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A Quantitative Structure−Activity Relationship Study of Herbicidal Analogues of α-Hydroxy-Substituted 3-Benzylidenepyrrolidene-2,4-diones

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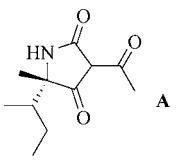
A series of pyrrolidine-2,4-dione and piperidine-2,4-dione derivatives were prepared and evaluated for their herbicidal activities where some of these compounds exhibited good bioactivity against *Echinochloa crus-galli* in comparison with sulcotrione. Quantitative structure−activity relationship studies were performed on these compounds using physicochemical parameters (hydrophobic, electronic, and Taft) as independent parameters and herbicidal activity as a dependent parameter, where herbicidal activity correlated best ($r > 0.8$) with hydrophobic ($\pi^o + \pi^p$), steric (Es), STERIMOL (**B4**), indicator (H_M), van der Waals volume (V), and electronic parameter ($\sigma^m + \sigma^p$) in this set of molecules; the optimum van der Waals volume for R^2 is about 41.8 Å^3; when **B4** is equal to 3, the target molecule possessed the lowest herbicidal activity.

KEYWORDS: Herbicide; triketone; pyrrolidine-2,4-dione; quantitative structure−activity relationship (QSAR)

INTRODUCTION

4-Hydoxyphenylpyruvate dioxygenase (4-HPPD) catalyzes the conversion of the 4-hydroxyphenylpyruvate to homogentisate in the biosynthesis pathway of plastoquinone and α-tocopherol. Inhibition of the production of homogentisate by 4-HPPD inhibitors down-regulates the production of plastoquinone, which is thought to be an acceptor of hydrogen from phytoene. Therefore, the absence of plastoquinone leads to an accumulation of the phytoene, which results in the impairment of carotenoid biosynthesis that is essential for the growth and survival of herbs. Thus, the inhibitors of 4-HPPD, classified as bleaching herbicides, have been intensively studied since the 1990s. Their herbicidal activities have proven to be comparable to acetolactate synthase and protoporphyrinogen-IX oxidase inhibitors, exhibiting excellent herbicidal activities even at low dosages.



A

A survey of the known 4-HPPD inhibitors revealed that most of them have very similar structural characteristics, i.e., their benzoyl groups are substituted with various electron-withdrawing groups such as chlorine, trifluoromethyl, nitro, or methanesulfonyl functional groups at ortho- and/or para-positions of the benzene rings (*1*, *2*). Interestingly, a different substitution effect was observed in the series of α-hydroxy-substituted 3-benzylidenepyrrolidene-2,4-diones (**B**) 4-HPPD inhibitors in our previous work (*3*−*5*). 3-Benzoyl pyrrolidine-2,4-diones were discovered as 4-HPPD inhibitors in our group through modification of the natural product **A**, which was inhibitory toward 4-HPPD with an $IC_{50} = 18$ μM (*6*), by the replacement of an acetyl group with substituted benzoyl groups. The 4-HPPD bioassay results showed that when R^1 was electron-donating, **B** (**Table 1**) exhibited better herbicidal activities. In contrast to most of the known 4-HPPD inhibitors, the electron-donating groups were preferred both at 2- and/or 4-positions of the benzene ring. In the meantime, the herbicidal activity of **B** against *Echinochloa crus-galli* and *Digitaria sanguinalis* varied obviously with R^1 and R^2. In particular, when R^1, R^2, and R^3 were 2,4-dimethoxy, *iso*-propyl, and hydrogen, respectively (**B30**), it provided 93% control of *E. crus-galli* with crop selectivity on corn and soybeans at pre-emergence at 187.5 g/ha. As compared with sulcotrione, some of these compounds were much more effective.

At present, quantitative structure−activity relationships (QSARs), an important area of chemometrics, have been widely utilized to study the relationship between chemical structures and biological or other functional activities. QSAR has become increasingly helpful in understanding many aspects of chemical−biological interactions in drug and pesticide research as

