17	6a,11a-dehydrotuberosin	2.53	46.0	37.4

[a] Percent inhibition of the radial growth (Van Etten, 1976).

HPLC can provide absolute lipophilicities when suitable standards, whose log P values are known by direct determination, are used (Caron and Shroot, 1984). We have chosen six compounds whose log P values are in the range 1.49 (phenol) to 4.04 (biphenyl); values are from a paper of Nys and Rekker (1974). As we lacked perfectly "congeneric" standards (Koopmans and Rekker, 1984), we chose only aromatic compounds: phenols in the case of low log P and polynuclear aromatics in the case of high log P. These standards have some structural similarities with isoflavonoid phytoalexins. By eq 3 the log P values of the phytoalexins on hand were obtained.

The log P values of the other phytoalexins (Table II) were obtained by the hydrophobic constants (Hansch and Leo, 1979). This method can be applied with success when the lipophilicity of a parent structure is known, and analogues can be obtained by simple substitution of groups, with better results if they are aromatic substituents, where conformation effects are less important. The log P values of two pterocarpans (**11**, **19**), one pterocarpene (**18**), two 6a-hydroxypterocarpans (**1**, **16**), two isoflavans (**6**, **7**), one isoflavone (**8**), and one coumestan (**9**) had been determined experimentally. Comparison of log P values of compounds **6** and **7** indicated that the normal values generally indicated as π (Hansch and Leo, 1979) could be used also in this case. They are $\pi(OCH_3)$ = −0.02, π(OH) = −0.67, and $\pi(OCH_2O)$ = −0.05 and were used for obtaining log P values of compounds **2**, **5**, **10**, and **17**. The unavailable value for the dimethylchromene group was calculated as +0.92, by comparison of compounds **11** and **19**, and was used to calculate log P values of **12** and **13** from **6** and **7** and of **3** and **4** from **17** and **18**. In general, this method assumes that each group has the same effect on lipophilicity independent of its position; i.e., compounds **14** and **15** are supposed to have the same lipophilicity as **16** and **17**, respectively. The effect of the OH in position 6a can be derived from data for **11** and **16**. Compound **16** can be formally obtained from **11** by removing a hydrogen (+0.23) and adding an OH. Therefore, the contribution of this OH can be calculated as −0.75. This value is rather low with respect to a normal aliphatic (−1.64) or benzylic OH (−1.34), probably owing to the difficult approach of water molecules due to steric hindrance.

The values obtained seem reasonable, especially taking into account that in the traditional shaking-flask determination the experimental error of log P is often up to 0.4 (Broto et al., 1984) and generally is not reported.

Table II also reports the effects of 0.1 mM solutions on the radial growth of *A. euteiches* and *F. solani* f.sp. *cucurbitae* expressed as percent inhibition. These data are taken from the paper of Van Etten (1976). Maackiain (**19**) and 3-*O*-methyldehydrotuberosin (**18**) activities were not reported in that paper and will not be treated in the following discussion.

The activity on each fungus was plotted against log P (Figure 1); each compound is indicated by its number and a symbol indicating its structure. The two plots are similar, apart from minor differences. In the plot of *A. euteiches*, three neat groups appear: cluster A of inactive compounds (activity ≤ 10%) containing **2**, **3**, **9**, and **10**; cluster B of low activity (activity ≤15–45%) containing compounds **1**, **8**, **5**, **15**, **4**, **7**, and **17**; cluster C of very active compounds **11**–**14** and **16**. In the plot of *F. solani* the groups are similar: A containing **2**, **3**, **9**, and **10**; B containing **4**, **6**, **8**, **15**, and **17**; C containing compounds **1**, **5**, **7**, **11**–**14**, and **16**.

Lipophilicity certainly plays an important role in determining the antifungal activity of these classes of compounds. The most active compounds have a log P greater than 2.6 either in the case of *A. euteiches* or in the case of *F. solani*, and at least in some classes more active compounds are more lipophilic (see for example **6**, **17**, **12**, **13** or **5**, and **11** on *F. solani*), but lipophilicity alone cannot explain the plots obtained. The classes whose structure contains a double bond in ring B have been indicated by a blank symbol. They group together in the lower part of the plots whichever lipophilicity they have. It is very probable that this structural feature is responsible for their low antifungal properties. This effect is particularly strong for the two coumestans **9** and **10** and isoflavone **8**. On the contrary, especially on *F. solani*, saturated compounds (filled symbol) are in cluster C, with the exception of compounds **2**, which is very hydro-

