and tested at 28 °C. *Streptococcus pyogenes C, Actinomyces israelii, Clostridium novyi, Propionibacterium acnes*, and *Bacteriodes fragilis* were grown in thioglycolate broth and tested in this broth or on brain–heart infusion agar, anaerobically at 37 °C.

Fungal Strains. *Candida albicans, Saccharomyces cerevisiae, Trichophyton mentagrophytes*, and *Epidermophyton floccosum* were grown in Sabouraud's dextrose broth and tested in broth or agar at 37 °C, except for *T. mentagrophytes* and *E. floccosum*, which were grown and tested at 28 °C.

Protozoal Strains. *Trichomonas vaginalis* was grown in Tripticase yeast maltose basal medium (TYM) 721, *T. foetus* in TYM 359, and *Entamoeba histolytica* (J 190) in modified Boeck Drbohlav medium, all at 37 °C.

Preparation of Drugs. Stock solutions of the anisomycins **1a–g** were prepared at a concentration of 1 mg/mL for agar diffusion and at 3.2 mg/mL for tube dilution testing. Me_2SO–EtOH (1:9) was used to solubilize the compounds.

Determination of Antibacterial and Antifungal MIC and Zone Size. Agar diffusion (zone size, millimeter diameter) and tube dilution (minimum inhibitory concentrations, MICs) tests were done in the appropriate media cited above. Inocula for seeding agar plates and tubes were obtained from 24-h bacteria and yeast cultures, 48-h anaerobe cultures, and 4–5 day dermatophyte cultures. Inocula for seeding agar plates was used as a 1:100 dilution in agar. Inocula for MICs was 0.05 mL of undiluted culture for *S. pyogenes C, A. israelii, C. novyi, P. acnes*, and *B. fragilis*; a 1:10 dilution in saline for *T. mentagrophytes* and *E. floccosum*; a 1:100 dilution in saline for *M. fortuitum, S. griseus*, and *N. asteroides*; and a 1:1000 dilution in saline for the rest of the organisms. For agar diffusion tests, a solution containing 0.05 mg of the drug was absorbed onto paper disks, placed on the agar, and incubated. For MICs (which used ca. 3 mL of broth/tube), the drug concentrations ranged from 32 to 0.06 μg/mL with twofold serial dilutions. The concentration of Me_2SO–EtOH used showed no inhibitory effect on any of the test organisms. Zone sizes and MICs were determined after incubation for 24 h for bacteria and 48 h for fungi. The MIC was defined as the lowest concentration of drug at which no visible bacterial or fungal growth was observed.

Determination of Antiprotozoal Activity. Protozoa were grown in appropriate media cited above for 48 h and then pooled. Tubes containing 10 mL of media and drug concentrations ranging from 32 to 0.06 μg/mL were inoculated with 0.6×10^6 organisms and incubated for 48 h. Drug-treated tubes were compared with untreated controls and scored, based on microscopic examination through the tube, as either 100, >95, 95 to 25%, or <25% inhibition.

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Registry No. (–)-**1a**, 22862-76-6; (±)-**1a**, 21497-40-5; (±)-**1b**, 82892-50-0; (±)-**1c**, 82892-51-1; (±)-**1d**, 84109-88-6; (±)-**1e**, 84109-89-7; (±)-**1f** (isomer 1), 84109-90-0; (±)-**1f** (isomer 2), 84110-19-0; **1g**, 84109-91-1; **2d**, 79499-36-8; **2e**, 79499-35-7; (±)-**2f**, 84110-05-4; (±)-**2g**, 84110-07-6; (±)-**3d**, 84109-92-2; (±)-**3e**, 84109-93-3; (±)-**3e**·HCl, 84110-04-3; **3f**, 84109-94-4; **3f**·HCl, 84110-06-5; **3g**, 84109-95-5; (±)-**4d**, 84109-96-6; (±)-**4e**, 84109-97-7; **4f**, 84109-98-8; **4g**, 84117-58-8; (±)-**5d**, 84110-08-7; (±)-**6d**, 84109-99-9; (±)-**6e**, 84110-00-9; **6f**, 84110-01-0; **6g**, 84110-02-1; (±)-**7d**, 84110-09-8; (±)-**7e**, 84110-13-4; **7f**, 84110-16-7; **7g**, 84110-03-2; (±)-**9d**, 84110-11-2; (±)-**9e**, 84110-14-5; **9f**, 84110-17-8; (±)-**10d**, 84110-12-3; (±)-**10e**, 84110-15-6; **10f**, 84110-18-9; **11**, 84117-57-7; 2,2,2-trichloroethyl chloroformate, 17341-93-4; *N*-iodosuccinimide, 516-12-1; 9-fluorenylmethyl 4,6-dimethyl-2-pyrimidylthiocarbonate, 84110-10-1.

