with most of the loss occurring between 0.17 and 1 h after fumigation. This disappearance curve was generally different from the curve observed for citrus (King et al., 1981) at the 64 g/m^3 dose, due to the fact that the rate of loss (b = 0.17 g/m^3 per h) from mango is greater than for grapefruit (b = 0.084 g/m^3 per h) (King et al., 1981) as determined by exponential regression equation. In addition, the intercept for grapefruit is greater (25.36) as determined by King et al. (1981) than the 14.02 shown for mango in Table III. Also, the loss curve data for grapefruit gave a better fit (R^2 = 0.98) by the exponential regression equation than that indicated by the same equation for mango (R^2 = 0.79). However, both values were statistically significant (P = 0.05).

If total residue concentration of MB in mangos is used to compare with the established grapefruit levels of 20 mg/kg, then at 1 h after evacuation of the MB from the chamber and thereafter, MB residues in mangos of all dosages tested are below the tolerance level for grapefruit. If residue levels in the peel or pulp are the only criteria for comparison, mangos may be fumigated for 2 h at MB dosages of 16, 48, and 56 mg/kg without exceeding the acceptable levels established for grapefruit at 10 min after evacuation of MB from the chamber.

The fumigation method and the headspace analysis procedure for citrus (King et al., 1981) provide a means to treat and determine MB residues in mango fruit. The exponential regression equations can be applied to calculate the MB loss curve in mangos at the specified treatment dose while the linear analysis equations in Table IV can be used to calculate expected residues levels at the zero hour, in this case 0.17 h.

Registry No. MB, 74-83-9.

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Structure–Activity Studies on the Inhibition of Photosystem II Electron Transport by Phenylbiurets

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The inhibition of photosynthetic electron transport by phenylbiurets has been investigated. The chemical structure of this class of molecules bears some similarity to that of other well-known photosystem II (PS II) inhibitors, such as the carboxy anilides and the phenylureas. However, some important differences have been found in the structural requirements for maximum inhibition by these PS II inhibitors and the phenylbiurets. For example, some ortho-substituted phenylbiurets show enhanced activity. In contrast ortho substitution in the phenylureas considerably reduces activity. Moreover, electronic effects are important in increasing the ability of the phenylbiurets to inhibit electron transport. Finally, the biological activity of the phenylbiurets has been compared to that of other well-known PS II inhibitors, and it appears that, as in the case of the latter compounds, a log P maximum of about 3 is required for optimum biological activity.

Members of a large group of compounds that inhibit photosystem II (PS II) electron transport belong to a number of different chemical classes but have the common structural features, shown in I. Examples are carboxy anilides (R_3 = alkyl), phenylureas (R_3 = mono- or dialkylamino), phenyl(methoxymethyl)ureas (R_3 = (methoxyalkyl)amino), and carbamates (R_3 = alkoxy). These compounds are thought to bind to an integral membrane protein component of the PS II reaction center called the 32-kDa or D1 protein. An important requirement for the binding of these molecules to the protein is a nitrogen atom attached to a hydrophobic phenyl group and an electron-deficient carbon atom.

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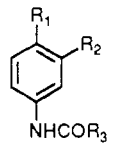
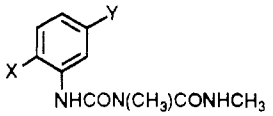


I

Over the last 20 years several quantitative structure–activity relationships (QSAR) have been reported that deal with the physicochemical characteristics required for inhibition by a particular class of these PS II inhibitors (Hansch and Deutsch, 1966; Hansch, 1969; Seewald et al., 1978; van den Berg and Tipker, 1982; Kakkis et al., 1984; Takemoto et al., 1984, 1985; Mitsutake et al., 1986; Camilleri et al., 1987). Without exception, these studies emphasize the importance of hydrophobicity in determining the potency of inhibition within a class of molecules. In the study by Mitsutake et al. (1986) it was also shown that, besides hydrophobic and electronic parameters, the inclusion of steric parameters for the R_2 and R_3 substituents in the case of anilides, ureas, and carbamates was important to account for the observed Hill inhibition. No steric parameters were necessary for R_1.

Steric requirements at positions ortho to the amide group in I are generally very strict. In the case of phenylureas, the replacement of the ortho hydrogen atoms by groups bigger than fluorine reduces the ability to inhibit PS II electron transport considerably. It is possible that substitution in these positions alters the orientation of the amide group with respect to the phenyl ring (Camilleri et al., 1987), resulting in a conformation that prevents the compounds from binding tightly to the site of action.