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Table 1. Compounds **B**–**E**

compd	R^1	R^2	R^3	compd	R^1	R^2	R^3
B1	4-*i*-C_3H_7O	*sec*-C_4H_9	H	**B38**[b]	4-Cl	*iso*-C_3H_7	H
B2	2-CH_3O-4-C_2H_5O	*sec*-C_4H_9	H	**B39**[b]	3-CH_3	*iso*-C_3H_7	H
B3	2-CH_3O-4-*i*-C_3H_7O	*sec*-C_4H_9	H	**B40**[b]	4-CH_3O	*iso*-C_3H_7	H
B4	2,4-$(CH_3O)_2$	*sec*-C_4H_9	H	**B41**[b]	4-CH_3	*iso*-C_3H_7	H
B5	4-C_2H_5O	*sec*-C_4H_9	H	**B42**[a]	3,5-$(CH_3)_2$	*iso*-C_3H_7	H
B6	4-*n*-C_3H_7	*sec*-C_4H_9	H	**B43**[a]	3-C_6H_5O	*iso*-C_3H_7	H
B7	3-*n*-C_4H_9O	*sec*-C_4H_9	H	**B44**[b]	2-CH_3O	*iso*-C_3H_7	H
B8	4-*n*-C_4H_9O	*sec*-C_4H_9	H	**B45**[a]	2,4-$(CH_3O)_2$	cyclo-C_3H_5	H
B9	4-CH_3O	*sec*-C_4H_9	H	**B46**[a]	3-C_6H_5O	cyclo-C_3H_5	H
B10	3,5-$(CH_3)_2$	*sec*-C_4H_9	H	**B47**[a]	4-C_2H_5O	cyclo-C_3H_5	H
B11	3-C_6H_5O	*sec*-C_4H_9	H	**B48**[a]	4-*n*-C_5H_{11}	cyclo-C_3H_5	H
B12	2,4,5-$(CH_3O)_3$	*sec*-C_4H_9	H	**B49**[a]	4-CH_3O	cyclo-C_3H_5	H
B13	3,4-$(CH_3O)_2$	*sec*-C_4H_9	H	**B50**[b]	3-CH_3	$C(CH_3)_3$	H
B14	4-CH_3O	*iso*-C_3H_7	CH_3	**B51**[b]	4-CH_3	$C(CH_3)_3$	H
B15	2-CH_3O-4-*i*-C_3H_7O	*iso*-C_3H_7	CH_3	**B52**[a]	4-*i*-C_3H_7	$C(CH_3)_3$	H
B16	2-methoxy-4-allyloxy	*iso*-C_3H_7	CH_3	**B53**[b]	4-CH_3O	$C(CH_3)_3$	H
B17	2-CH_3O-4-OC_2H_5	*iso*-C_3H_7	CH_3	**B54**[b]	2-CH_3O	$C(CH_3)_3$	H
B18	2,4-$(CH_3O)_2$	*iso*-C_3H_7	CH_3	**B55**[b]	2-CH_3	$C(CH_3)_3$	H
B19	4-*i*-C_3H_7O	*iso*-C_3H_7	H	**B56**[b]	4-$C(CH_3)_3$	$C(CH_3)_3$	H
B20	2-CH_3O-4-C_2H_5O	*iso*-C_3H_7	H	**B57**[c]	H	$C_6H_5CH_2$	H
B21	2-CH_3O-4-*i*-C_3H_7O	*iso*-C_3H_7	H	**B58**[c]	4-CH_3	$C_6H_5CH_2$	H
B22	3-*n*-C_4H_9O	*iso*-C_3H_7	H	**B59**[c]	2-OCH_3	$C_6H_5CH_2$	H
B23	4-*n*-C_4H_9O	*iso*-C_3H_7	H	**B60**[c]	3-CH_3	$C_6H_5CH_2$	H
B24	4-*n*-C_3H_7O	*iso*-C_3H_7	H	**B61**[c]	2-CH_3	$C_6H_5CH_2$	H
B25	2,4-$(C_2H_5O)_2$	*iso*-C_3H_7	H	**B62**[c]	4-OCH_3	$C_6H_5CH_2$	H
B26	4-$C_6H_5CH_2O$	*iso*-C_3H_7	H	**B63**[b]	3-CH_3	CH_3	H
B27	3-*i*-C_3H_7O	*iso*-C_3H_7	H	**B64**[b]	4-*n*-C_5H_{11}	CH_3	H
B28	2-methoxy-4-allyloxy	*iso*-C_3H_7	H	**B65**[b]	3-C_6H_5O	CH_3	H
B29	4-allyloxy	*iso*-C_3H_7	H	**E1**	4-CH_3O		
B30[a]	2,4-$(CH_3O)_2$	*iso*-C_3H_7	H	**E2**	4-C_2H_5O		
B31[a]	4-C_2H_5O	*iso*-C_3H_7	H	**E3**	2,4-$(CH_3O)_2$		
B32[a]	4-C_3H_7	*iso*-C_3H_7	H				
B33[a]	4-C_5H_{11}	*iso*-C_3H_7	H				
B34[b]	2-CH_3	*iso*-C_3H_7	H		R^1	M	*n*
B35[a]	4-$C(CH_3)_3$	*iso*-C_3H_7	H	**C1**	2,4-$(CH_3O)_2$	Na	1
B36[a]	2,4-$(CH_3)_2$	*iso*-C_3H_7	H	**C2**	4-C_2H_5O	Zn	2
B37[b]	2-Cl	*iso*-C_3H_7	H	**C3**	2,4-$(CH_3O)_2$	Zn	2

[a] From ref *5*. [b] From ref *4*. [c] From ref *3*.