Quantitative Structure–Activity Relationships for 2-[(Phenylmethyl)sulfonyl]pyridine 1-Oxide Herbicides

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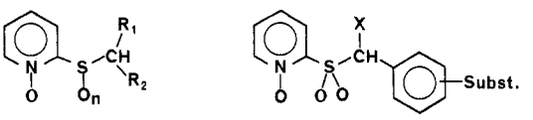
Phenyl-substituted analogues of 2-[(phenylmethyl)sulfonyl]pyridine 1-oxide preemergent herbicides were examined in order to determine quantitative relationships between structure and activity against the following three weed species: switch grass (*Panicum virgatum* L.), barnyard grass (*Echinochloa crusgalli* L. Beauv.), and green foxtail (*Setaria viridis* L. Beauv.). Analogues were chosen to provide maximum parameter orthogonality. Regression analysis yielded structure–activity relationships wherein the most significant substituent parameters associated with herbicidal activity were found to be the partition coefficient (π), the molar refractivity (MR), and two indicator variables, Z (denoting the presence of an α-methyl group) and H (denoting an ortho substituent capable of hydrogen bonding). For green foxtail, the structure–activity relationship was found to be: $-\log ED50 = 0.43\pi - 0.052MR + 0.50H + 0.24Z + 0.61$, where ED50 is expressed in moles per acre. The regression equations were found to explain 79–93% of the bioactivity for the three weed species studied. It was further shown that these equations represent the best possible correlations within the limitations of the biological data.

For some time we have been interested in demonstrating the utility of QSAR (quantitative structure–activity relationships) in our crop-protection research programs. This study was undertaken to prove the utility of in vivo whole plant biodata as a resource for meaningful and predictive QSAR equations.

The class of preemergent herbicides of general formula **1** was recently patented.[1,2] Highly active members of the series are effective control agents for a wide variety of weed



1 n = 1, 2; R_1 = H, CH_3; R_2 = alkyl, aryl

2 X = H, CH_3

species, e.g., yellow nutsedge (*Cyperus esculentus* L.), barnyard grass (*Echinochloa crusgalli* L. Beauv.), switch grass (*Panicum virgatum* L.), and Johnson grass (*Sorgum halepense* L. Pets.). Although many subclasses were synthesized to fully explore structure–activity dependencies, the present study was directed to the structural

(1) H. L. Plant and A. R. Bell, U.S. Patent 3960542 (1976).
(2) H. L. Plant, J. W. Zukel, and A. R. Bell, U.S. Patent 4019893 (1977).

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Table I. Substituent Parameters and Herbicidal Activities of the Selected Subset (3-21)

compd	substitution	π^a	MR[a]	Z	H	herbicidal act.: −log ED50, mol/acre switch grass	barnyard grass	green foxtail
3	H	0.00	5.15	0	0	0.04	0.29	0.14
4	2-Cl	0.76	9.95	0	0	0.40	0.85	0.43
5	2-I	0.93	17.95	0	0	0.32	0.52	0.22
6	2-CN	−0.33	10.35	0	0	−0.22	0.18	−0.01
7	$2\text{-}OC_6H_5$	0.97	31.75	0	1	0.11	−0.12	−0.03
8	$3\text{-}OC_4H_9$	1.62	25.85	0	0	−0.15	0.15	−0.15
9	$2,5\text{-}(CH_3)_2$	1.36	14.55	0	0	0.99	1.09	0.39
10	$2\text{-}OCH_3\text{-}5\text{-}CH_3$	0.19	16.35	0	1	0.73	1.02	0.41
11	$2,3,6\text{-}(CH_3)_3$	2.20	19.25	0	0	0.70	0.70	0.70
12	$3,4,5\text{-}(OCH_3)_3$	0.21	22.59	0	0	−0.77	−0.77	−0.79
13	$4\text{-}NO_2$	0.22	11.15	1	0	0.43	0.43	0.23
14	$4\text{-}SO_2CH_3$	−1.20	17.65	1	0	−0.35	−0.43	−0.43
15	$2,5\text{-}F_2$	0.22	4.29	1	1	1.22	1.22	1.17
16	2-F-3-Cl	0.77	9.49	1	1	1.24	1.36	1.05
17	$2\text{-}Cl\text{-}5\text{-}CH_3$	1.28	14.65	1	0	0.82	1.35	0.66
18	$2\text{-}CH_3\text{-}5\text{-}CF_3$	1.94	13.79	1	0	1.09	0.79	1.09
19	$2\text{-}CH_3\text{-}5\text{-}i\text{-}Pr$	2.17	23.85	1	0	0.70	0.89	0.57
20	$2,5\text{-}(i\text{-}Pr)_2$	3.10	33.15	1	0	0.19	0.78	0.19
21	$2,4\text{-}Cl_2\text{-}3\text{-}CH_3$	2.01	19.45	1	0	1.00	0.68	0.89