In this paper we introduce some novel PS II inhibitors that are members of the wide structural class (I) and have a biuret group as the substituent R_3. The general structure of these phenylbiurets is II. We have examined the



II

Hill inhibition activity of these molecules and have analyzed this in terms of molecular requirements determined by the nature of the substituents X and Y. It will be shown that, unlike the case of the phenylureas, replacement of the hydrogen atoms ortho to the biuret moiety by other substituents can enhance potency of inhibition of the Hill reaction. These and other observations lead to conclusions regarding structural features at the binding site of the phenylbiurets.

EXPERIMENTAL SECTION

All biurets were synthesized by the Organic Chemistry Division at Shell Research in Sittingbourne. The procedure detailed by us in a previous report (Camilleri et al., 1987) was used to assay the Hill inhibition potency of these compounds.

The 1-octanol–water partition coefficient (P) of a selected number of biurets was measured by the shake-flask method. The concentration of a compound in the 1-octanol and water phases was analyzed by absorption measurements at an appropriate wavelength. The logarithms of the partition coefficients of other analogous biurets were determined by an HPLC method using a C_{18} reversed-phase column (Spherisorb ODS2), 150-mm length. Compounds were eluted by a mixture of acetonitrile and water (70:30, v/v) at a flow rate of 1 mL min^{-1}. A Hewlett-Packard 1084 was used to monitor compounds at a wavelength of 240 nm. A relationship between log P values determined directly by the shake-flask method and the corresponding retention times (RT) was used to estimate the partition coefficient of other biurets from retention time measurements. Log P values determined by this indirect method are identified in Table I.

Table I. HPLC Retention Times (RT) and Log P Values of the Phenylbiurets in Table IV

compd	log P	log RT
4	2.12[a]	0.476
21	4.46[a]	0.958
22	3.08[a]	0.632
23	2.28[a]	0.493
24	3.23[a]	0.634
25	3.58[a]	0.714
26	3.53[a]	0.719
27	2.30[a]	0.517
28	1.87	0.433
29	4.58[a]	1.032
30	2.40	0.517
31	1.82	0.425
32	3.90	0.756
33	3.78	0.737
34	2.14	0.476
35	3.96	0.765

[a] Measured by shake-flask method. The rest were calculated from log P = 6.32 log RT − 0.86. This equation was derived from a regression analysis of the measured values.

Table II. Hill Inhibition by Ortho-Substituted Phenylbiurets

no.	X	σ_X	pI_{50} (obsd)	pI_{50} (calcd) (eq 1)	$\lvert\Delta\rvert$
1	H	0.00	5.59	5.67	0.07
2	Cl	0.23	6.38	6.49	0.11
3	OCH_3	−0.27	3.70	3.60	0.10
4	F	0.06	6.55	6.18	0.37
5	CH_3	−0.17	5.00	5.22	0.22
6	CF_3	0.54	5.10	4.99	0.11
7	2,6-Cl_2	0.46	4.68	4.82	0.14

Table III. Hill Inhibition by Phenylbiurets with a Meta Substituent

no.	Y	π_Y	σ_Y	pI_{50} (obsd)	pI_{50} (calcd) (eq 4)	$\lvert\Delta\rvert$
1	H	0.00	0.00	5.59	5.40	0.19
8	Cl	0.71	0.37	5.70	5.84	0.14
9	OCH_3	−0.02	0.12	5.45	5.31	0.14
10	F	0.14	0.34	5.46	5.34	0.12
11	CH_3	0.56		5.82	5.98	0.16
12	SCH_3	0.61	0.15	6.00	5.89	0.11
13	$COCH_3$	−0.55	0.38	4.36	4.54	0.18
14	i-C_3H_7	1.53	−0.07	6.40	6.66	0.26
15	O-i-C_3H7_7	0.85	0.10	6.30	6.12	0.18
16	CF_3	0.88	0.43	6.04	5.94	0.10
17	Br	0.86	0.39	5.92	5.95	0.03
18	Ph	1.96	0.06	6.98	6.78	0.20
19	I	1.12	0.35	6.00	6.16	0.16
20	$N(Me)_2$	0.18	−0.15	5.58	5.68	0.10