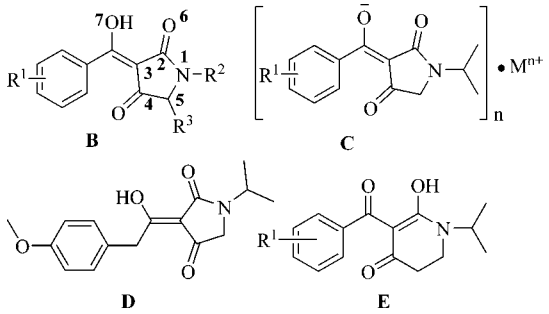


Figure 1. Chemical structures of **B**–**E**.

well as many other areas (*7*). The objectives of this study were to (i) prepare the analogues **B**−**E** (**Figure 1** and **Table 1**) to further explore pharmacophoric characters of 3-benzoyl pyrrolidine-2,4-diones and (ii) understand the QSAR for R^1 and R^2.

MATERIALS AND METHODS

Compounds. The compounds used in this study were substituted 3-benzoyl pyrrolidine-2,4-dione as listed in **Table 1**. **B1**−**29** and **C**−**E** (**Figure 1** and **Table 1**) were prepared according to the references described (*3*, *4*, *5*, *8*), and their structures were confirmed by elementary and ^{1}H NMR analyses (see the Supporting Information). **B30**−**65** (**Figure 1** and **Table 1**) were reported in our previous papers (*3*−*5*).

Herbicidal Activity Tests. Herbicidal activities of **B**−**E** and the triketone, sulcotrione [2-(2-chloro-4-mesylbenzoyl)cyclohexane-1,3-dione], were evaluated by a procedure described in our previous paper (*5*). A mixture of the same amount of water, *N*-dimethylformamide, and Tween 20 was used as a negative control. The inhibition rate *I* (%) is summarized in **Tables 2**, **3**, and **6**. Each value is the mean for three independent reproducible repetitions.

Table 2. Herbicidal Activity Against *E. crus-galli* at 10 μg/mL (% I)

compd	**B1**–**29**	**D**	**E1**	**E2**	**E3**
I (%)	see **Table 6**	5 ± 1	0	15 ± 1	6 ± 1

Molecular Docking. The A chain of the dimeric crystal structure (PDB 1T47) (*9*) was used as the core structure for our docking study. Preparation of the ligand input files was carried out using SYBYL6.9 (Tripos Inc.). The receptor description file was used to describe the HPPD. The ligand (NTBC) from PDB 1T47 was used as the reference compound of the coordinate, and the test ligand was produced by extracting it from PDB 1T47, atom typing the test compound and **B30**, and then adding hydrogens, followed by energy minimization. In this study, all carboxylic acid and phosphoric acid groups were ionized, and all amino, amidino, and guanidine groups (but no amide groups) were protonated. Assignments of hydrogen positions for the receptor were made on the basis of default rules, except for the definition of the torsion angles at the hydroxyl groups of the amino acids serine, threonine, and tyrosine and the hydrogen position inside the histidine side chain. Suitable torsion angles and the optimal tautomeric histidine state, respectively, were selected by visual inspection of the protein. The residues of lysine and arginine were protonated, and the acid groups of aspartic and glutamic acid were ionized. The ferric ion was set as Fe^{2+}. To define the active site of the protein, 16 residues were selected that are located no farther than 6.5 Å apart from the ligand atom at its crystalline position. All water molecules of the PDB file were removed.