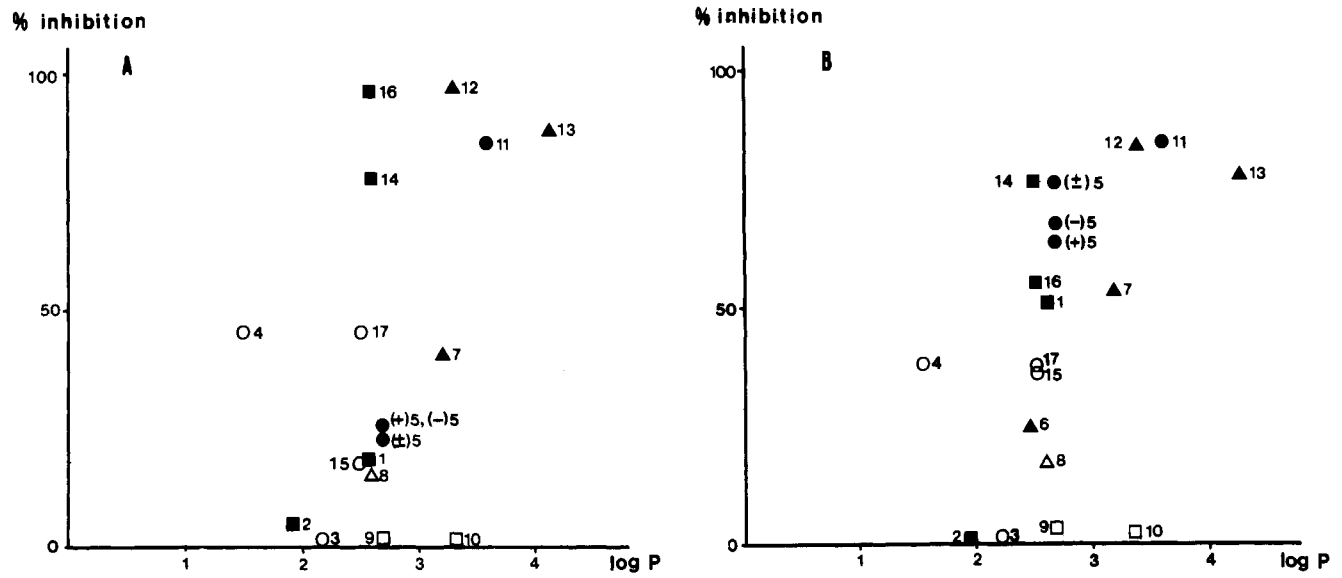


Figure 1. Effect of 0.1 mM solutions of isoflavonoid phytoalexins expressed as percent inhibition of radial growth on (A) *A. euteiches* and (B) *F. solani* f.sp. *cucurbitae* (Van Etten, 1976) plotted against log *P* of phytoalexins: ●, pterocarpans; ○, pterocarpenes; ▲, isoflavans; △, isoflavones; ■, 6a-hydroxypterocarpans; □, coumestans.

philic, and **6**. Also for this last compound low lipophilicity can be an explanation; in fact, the slight modification to **7** enhances both log *P* and activity. The low activity of compound **1** against *A. euteiches* could be explained, on the contrary, by the lack of a free phenolic OH.

Perrin and Cruickshank (1969) observed a similar effect of double bonds in ring B and proposed that the two aromatic rings should be almost perpendicular to one another to obtain high fungitoxicity. It could, however, be possible that not the shape but the presence of hydrogens in positions 6a and 11a of pterocarpans or, respectively, 3 and 4 of isoflavans is important. Bakker et al. (1983) in fact have shown that some isoflavonoid phytoalexins, upon irradiation with ultraviolet light, generate free radicals. They detected them by ESR but could not establish their structures. The formation of 6a,11a-epoxypisatin among other unidentified products seems, however, to indicate that the radical could be on carbon 11a. In this case all the groups that can lower the oxidation potential, i.e., OH or other oxygen functions para on the phenyl rings and especially unsaturated groups as the dimethylchromene, would favor the formation of a radical in position 11a or 6a and therefore enhance the fungitoxicity. These observations are confirmed by the fact that compounds with electron-withdrawing groups such as isoflavones and coumestans are completely devoid of activity.

Some authors (Harborne and Ingham, 1978; Adesanya et al., 1986; Smith, 1978) have pointed out that dimethylallyl substituents enhance the fungitoxicity of the parent compounds and have explained this effect with lipophilicity. Besides this positive contribution, it is also possible in these cases that free radicals are generated on the benzylic carbon of the chain. A recent work of ours (Arnoldi et al., 1989) has shown in one case that an *o*-propenyl substituent generates nonfungitoxic hydroxystilbenes, whereas an *o*-allyl group has a particularly good effect, their lipophilicity being equal.

All the isoflavans, pterocarpans, and 6a-hydroxypterocarpans containing a dimethylchromene group are in cluster C. Certainly the introduction of this group increases the lipophilicity of the compounds, but its contribution to the activity could be more complicated. For example, it could stabilize free radicals (compare **16** vs **2** with respect to **1** vs **2**, or **12** vs **6** and **13** vs **7** with respect to **7** vs **6**).

With regard to isoflavonoid phytoalexin mobility, research in the field of systemic fungicides during the last 20 years has shown that lipophilicity governs translocation of compounds in plants (Edgington, 1981). When log *P* is higher than 3.5, compounds are retained in membranes. This seems to appear also in the case of the most fungitoxic isoflavonoid phytoalexins, which are very lipophilic.

It seems, therefore, that the search for analogues of phytoalexins with greater fungitoxicity and systemic activity should be undertaken among compounds with lower redox potential and a slightly lower lipophilicity (log *P* $\approx$ 3.0). This should facilitate distribution, at the same time maintaining affinity for membranes that could contain the targets for the free radical formed.

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