[a] $\pi = \Sigma\pi$ and MR = ΣMR for all aryl substituents.

subclass 2 to focus on the effects of phenyl ring substitution and the role of the α-methyl moiety.

At the time of this study, 78 compounds of subclass 2 were available. The primary screening data were generally unsuitable for accurately determining a useful biological response (e.g., ED50) required in QSAR analysis. Since the measurement of herbicidal ED50 for several weed species requires substantial time and effort, it was desirable to restrict the quantitative follow-up testing to that number of compounds necessary for a statistically sound structure–activity correlation. Since it is generally held that about five structures and corresponding biological activity are needed for each parameter invoked in the correlation equation, and we anticipated the need for as many as four significant parameters, we sought a group of about 20 analogues for the ED50 determinations. This approach also requires that this group be as structurally diverse as possible, i.e., the group members should approach orthogonality in the multidimensional space representing the physicochemical parameters of the substituents. Initially, no assumptions were made about the relative importance of the parameters examined: π, F, R, MR, and Z (indicator variable equal to 1 when X = CH_3, equal to 0 when X = H).

Experimental Section

Selection of Analogues for ED50 Determinations. The physicochemical parameter set was assembled from the following sources. Position-dependent values for π were taken whenever available from the self-consistent data set of Norrington et al.[3] Other required values of π were taken from Hansch and Leo,[4] the constants of $\mathcal{F}$ and $\mathcal{R}$ were computed from σ_m and σ_p by using the scaling described by Hansch et al.[5] The position-descriptive parameters, F and R, were then computed by the method of Norrington et al.[3] Values for MR were taken from either Norrington et al.[3] or Hansch and Leo.[4]

The set of values for each parameter was normalized to the range 0–1. The entire data set of normalized parameters was examined to select a subset having greatest parameter diversity by a program that employed the algorithm of Wooton et al.[6] in a repetitive manner. Using 78 compounds of structural subclass 2, this process generated 78 subsets of selected analogues. By choosing the subset with the lowest correlation between parameter values, the group of analogues most closely approaching orthogonality in multidimensional parameter space was obtained.

In preliminary studies, six parameters were examined in the above manner. These were π, F, R, MR_o, MR_{m+p} and Z. When the minimum Euclidean distance of 0.35 was applied as the selection criterion on the full set of 78 compounds, a 24-member subset was obtained. Regression analysis on the herbicidal activity of this subset suggested the terms π, MR_{total}, and Z to be most significantly correlated to activity.

A similar selection routine was applied to a set of 38 compounds of subclass 2 for which ED50 data had been accumulated. The selection was based on the π, MR, and Z parameters. A minimum Euclidean distance of 0.14 yielded a subset of 19 analogues having the lowest sum of off-diagonal r^2 values (0.305). This subset is listed as compounds 3–21 in Table I. The indicator variable H will be treated under Results and Discussion.

Herbicidal Assay. Each compound was dissolved or dispersed in a mixture of acetone and Tween 20 and then diluted to a given concentration with distilled water. For example, 25 mg of X was dissolved in 5 mL of acetone and 15 mg of Tween 20. Then 95 mL of distilled water was added to yield a solution containing 250 ppm of X. At least three concentrations of each compound were selected based on previous tests in order to bracket the expected ED50.