Table 3. Herbicidal Activity of Compounds (% Inhibition)[a]

		pre-emergence treatment	
compd	rate (g/ha)	*E. crus-galli*	*D. sanguinalis*
B4	750	100 ± 0	80 ± 1
	375	76 ± 1	63 ± 1
	187.5	14 ± 1	4 ± 1
	93.75	13 ± 2	0
B5	750	93 ± 1	96 ± 1
	375	82 ± 1	59 ± 1
	187.5	28 ± 1	41 ± 1
	93.75	7 ± 1	18 ± 1
B30	750	99 ± 2	95 ± 1
	375	94 ± 1	95 ± 1
	187.5	56 ± 1	84 ± 2
	93.75	10 ± 2	20 ± 1
B31	750	100 ± 0	93 ± 1
	375	100 ± 0	77 ± 1
	187.5	95 ± 1	66 ± 2
	93.75	36 ± 2	5 ± 1
B29	750	100 ± 0	79 ± 2
	375	95 ± 1	74 ± 1
	187.5	55 ± 1	36 ± 2
	93.75	30 ± 2	0
C1	750	100 ± 0	100 ± 0
	375	100 ± 0	100 ± 0
	187.5	100 ± 0	90 ± 1
	93.75	73 ± 2	10 ± 1
C2	750	100 ± 0	100 ± 0
	375	100 ± 0	100 ± 0
	187.5	96 ± 1	64 ± 1
	93.75	57 ± 2	8 ± 1
C3	750	100 ± 0	100 ± 0
	375	100 ± 0	100 ± 0
	187.5	85 ± 1	82 ± 1
	93.75	72 ± 1	15 ± 1
sulcotrione	750	100 ± 0	100 ± 0
	375	100 ± 0	100 ± 0
	187.5	93 ± 2	100 ± 0
	93.75	70 ± 1	100 ± 0

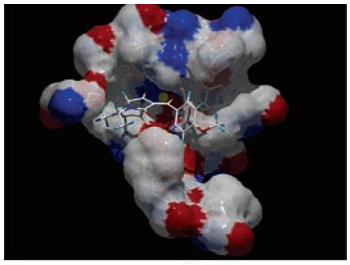
[a] **B30** and **B31** were reported in ref *5*, and their herbicidal activities were determined under the same conditions as **B4**,**5**, **B29**, **C1**–**3**, and sulcotrione.

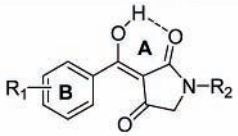
After the extracted NTBC (the ligand in PDB 1T47) was redocked into the active pocket successfully, **B18** was docked. The docking results were sorted by FlexX score and Cscore, and rational binding conformations were selected.

RESULTS AND DISCUSSION

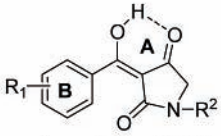
Bioassay. In our previous reports (*3*−*5*), it was found that when R^1 was 4-methoxy, 4-ethoxy, or 2,4-dimethoxy, the target molecule always displayed a better herbicidal activity. As shown in **Table 2**, when the substituted benzoyl group was replaced by a phenylacetyl group (**D**), the herbicidal activity decreased dramatically, which indicates that the benzoyl moiety at the 3-position is very important for their bioactivity. While R^2 was *iso*-propyl, R^1 was fixed such as 2,4-dimethoxy (**B30**), 4-ethoxy (**B31**), or 4-methoxy(**B40**), and the five-member ring was modified into a piperidine ring (**E1**−**3**); the target molecules showed very low or even no herbicidal activity against *E. crus-galli* at 10 μg/mL, which differentiates this class of compounds in SARs from other kinds of 4-HPPD inhibitors as herbicides (such as 1,3-cyclohexane-diones). When R^3 was a methyl group, their inhibition rate to *E. crus-galli* (**B14**−**18**) at 10 μg/mL was decreased significantly in comparison with the parent molecules (R^3 = H) (**B20**, **B21**, **B28**, **B30**, and **B40**). In order to explain this phenomenon and obtain information regarding the steric requirements, **B30** was docked into the HPPD from *Streptomyces avermitilis* (**Figure 2**). It was found that the docking configuration was the trans-form not the cis-form, which compound **B30** adopted in the crystal state (**Figure 2**) (*10*). According to this result, it may be deduced that the area formed by the pyrrole ring, Fe^{2+} and HPPD, may be more narrow and the introduction of a methyl group was not in favor for binding. In this docking model, the dihedral angle between plane A and plane B for the inhibitor was about 60°. It was also noticed that the closer the dihedral angles for **B30**, **B44**, **B53**, or **B57** (*10*−*13*) were to 60°, the higher the herbicidal activity was (**Table 4**). This may indicate that the configuration for planes A and B was the optimal for compound **B**.