RESULTS AND DISCUSSION

In the initial phases of our structure–activity studies on phenylbiurets (II), we derived a correlation for the Hill inhibition of seven ortho-substituted molecules, listed in Table II. Multiple linear regression analyses gave eq 1,

$$pI_{50} = 4.41\ (\pm 2.05)\sigma_X - 12.55\ (\pm 2.56)\sigma_X^2 + 5.93\ (\pm 0.51) \quad (1)$$

$$n = 7,\ r = 0.87,\ s = 0.47$$

which relates in vitro activity to the electronic characteristics of the ortho substituent, X. pI_{50} is the molar

Table IV. Hill Inhibition and log *P* Data of Phenylbiurets Containing Ortho Fluoro Groups and Meta Substituents

no.	Y	log *P*	π_Y	σ_Y	pI_{50} (obsd)	pI_{50} (calcd) (eq 7)	$\lvert\Delta\rvert$	pI_{50} (calcd) (eq 11)	$\lvert\Delta\rvert$
4	H	2.12	0.00	0.00	6.55	6.61	0.06	6.62	0.07
21	$CH(Et)_2$	4.46	2.67	−0.07	7.21	7.08	0.13	7.04	0.17
22	O-*i*-Pr	3.08	0.85	0.10	7.14	7.01	0.13	6.97	0.17
23	CO_2Me	2.28	−0.01	0.37	6.44	6.45	0.01	6.35	0.09
24	Et	3.23	1.02	−0.07	6.96	7.04	0.08	7.18	0.22
25	I	3.58	1.12	0.35	7.00	6.94	0.06	6.78	0.22
26	*i*-Pr	3.53	1.53	−0.07	7.02	7.14	0.12	7.21	0.19
27	NO_2	2.30	−0.28	0.71	5.82	5.74	0.08	6.02	0.20
28	SO_2-*i*-Pr	1.87	−0.55	0.60	5.59	5.76	0.16	5.82	0.23
29	C-Hx	4.58	2.01	−0.15	7.08	7.67	0.01	7.07	0.01
30	F	2.40	0.14	0.34	6.70	6.56	0.14	6.45	0.25
31	COMe	1.82	−0.55	0.38	5.96	6.07	0.11	6.00	0.04
32	CH_2Ph	3.90	2.01	−0.08	7.10	7.16	0.06	7.20	0.10
33	Ph	3.78	1.96	0.06	7.09	7.19	0.10	7.07	0.02
34	OMe	2.14	−0.02	0.12	6.85	6.60	0.25	6.52	0.33
35	$C(CH_3)_3$	3.96	1.98	0.10	7.02	7.15	0.13	7.21	0.19
36	$CH{=}CH_2$		0.82	0.05	7.00	7.00	0.00		
37	COPh		1.05	0.34	6.64	6.94	0.30		
38	$N(Et)_2$		1.18	0.23	7.17	7.05	0.12		
39	CF_3		0.88	0.43	7.00	6.79	0.21		

concentration of phenylbiuret that causes 50% inhibition of the Hill reaction, n is the number of compounds, r is the correlation coefficient, and s is the standard deviation from the regression. For the Hammett σ_X values of the substituents ortho to the biuret moiety, the corresponding para substituent constants have been used. Nishioka et al. (1975) have shown that the electronic effect of ortho substituents can be satisfactorily approximated by σ_{para}. Equation 1 indicates that an optimum electronic effect is desirable for good binding ability. The small number of ortho-substituted phenylbiurets examined did not allow us to investigate any other properties (besides electronic characteristics) of X important in affecting the binding efficacy of the phenylbiurets (II) at their site of action. However, it is evident from eq 1 that molecules bearing a halogen ortho substituent such as fluorine or chlorine are the most active, even more so than the unsubstituted phenylbiuret (1).

In order to understand the effect of other substituents on the phenyl moiety of the phenylbiuret (II), we analyzed the Hill inhibition of a number of compounds having either a hydrogen or a fluorine atom as X and varying the substituent Y meta to the biuret moiety in II. Equations 2–4 are a summary of the results obtained from the Hill inhibition data (Table III) for compounds having a hydrogen atom as the substituent X.