Well-drained greenhouse soil, contained in test pots 11.3 cm in diameter and 8.5 cm deep, was sown with ca. 200 seeds of each weed species: switch grass (*Panicum virgatum* L.), barnyard grass (*Echinochloa crusgalli* L. Beauv.), and green foxtail (*Setaria viridis* L. Beauv.). The seeds were covered with 3–6 mm of soil and initially watered by subirrigation at 100–120 mL per pot. The test solutions (46 mL each) were then applied evenly to the soil surface in each pot. The 46-mL drench of a 250-ppm solution applied to 11.3-cm diameter pot corresponds to a field rate of 11.2 kg/ha (10 lb/acre). After initial watering, soil in each pot was brought up to field capacity twice daily by subirrigation. Each test was conducted in duplicate.

After 2 weeks, herbicidal activity was determined as the percent control of each species by visual comparison with untreated pots. Herbicidal activity for each compound was then determined for each weed species as the dose in moles per acre required for 50% control (ED50). These data are shown in Table I.

(3) F. E. Norrington, R. M. Hyde, S. G. Williams, and R. Wooton, *J. Med. Chem.*, 18, 604 (1975).
(4) C. Hansch and A. Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology"; Wiley, New York, 1979, p 6.
(5) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikiatani, and E. J. Lien, *J. Med. Chem.*, 16, 1207 (1973).
(6) R. Wooton, R. Cranfield, G. C. Sheppey, and P. J. Goodford, *J. Med. Chem.*, 18, 607 (1975).

Table II. Regression Equations Generated from the Selected Subset for Herbicidal Activities on Switch Grass, Barnyard Grass, and Green Foxtail[a]

−log ED50[b] =	π	MR	H	Z	constant	eq	s	r^2	F
				Switch Grass					
	0.43	−0.055			+0.97	1a	0.38	0.60	12.01
	(4.289)	(4.244)			(3.790)				
	0.49	−0.056	+0.64		+0.79	1b	0.27	0.81	21.02
	(6.659)	(5.981)	(4.025)		(6.644)				
	0.45	−0.052	+0.61	+0.24	+0.65	1c	0.25	0.85	20.20
	(6.512)	(6.035)	(4.271)	(2.054)	(7.411)				
				Barnyard Grass					
	0.43	−0.058			+1.12	2a	0.37	0.64	14.18
	(4.690)	(4.579)			(5.333)				
	0.50	−0.058	+0.53		+0.97	2b	0.30	0.78	17.52
	(6.274)	(5.693)	(3.062)		(7.153)				
	0.48	−0.056	+0.52	+0.13	+0.89	2c	0.30	0.79	13.23
	(5.763)	(5.358)	(2.970)	(0.925)	(7.154)				
				Green Foxtail					
	0.42	−0.055			+0.89	3a	0.30	0.71	19.47
	(5.376)	(5.486)			(3.590)				
	0.46	−0.056	+0.52		+0.74	3b	0.20	0.88	35.75
	(8.750)	(8.245)	(4.539)		(6.988)				
	0.43	−0.052	+0.50	+0.24	+0.61	3c	0.16	0.93	45.46
	(9.810)	(9.571)	(5.494)	(3.167)	(8.984)				

[a] Values in parentheses are t distributions (t = 2.13 for 95% confidence level). Compounds 3–21 were used to generate the above data (N = 19). [b] ED50 = 50% control in moles per acre.

Results and Discussion

The data of Table I were correlated by using a computer-assisted first- and second-order regression analysis, employing the step-up technique originally described by Hansch et al.[7-9] This multiparameter approach yielded the linear combination of terms summarized in Table II, wherein the parallel introduction of terms is illustrated for each of the three weed species under study.

The two parameters of greatest significance were found to be π and MR. The positive contribution to activity from π is effectively counterbalanced by a negative MR term. This relationship is illustrated in the data of Table I where, for example, compound **12** has a low ED50 due to the large positive MR value, while compound **19** has relatively good activity despite a large MR because of the positive contribution from a large π. Compound **14** is an example of an analogue with a negative π value and correspondingly low bioactivity. Statistically, the π and MR parameter values explain most of the bioactivity, since the correlation terms (r^2) for equations 1a, 2a, and 3a are relatively high (0.60–0.71).