When **B30** and **B31** were transformed into their sodium (or zinc) salts (**C1**−**3**), respectively, their herbicidal activities were improved significantly: They exhibited better herbicidal activities against *E. crus-galli* in comparison with sulcotrione at the rate of 93.75 g/ha (**Table 3**). It can be rationalized that the transformation is helpful to improve the test compounds' uptake and distribution and/or strengthen the target molecule's combination with Fe^{2+}—the reaction center of the HPPD enzyme. It was also noticed that **C1**'s herbicidal activity against *D. sanguinalis* dropped from 90 to 10 with only a 2-fold loss in





cis-(**HO** vs N-**CO**)



trans-(**HO** vs N-**CO**)

Figure 2. Docking model of **B30** with HPPD from *Streptomyces avermitilis* and the scheme for planes A and B.

Table 4. Herbicidal Activity (% Inhibition) and the Dihedral Angle (°) between Planes A and B

		E. crus-galli cup test	pre-emergence treatment for *E. crus-galli* (g/ha)			
compd	dihedral angle for A and B (°)	10 μg/mL	750	375	187.5	93.75
B30	62	78 ± 1	100 ± 0	100 ± 0	94 ± 1	34 ± 2
B44	53	77 ± 1	73 ± 1	28 ± 1	0	0
B53	21	10 ± 2	14 ± 2	0	0	0
B57	10	2 ± 1	0	0	0	0

Table 5. Value of the Van Der Waals Volume (*V*) for R^2

R^2	CH_3	$CH(CH_2)_2$	$CH(CH_3)_2$	CH_3CH-CH_2CH_3	$C(CH_3)_3$	$C_6H_5CH_2$
V (Å^3)[a]	25	47	59	76	76	97

[a] The volumes are calculated according to ref *14*.