$$pI_{50} = 0.83\ (\pm 0.19)\pi_Y + 5.30\ (\pm 0.17) \quad (2)$$
$$n = 14,\ r = 0.92,\ s = 0.23$$

$$pI_{50} = 1.05\ (\pm 0.37)\pi_Y - 0.15\ (\pm 0.22)\pi_Y^2 + 5.29\ (\pm 0.17) \quad (3)$$
$$n = 14,\ r = 0.93,\ s = 0.22$$

$$pI_{50} = 1.05\ (\pm 0.31)\pi_Y - 0.17\ (\pm 0.19)\pi_Y^2 - 0.60\ (\pm 0.51)\sigma_Y + 5.40\ (\pm 0.17) \quad (4)$$
$$n = 14,\ r = 0.95,\ s = 0.19$$

π_Y and σ_Y in the above equations are the Hansch–Fujita hydrophobicity and the Hammett σ_{meta} electronic parameters, respectively. The high percentage variance for the expression relating in vitro activity to π_Y (eq 2) is a clear indication of the importance of the hydrophobic nature of the substituent Y in determining the ability of the phenylbiurets to inhibit PS II electron transport. The fact that the coefficient with π_Y approaches unity could suggest that the binding site occupied by Y is a deep hydrophobic cleft or a large hydrophobic surface that can accommodate lipophilic groups larger than those used in this analysis. This situation has been found in other QSAR studies (Smith et al., 1982; Hansch et al., 1986; Morgenstern et al., 1987). Moreover, eq 3 and 4 show that no significant correlations exist with either π_Y^2 or σ_Y, and the introduction of these terms gives very little improvement in the percentage variance. The absence of a correlation with π_Y^2 could imply that an optimum value of hydrophobicity had not been approached in the range of molecules studied, so that compounds with more lipophilic meta substituents could be expected to show even greater in vitro activity. Unfortunately no additional molecules, other than those shown in Table II, were available to prove this point. The small effect on the percentage variance when the electron parameter σ_Y is included in the analysis (eq 4) shows that, unlike the case of substituents ortho to the biuret moiety, the electronic properties of meta substituents do not control the binding efficacy of the phenylbiurets.

Equations 5–7 have been derived from data in Table IV for compounds with X = F and a different substituent Y.

$$pI_{50} = 0.37\ (\pm 0.13)\pi_Y + 6.41\ (\pm 0.18) \quad (5)$$
$$n = 20,\ r = 0.79,\ s = 0.29$$

$$pI_{50} = 0.81\ (\pm 0.23)\pi_Y - 0.22\ (\pm 0.10)\pi_Y^2 + 6.41\ (\pm 0.13) \quad (6)$$
$$n = 20,\ r = 0.89,\ s = 0.21$$

$$pI_{50} = 0.66\ (\pm 0.22)\pi_Y - 0.21\ (\pm 0.09)\pi_Y^2 - 0.63\ (\pm 0.48)\sigma_Y + 6.62\ (\pm 0.20) \quad (7)$$
$$n = 20,\ r = 0.92,\ s = 0.18$$

Unlike the case where X is a hydrogen atom, the introduction of a squared term in π_Y does improve the correlation as shown by eq 6. σ_Y has again a smaller effect in accounting for the variance in the in vitro activity. The introduction of the ortho fluorine substituent has reduced the coefficient for π_Y (average of 0.5 from eq 5–7) in comparison to that with an ortho hydrogen substituent. This observation, together with the increased dependence on the π_Y^2 term, implies that, in the ortho fluorine substituted molecules, the binding site of the substituent Y is now on a more limited hydrophobic domain.

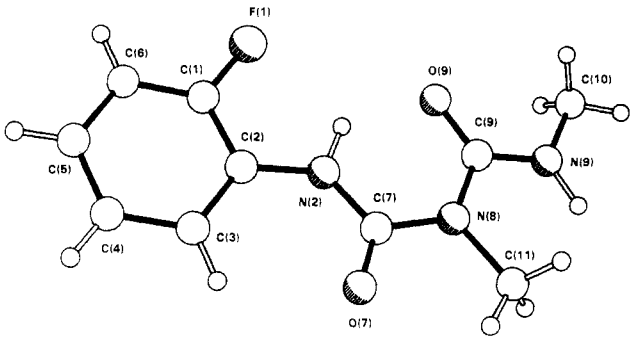


Figure 1. X-ray crystal structure of 4.