Further examination of the predictivity of equations 1a, 2a, and 3a suggested the possible need for indicator variables H and Z. The H term is defined as equal to 1 when a group capable of hydrogen bonding (as a hydrogen acceptor) is present at the ortho position. More specifically, H = 1 when an ortho fluorine or oxygen is present contiguous to the ring. The introduction of the H term was found to be highly significant for all three weed species (eq 1b, 2b, and 3b), as is evident by lower standard deviations (s) and concomittant increases in r^2 and F values.

The introduction of the Z term was not as clearly justified as was the case for the H term. The Z term in equation 3c was found to be statistically sound in the case of green foxtail (t = 3.167), while for switch grass, in equation 1c it had a marginal 94% confidence level (t = 2.054). For barnyard grass (eq **2c**), the Z term was not statistically warranted (t = 0.925). In order to more clearly define the possible role of the Z term (the effect of an α-methyl group), it was of interest to see how well the regression equations in Table II could predict activities of compounds outside the selected subset (**3–21**) with and without invoking the Z term. A comparison of the predictive abilities of equations 1b, 2b, and 3b with 1c, 2c, and 3c is shown in Table III. The standard deviation (error) between predicted and actual activities was found to be notably larger when Z was omitted in the case of all three weed species. It is therefore quite likely that the Z term plays a significant role in the herbicidal activity of both selected (**3–21**) and test (**22–40**) compounds and that the best equations are 1c, 2c, and 3c based on regression analysis and predictivity.

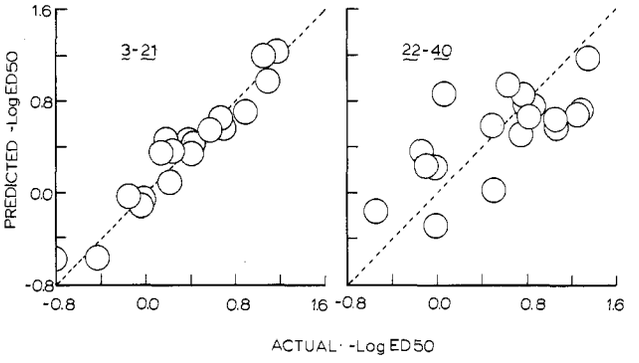

Figure 1. Actual preemergent herbicidal activities compared to predicted activities for compounds **3–21** and **22–40** by using equation **3c** for green foxtail control.

Comparison of predicted and actual activities by using equations 1c, 2c, and 3c was made for compounds **3–21** and **22–40**. The results of this comparison are shown in Figure 1 by using the data for green foxtail as a representative example. Predicted and actual values for −log ED50 are plotted so that a theoretically perfect agreement would result in a line with a slope of unity. The distribution of points in the case of the selected subset (**3–21**) is relatively tight and well spread, reflecting the low standard deviation

(7) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
(8) C. Hansch, *Acc. Chem. Res.*, **2**, 232 (1969).
(9) C. Hansch, "Drug Design", Vol. I, E. J. Ariens, Ed., Academic Press, New York, 1971, p 271.

Table III. Predicted Herbicidal Activities Computed by Equations 1b, 1c, 2b, 2c, 3b, and 3c Compared to Actual Activities of the Test Set (22-40)