Table 6. Topological and Physicochemical Parameters of Compounds **B1**–**B65***

compd	Es	$\Sigma(\sigma^m+\sigma^p)$	**B4**	(**B4**)^2	H_M	$\Sigma(\pi^o+\pi^p)$	V_N	$(V_N)^2$	I (%)	X^{obs}	X^{calcd}
B1	0	–0.45	0	0	1	0.36	0.76	0.58	46	–2.57	–2.55
B2	–0.55	–0.24	0	0	1	0.38	0.76	0.58	68	–2.20	–2.41
B3	–0.55	–0.45	0	0	1	0.36	0.76	0.58	33	–2.85	–2.40
B4	–0.55	–0.27	0	0	1	–0.04	0.76	0.58	79	–1.93	–2.18
B5	0	–0.24	0	0	1	0.38	0.76	0.58	78	–1.93	–2.56
B6	0	–0.13	0	0	1	1.55	0.76	0.58	18	–3.14	–3.20
B7	0	0.1	4.79	22.94	1	0	0.76	0.58	32	–2.85	–3.14
B8	0	–0.32	0	0	1	1.03	0.76	0.58	28	–2.93	–2.91
B9	0	–0.27	0	0	1	–0.02	0.76	0.58	64	–2.21	–2.34
B10	0	–0.14	2.04	4.16	1	0	0.76	0.58	9	–3.46	–3.24
B11	0	0.25	5.89	34.69	1	0	0.76	0.58	58	–2.41	–2.68
B12	–0.55	–0.15	2.87	8.24	1	–0.04	0.76	0.58	18	–3.20	–3.20
B13	0	–0.15	2.87	8.24	1	–0.02	0.76	0.58	9	–3.51	–3.36
B14	0	–0.27	0	0	0	–0.02	0.59	0.35	4	–3.84	–3.15
B15	–0.55	–0.45	0	0	0	0.34	0.59	0.35	9	–3.55	–3.19
B16	–0.55	–0.25	0	0	0	0.58	0.59	0.35	44	–2.64	–3.32
B17	–0.55	–0.24	0	0	0	0.36	0.59	0.35	32	–2.85	–3.20
B18	–0.55	–0.27	0	0	0	–0.04	0.59	0.35	25	–2.98	–2.99
B19	0	–0.45	0	0	1	0.36	0.59	0.35	79	–1.91	–2.20
B20	–0.55	–0.24	0	0	1	0.38	0.59	0.35	69	–2.16	–2.06
B21	–0.55	–0.45	0	0	1	0.34	0.59	0.35	57	–2.40	–2.03
B22	0	0.1	4.79	22.94	1	0	0.59	0.35	47	–2.55	–2.79
B23	0	–0.32	0	0	1	1.03	0.59	0.35	21	–3.08	–2.56
B24	0	–0.25	0	0	1	1.05	0.59	0.35	73	–2.05	–2.57
B25	0.04	–0.24	0	0	1	0.76	0.59	0.35	26	–2.98	–2.43
B26	0	–0.23	0	0	1	1.66	0.59	0.35	39	–2.74	–2.90
B27	0	0.1	3.61	13.03	1	0	0.59	0.35	9	–3.49	–3.02
B28	–0.55	–0.25	0	0	1	0.58	0.59	0.35	77	–2.00	–2.17
B29	0	–0.25	0	0	1	0.6	0.59	0.35	78	–1.93	–2.33
B30	–0.55	–0.27	0	0	1	–0.04	0.59	0.35	78	–1.94	–1.83
B31	0	–0.24	0	0	1	0.38	0.59	0.35	79	–1.89	–2.21
B32	0	–0.13	0	0	1	1.55	0.59	0.35	27	–2.89	–2.84
B33	0	–0.15	0	0	1	2.93	0.59	0.35	6	–3.69	–3.59
B34	–1.24	0	0	0	1	0.56	0.59	0.35	77	–1.89	–1.96
B35	0	–0.2	0	0	1	1.98	0.59	0.35	28	–2.89	–3.08
B36	–1.24	–0.17	0	0	1	1.12	0.59	0.35	74	–1.98	–2.27
B37	–0.97	0	0	0	1	0.71	0.59	0.35	51	–2.43	–2.12
B38	0	0.23	0	0	1	0.71	0.59	0.35	25	–2.92	–2.39
B39	0	–0.07	2.04	4.16	1	0	0.59	0.35	49	–2.43	–2.89
B40	0	–0.27	0	0	1	–0.02	0.59	0.35	80	–1.84	–1.99
B41	0	–0.17	0	0	1	0.56	0.59	0.35	77	–1.89	–2.31
B42	0	–0.14	2.04	4.16	1	0	0.59	0.35	22	–2.99	–2.89
B43	0	0.25	5.89	34.69	1	0	0.59	0.35	57	–2.41	–2.33
B44	–0.55	0	0	0	1	–0.02	0.59	0.35	77	–1.92	–1.84
B45	–0.55	–0.27	0	0	1	–0.04	0.47	0.22	78	–1.94	–1.71
B46	0	0.25	5.89	34.69	1	0	0.47	0.22	58	–2.39	–2.21
B47	0	–0.24	0	0	1	0.38	0.47	0.22	78	–1.91	–2.09
B48	0	–0.15	0	0	1	2.93	0.47	0.22	5	–3.74	–3.48
B49	0	–0.27	0	0	1	–0.02	0.47	0.22	62	–2.22	–1.87
B50	0	–0.07	2.04	4.16	1	0	0.76	0.58	5	–3.72	–3.24
B51	0	–0.17	0	0	1	0.56	0.76	0.58	36	–2.69	–2.66
B52	0	–0.15	0	0	1	1.53	0.76	0.58	10	–3.43	–3.18
B53	0	–0.27	0	0	1	–0.02	0.76	0.58	79	–1.89	–2.34
B54	–0.55	0	0	0	1	–0.02	0.76	0.58	75	–1.98	–2.19
B55	–1.24	0	0	0	1	0.56	0.76	0.58	64	–2.19	–2.32
B56	0	–0.2	0	0	1	1.98	0.76	0.58	4	–3.88	–3.43
B57	0	0	0	0	1	0	0.97	0.94	20	–3.07	–3.09
B58	0	–0.17	0	0	1	0.56	0.97	0.94	8	–3.53	–3.39
B59	–0.55	0	0	0	1	–0.02	0.97	0.94	14	–3.29	–2.93
B60	0	–0.07	2.04	4.16	1	0	0.97	0.94	12	–3.35	–3.98
B61	–1.24	0	0	0	1	0.56	0.97	0.94	15	–3.24	–3.05
B62	0	–0.27	0	0	1	–0.02	0.97	0.94	14	–3.30	–3.08
B63	0	–0.07	2.04	4.16	1	0	0.25	0.06	25	–2.84	–2.87
B64	0	–0.15	0	0	1	2.93	0.25	0.06	16	–3.18	–3.57
B65	0	0.25	5.89	34.69	1	0	0.25	0.06	53	–2.44	–2.31

applied herbicide (**Table 3**), which may be a result from the soil's metabolism and *D. sanguinalis*'s sensitivity to **C1** at a lower dosage.

According to our previous works (*3*−*5*), when R^1 was fixed, the target molecule **B**'s herbicidal activity changed with R^2 and the rank of them is iso-propyl > cyclopropyl > *tert*-butyl, methyl > benzyl. The van der Waals volume (V) for R^2 is listed in **Table 5**, and the optimal V should exist. In order to validate the hypothesis and to perform the QSAR study, some analogues (**B1**−**13**) (R^2 = *sec*-butyl) were prepared. The bioassay results (**Tables 2** and **3**) showed that they exhibited better herbicidal activities but worse than corresponding N-*iso*-propyl analogues.