Unfortunately the number of compounds that could be analyzed with X = Cl and a different substituent Y was only 3 (Y = Cl, pI_{50} = 6.38; Y = OCH_3, pI_{50} = 6.59; Y = C_2H_5, pI_{50} = 6.80). Despite the bigger chlorine atom compared to either hydrogen or fluorine, the Hill inhibitory activity is very high and again emphasizes the importance of an ortho substituent such as a fluorine or a chlorine atom in substantially increasing the binding ability of the phenylbiurets. The X-ray structure of compound 4 shows that this molecule adopts a nearly planar conformation in the crystalline state (Figure 1). This is in direct contrast to the crystal structure of the phenylureas where the phenyl ring is at an angle to the plane of the urea moiety. For example, the angle between these two planes in *N,N*-dimethyl-*N'*-(3,4-dichlorophenyl)urea (diuron) is about 31° (Baughman et al., 1980). The introduction of an ortho substituent in the latter class of compounds considerably reduces their ability to inhibit the Hill reaction (Camilleri et al., 1987), presumably by altering the torsion angle between the phenyl and urea planes. The Hill inhibition by *N,N*-dimethyl-*N'*-phenylurea, *N,N*-dimethyl-*N'*-(2-fluorophenyl)urea, and *N,N*-dimethyl-*N'*-(2-chlorophenyl)urea has been measured as about 100%, 73%, and 27%, respectively, when applied at a concentration of 10^{-4} M. In direct contrast, all three phenylbiuret analogues, compounds 1, 2, and 4, show total inhibition of the Hill reaction at the same concentration. The pI_{50} values (see Table II) for the ortho halogen derivatives 2 and 4 indicate that they are almost 1 order of magnitude more effective than the unsubstituted compound 1 in inhibiting the Hill reaction.

A number of QSAR studies on other PS II inhibitors have used the logarithms of the 1-octanol–water partition coefficient (P), rather than π, as a measure of hydrophobicity (Kakkis et al., 1984; Mitsutake et al., 1986). In order to compare directly our results on the phenylbiurets with these studies, we measured the log P values of 16 molecules that have a fluorine atom as the ortho substituent X and vary from one another by having a different substituent in the meta position Y. Log P values were measured either directly by the shake-flask method or indirectly from HPLC retention time measurements (Table I).

We first examined the electronic effect of substituents on the hydrophobic character of these phenylbiurets. This study gave rise to eq 8, where log P_{calcd} was obtained by adding appropriate π constants to 2.12, the measured log P for compound 4.

$$\log P = 0.95\ (\pm 0.08) \log P_{calcd} + 0.57\ (\pm 0.39)\sigma_Y + 0.11\ (\pm 0.33) \quad (8)$$
$$n = 16, r = 0.99, s = 0.13$$

Equation 8 is in agreement with studies carried out by Kakkis et al. (1984) on dimethylphenylureas and (methoxymethyl)phenylureas. In fact all coefficients in the above equation are of the same order of magnitude as those determined by these authors in the two classes of compounds considered by them. Equation 8 has been useful in identifying any anomalies in the measured log P values.

From the pI_{50} data and the log P values in Table IV, eq 9–11 were derived.

$$pI_{50} = 0.41\ (\pm 0.18) \log P + 5.49\ (\pm 0.56) \quad (9)$$
$$n = 16, r = 0.74, s = 0.33$$

$$pI_{50} = 2.04\ (\pm 1.46) \log P - 0.26\ (\pm 0.22)\ (\log P)^2 + 3.15\ (\pm 2.14) \quad (10)$$
$$n = 16, r = 0.80, s = 0.30$$

$$pI_{50} = 1.67\ (\pm 1.03) \log P - 0.22\ (\pm 0.16)\ (\log P)^2 - 1.08\ (\pm 0.54)\sigma_Y + 4.16\ (\pm 1.56) \quad (11)$$
$$n = 16, r = 0.91, s = 0.21$$

The above equations show again that hydrophobicity, as expressed by log P, is the most significant physicochemical parameter. However, the coefficient in log P is higher than that found for individual classes of other PS II inhibitors (Kakkis et al., 1984; Mitsutake et al., 1986). This may indicate that the hydrophobic binding site occupied by the phenylbiurets is unique and does not overlap with that occupied by other well-characterized PS II inhibitors such as anilides, phenylureas, and triazines. Another difference between the inhibition of the Hill reaction shown by the latter molecules and the phenylbiurets is the importance of electronic effects in describing inhibitor potency. In fact, eq 10 and 11 show that the inclusion of σ_Y improves the structure–activity correlation considerably. This result is in agreement with eq 7 where both π_Y and σ_Y were found to be significant parameters, with π_Y the more important. The negative sign of the coefficient with σ_Y means that electron-donating groups, which are preferably also hydrophobic, enhance inhibition.