			switch grass			barnyard grass			green foxtail		
				Δ[a]			Δ			Δ	
compd	substitution	Z	−log ED50	1b	1c	−log ED50	2b	2c	−log ED50	3b	3c
22	2-F	0	0.77	0.39	0.24	0.37	0.85	0.77	0.07	0.92	0.79
23	4-*i*-Pr	0	0.62	−0.20	−0.32	−0.10	0.67	0.60	−0.10	0.43	0.33
24	4-C_6H_5	0	−0.19	−0.18	−0.09	−0.69	0.82	0.77	−0.54	−0.43	−0.37
25	2,5-(*i*-Pr)$_2$	0	−0.02	0.47	0.34	−0.02	0.62	0.54	−0.02	0.33	0.24
26	2,3,6-Cl_3	0	0.81	0.01	−0.15	0.81	0.17	0.08	0.49	0.21	0.09
27	3,4-$(OCH_3)_2$	0	0.23	−0.41	−0.48	0.13	−0.17	−0.21	−0.01	−0.22	−0.29
28	3-Br	0	0.03	0.52	0.39	0.16	0.55	0.48	−0.14	0.61	0.50
29	2,6-Cl_2	0	0.74	−0.03	−0.17	0.96	−0.09	−0.17	0.74	−0.13	−0.24
30	2-Br-5-OCH_3	0	0.95	−0.77	−0.87	0.60	−0.27	−0.33	0.50	−0.40	−0.48
31	2-CH_3-4-Cl	1	0.98	−0.24	−0.15	0.84	0.07	0.11	0.79	−0.15	−0.03
32	4-Cl	1	1.14	−0.55	−0.44	0.90	−0.14	−0.09	0.82	−0.30	−0.17
33	3,4-$(CH_3)_2$	1	1.24	−0.72	−0.60	1.31	−0.62	−0.57	1.07	−0.63	−0.49
34	2,5-$(CH_3)_2$	1	1.25	−0.61	−0.50	1.30	−0.49	−0.44	1.25	−0.70	−0.57
35	2-CH_3	1	1.29	−0.64	−0.53	1.58	−0.76	−0.71	1.29	−0.72	−0.59
36	2-Cl-5-CF_3	1	1.26	−0.34	−0.26	0.91	0.18	0.22	0.63	0.19	0.30
37	3-CF_3	1	1.37	−0.55	−0.46	0.46	0.53	0.58	0.77	−0.03	0.08
38	2-Cl-6-F	1	1.65	−0.38	−0.30	1.35	−0.02	0.02	1.35	−0.27	−0.17
39	2,5-$(C_2H_5)_2$	1	1.15	−0.53	−0.43	1.15	−0.38	−0.33	1.05	−0.56	−0.42
40	2,5-Cl_2	1	1.07	−0.36	−0.26	1.07	−0.19	−0.14	0.86	−0.24	−0.12
standard deviation				0.48	0.42		0.50	0.46		0.47	0.40

[a] Δ = predicted activity − actual activity.

Table IV. Dependence of Correlation (r^2) on Standard Deviation Inherent in Observed Data (s)

s	0.20	0.25	0.30
r^2 range[a]	0.8392–0.9465	0.7717–0.9139	0.7040–0.8533
av r	0.8845	0.8328	0.7785

[a] Ten determinations, where $N = 21$ and the equation used was $-\log ED50 = 0.52\pi - 0.050MR + 0.17Z + 0.74$. Standard deviations of 0.20–0.30 were obtained by methods described in the text.

(s = 0.16). For the test set (22–40), the points are also well spread and generally lie along the theoretical line, although the standard deviation is larger (s = 0.40). The data for switch grass and barnyard grass showed a similar degree of correspondence with s (3–21) = 0.25–0.30 and s (22–40) = 0.42–0.46. Thus, equations 1c, 2c, and 3c were found to be predictive and of value in guiding synthesis.

The ED50 determinations in a whole plant assay system were found to have a significant degree of uncertainty. Typically, at the dose ranges under study, ED50 reproducibility was found to be on the order of twofold, i.e., an ED50 value of 0.25 mol/acre means that the actual ED50 lies between 0.125 and 0.50 mol/acre. On a logarithmic scale the error of determination could be as much as 0.30. How this uncertainty determines the attainable correlation was investigated in a heuristic manner. A set of data with r^2 = 1.00 over the observed range of herbicidal activity was generated by computing predicted activities from a regression equation. A computer program generated normally distributed random numbers averaging zero and having specifiable standard deviation. These numbers furnished a set of errors that was added one on one to the computed activities. When errors with standard deviations of 0.20 to 0.30 were ramdonly superimposed on perfect sets of ED50 data, regression analysis provided equations with r^2 values shown in Table IV. Biological data with an estimate of error corresponding to a standard deviation of 0.25 was found to limit regression capability to r^2 values ranging from 0.77 to 0.91 (10 determinations). Interestingly, the r^2 values of equations 1c, 2c, and 3c ranged from 0.79 to 0.93. It is therefore reasonable to assume that these equations represent all that can be correlated to activity within the experimental limitations of the biological data.

Conclusions

Preemergent herbicidal activity for a series of recently patented 2-[(phenylmethyl)sulfonyl]pyridine 1-oxides was quantitatively characterized for three weed species by using appropriate physicochemical parameters. The uncertainty in the in vivo assay was related to potential effects on regression analysis, and despite the resultant statistical limitations, the overall predictive value of the regression equations remains high. The capacity of QSAR in providing directions for future synthesis in a given class of herbicidally active compounds by using in vivo data has been demonstrated.

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