QSAR Analysis. In order to gain insight into SARs, **B1**−**29** and **B30**−**65** (*3*−*5*) were analyzed by a physicochemical-based

QSAR (Hansch) approach using physicochemical parameters such as hydrophobic (π), Taft (Es), Verloop's sterimol (**B4**), indicator (H_M), van der Waals volume ($V_N = V/100$), and electronic parameters (Hammett's constants) as independent parameters, and the herbicidal activity data (% *I*) at 10 μg/mL was converted to log $\{I/[(100 - I) \times MW]\}$ (*15*) as dependent parameters. As listed in **Table 6**, when R^3 was methyl group, the target molecule showed very poor herbicidal activity in comparison with when R^3 was hydrogen. So, the indicator variable H_M was introduced and assigned to be zero for the methyl group, while it was one for hydrogen. The values of the physicochemical parameters in the study were taken from the literature (*16*), and multiparameter linear regression analysis was carried out using SYBYL 6.9 (Tripos Inc.). Variations in the herbicidal activities of N-*iso*-propyl compounds, **B19**−**44**, which constituted about half of these compounds, were first analyzed. Preliminary QSAR analysis showed the substituent R^1's hydrophobic parameter $[\sum(\pi^o + \pi^p)]$ for the ortho- and para-position ($r = 0.474$), Taft (Es) parameter for the ortho-position ($r = 0.407$), electronic parameter $[\sum(\sigma^m + \sigma^p)]$ for the meta- and para-position ($r = 0.263$), and Verloop's sterimol [**B4** and $(\mathbf{B4})^2$] parameter for the meta-position ($r = 0.369$); to a certain extent, showing correlation, stepwise regression analysis of different combinations of these parameters was studied, which led to the derivation of eq 1, with the best correlation ($r = 0.816$).

$$X = \log\{I/[(100 - I) \times MW]\}$$

where MW is molecular weight and

$$X = -2.111(\pm0.194) - 0.279(\pm0.196)\,Es - 0.581(\pm0.527)\sum(\sigma^m + \sigma^p) - 0.597(\pm0.181)\,\mathbf{B4} + 0.098(\pm0.033)\,(\mathbf{B4})^2 - 0.529(\pm0.114)\sum(\pi^o + \pi^p) \quad (1)$$

where $n = 26$, $r = 0.816$, $s = 0.3508$, and $F = 7.984$.

The analysis result indicated that the presence of R^1 at the ortho-position with a negative value for Taft parameter Es positively contributed to the activity, possibly due to intramolecular steric interaction, and suggested that the ortho-substituent in the benzene ring may be involved in the binding of these molecules with the active center of HPPD. For the electronic influence, the herbicidal activity mainly related to the substituents at the meta- and para-positions of the benzene ring. The presence of the electron-donating groups at the para-position may increase the electron density at O^6 or O^7 (**Figure 1**) and finally improve activity. The hydrophobicity impact of the substituents at the ortho- and para-positions of benzene ring was also important for herbicidal activity. **B4** represented the width of the substituent R^1 at the meta-position. In the case of dimeta-substituents, only one was under consideration. The coefficients of the $(\mathbf{B4})^2$ and **B4** terms meant that when the **B4** value for R^1 was about 3, the compound showed the lowest herbicidal activity. To further study the relationship between R^3 and their herbicidal activities, **B14**−**18** were exploited and gave eq 2.

$$X = -3.200(\pm0.200) - 0.339(\pm0.200)\,Es - 0.596(\pm0.195)\,\mathbf{B4} + 0.091(\pm0.037)\,(\mathbf{B4})^2 - 0.495(\pm0.121)\sum(\pi^o + \pi^p) + 1.517(\pm0.206)\,H_M \quad (2)$$

where $n = 31$, $r = 0.803$, $s = 0.3892$, and $F = 9.088$.