Although log P is the most important single parameter that describes the level of activity, the inclusion of the $(\log P)^2$ term in eq 10 and 11 further indicates that, in the case of ortho fluoro substituted biurets, there exists an optimum hydrophobicity value associated with maximal Hill inhibition potency. From eq 10 and 11 this optimum value of log P appears to be around 4, although it is difficult to put much reliance on this value, as the confidence limits in the log P and $(\log P)^2$ coefficients are wide and there are only 2 compounds out of 16 with log P values higher than 4.

In the final part of this report we present data on the activity of the ortho fluoro phenylbiurets (listed in Table IV) on whole plants. Compounds were applied preemergence at 1 kg ha^{-1} to eight species, namely maize (*Zea mays*), rice (*Oryza sativa*), barnyard grass (*Echinocloa crus-galli*), oat (*Avena sativa*), linseed (*Linum sativum*), mustard (*Sinapis alba*), sugar beet (*Beta vulgaris*), and soyabean (*Glycine max*).

Plant damage was assessed visually 10 days after treatment against the scale 0 (no effect) to 9 (total kill) for each species (giving a maximum score of 72 for all eight species). Results are shown in Figure 2. The accuracy of the biological data was not judged to be appropriate for quantitative analysis. However, some evidence can be drawn from Figure 2, indicating that a log P of about 2.5 is required for good herbicidal activity. The scatter

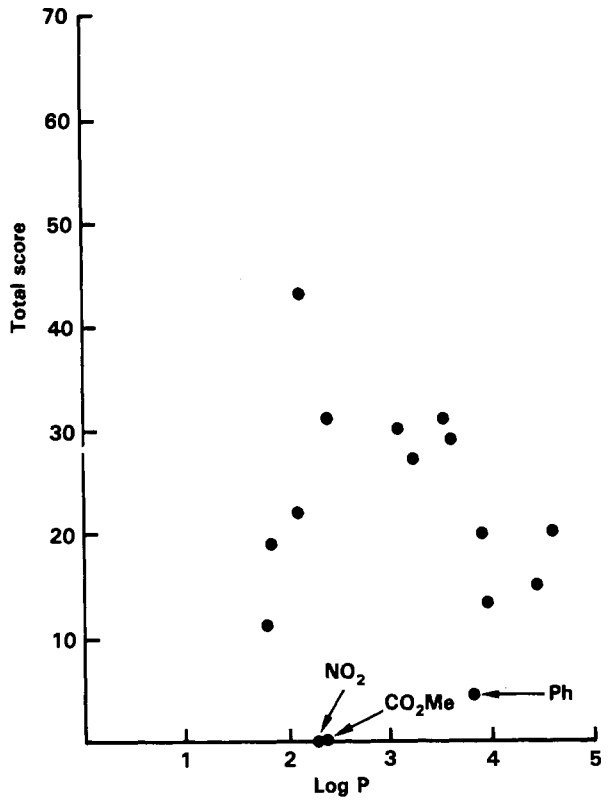


Figure 2. Preemergence herbicidal activity as a function of log P. Compounds were applied at 1 kg ha^{-1}. The 16 compounds can be identified from their respective log P values in Table IV.

in the plot could be an indication that factors other than hydrophobicity are of importance in determining the level of biological activity. The two points on the log P axis belong to compounds **23** (Y = CO_2CH_3) and **27** (Y = NO_2). The lack of activity shown by these molecules may be due to ease of metabolism. The optimum log P value of about 2.5 can be compared to that found for other well known Hill inhibitors, such as diuron (log P = 2.8), isoproturon (log P = 3.4), and atrazine (log P = 2.6). Although these molecules belong to four different chemical classes, it appears that the same transport characteristics are required for them to reach their site of action.

In future work, we intend to probe the binding site of phenylbiuret compounds on PS II by studying their effect on the EPR spectrum of the iron atom located close to the putative herbicide binding site (Diner and Petrouleas, 1987), measuring their inhibitory potency in herbicide-binding mutants (Phillips and Huppatz, 1987), and using photoaffinity labeling derivatives to tag amino acid residues around the binding site (Wolber and Steinback, 1984). In particular, we will look for any differences between ortho hydrogen and ortho fluorine substituted molecules.

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