Table 7. Correlation Matrix of the Parameters Used in QSAR Study

	Es	**B4**	$(\mathbf{B4})^2$	H_M	$\sum(\pi^o + \pi^p)$	V_N	$(V_N)^2$
Es	1.000						
B4	0.265	1.000					
$(\mathbf{B4})^2$	0.230	0.961	1.000				
H_M	0.170	0.141	0.117	1.000			
$\sum(\pi^o + \pi^p)$	0.109	−0.348	−0.287	0.109	1.000		
V_N	−0.101	−0.145	−0.179	0.115	−0.218	1.000	
$(V_N)^2$	−0.083	−0.117	−0.152	0.141	−0.214	0.982	1.000

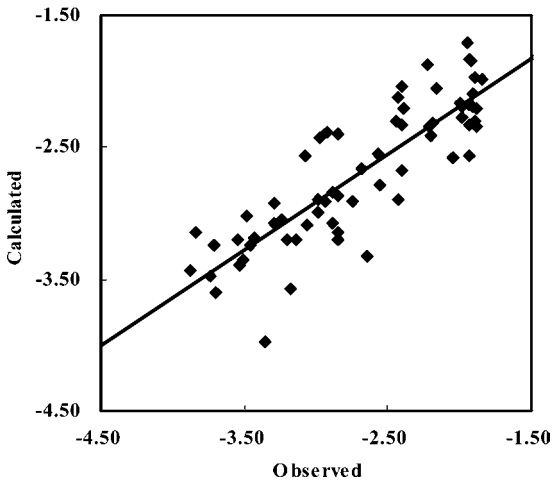


Figure 3. Relationship between observed and calculated activity.

In comparison with eq 1, the electronic parameter item $[\sum(\sigma^m + \sigma^p)]$ was not included in eq 2. The analysis result showed that when the substitute R^3 was introduced into **B**, its herbicidal activity was mainly correlated with R^1's steric and hydrophobic parameters and the steric effect on herbicidal activity was more important than the electronic effect. The coefficient of the H_M term meant that the compounds with $R^3 = H$ had a herbicidal activity about 33 times that of those with $R^3 = CH_3$ and also suggested that hydrogen was preferred for R^3. In order to gain more information about R^2, **B1**−**13** and **B45**−**65** were considered and gave eq 3.

$$X = -3.732(\pm0.513) - 0.275(\pm0.126)\,Es - 0.639(\pm0.096)\,\mathbf{B4} + 0.099(\pm0.017)\,(\mathbf{B4})^2 + 1.159(\pm0.169)\,H_M + 3.339(\pm1.448)\,V_N - 3.994(\pm1.091)\,(V_N)^2 - 0.544(\pm0.067)\sum(\pi^o + \pi^p) \quad (3)$$

where $n = 65$, $r = 0.853$, $s = 0.3416$, and $F = 21.795$.

V_N was 1% of the van der Waals volume (*V*) for R^2 at the nitrogen atom and calculated according to ref *14*. The coefficients of the $(V_N)^2$ and V_N terms meant that the van der Waals volume (*V*) for R^2 had an optimum value for **B** and was about 41.8 Å^3. This result was consistant with our docking result. The intercorrelation of variable was given in **Table 7**, and the calculated activities for **B1**−**65** by eq 3 were in good agreement with the observed activity (**Table 6** and **Figure 3**).

Conclusions. In summary, we further extended the study of SAR of 3-benzoyl pyrrolidine-2,4-diones series 4-HPPD inhibitors and gained insight of the pharmacophore through physicochemical-based QSAR study. At first, it was further proven that the pyrrolidine triketone compounds possessed different SARs between R^1 and their bioactivities from other kinds of herbicides (such as 1,3-cyclohexane diones), in which electron-donating groups were preferred for R^1. Second, when a substitute (R^3) was introduced into the five-member ring, compound **B**'s

herbicidal activity was mainly related to R^1's steric and hydrophobic parameters. Third, the van der Waals volume for R^2, the hydrophobic ($\pi^o + \pi^p$), Taft (Es) for the ortho-position, STERIMOL (**B4**) for the meta-position, and electronic parameter [$\sum(\sigma^m + \sigma^p)$] for the meta- and para-positions for R^1 of the benzoyl group were very important for herbicidal activity in this class of compounds; hydrogen was preferred for R^3, and when the B4 was equal to 3, the target molecules possessed the lowest herbicidal activity. Fourth, when the R^1 was fixed and R^3 was hydrogen, the herbicidal activity against *E. crus-galli* rank for R^2 was *iso*-propyl > *sec*-butyl > cyclo-propyl > *tert*-butyl, methyl > benzyl and its optimum volume was about 41.8 $Å^3$. Fifth, the translation of **B** to its salt may strengthen its combination with the Fe^{2+} of HPPD therefore exhibited better herbicidal activity. Finally, the benzoyl group's existence was essential for their herbicidal activities.

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Supporting Information Available: Chemical structures of **B**−**E**; synthetic procedures; synthesis schemes; mps, yields, and elemental analyses of compounds **A**−**D**; and ^{1}H NMR of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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