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Synthesis, Herbicidal Activity, and Structure-Bioactivity Relationship of Pyridyl-Containing 2-Phenyliminothiazolidines

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Summary. A series of novel 2-phenyliminothiazolidine derivatives were designed and synthesized. All title compounds were characterized by ^{1}H NMR and, in some cases, by ^{13}C NMR, IR, and HRMS. Their agricultural bioactivities were evaluated and some of these compounds exhibited efficient herbicidal activities against *Echinochloa crusgalli*, *Sorghum vulgare*, *Digitaria sanguinalis*, *Eclipta prostrasta*, *Cucumis sativus*, and *Brassica campestris* at 50 $\mu g/cm^3$. Analysis of the quantitative structure-activity relationship (QSAR) showed that the electronic parameter was the main factor to affect herbicidal activities.

Keywords. 2-Phenyliminothiazolidine; Synthesis; Herbicidal activity; QSAR.

Introduction

Crop protection continually needs the discovery of novel herbicides. Since the discovery of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-*D*), the agrochemical industry has successfully developed a wide array of herbicides with various chemical structures and modes of action [1]. However, an inevitable problem associated with the use of herbicides is the occurrence of herbicide resistant weeds [2]. Therefore, it is necessary to develop efficient herbicides with novel structures or modes of action to overcome the resistance of weeds.

In the study of pharmaceuticals and agrochemicals, the introduction of pyridine into a parent compound may improve the properties and biological activities of the compounds, and many pyridyl-containing compounds are also known to possess a wide range of biological and pharmacological activities [3–6], as well as low toxicity toward mammals. On the other hand, the 2-iminothiazolidine ring system has received much attention in biologically active molecules, such as potent inhibitors of indoleethylamine *N*-methyltransferase [7, 8], octopaminergic agonists [9, 10], anthelmintics [11], diuretic agents [12], trehalase inhibitors [13, 14], and insecticidal agents [15]. However, few 2-iminothiazolidine derivatives with herbicidal activity were reported [16]. It was presumed that this class of compounds probably possess high potentials on herbicidal activity. Therefore, we adopted the 2-phenyliminothiazolidine ring as pharmacophore and simultaneously introduced pyridinemethyl into the 3-position of 2-phenyliminothiazolidine. The methylene group between pyridyl and 2-phenyliminothiazolidine enhanced the flexibility of the whole molecule and further influenced the biological activities. Herein, a series of novel pyridyl-containing 2-phenyliminothiazolidine derivatives were conveniently synthesized, and the semiempirical quantum chemical method and molecular modeling

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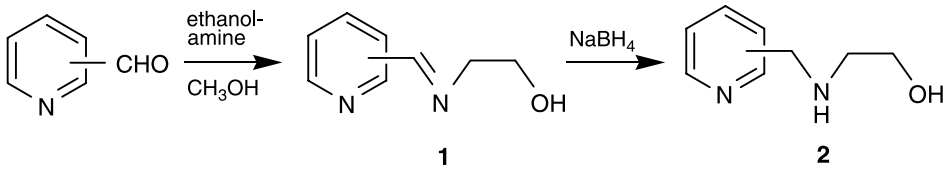


Scheme 1

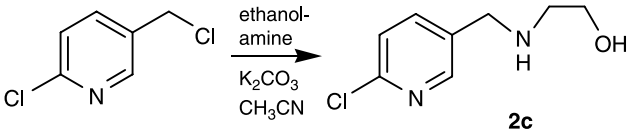
were also used to study the structure-bioactivity relationship of the synthesized compounds against the tested weeds.

Results and Discussion

Synthesis

The intermediates **2a** and **2b** were synthesized by a convenient one-pot procedure (Scheme 1). Reaction of pyridylaldehyde with ethanolamine gave **1**, which were directly reduced to give **2a** and **2b** in 90–93% yields based on the consumed pyridylaldehyde. The intermediate **2c** was prepared in refluxing acetonitrile in 70% yield (Scheme 2).

The target products **4** were prepared as shown in Scheme 3. Hydroxyeththioureas **3** were obtained by reaction of aminoethanols **2** with the corresponding aryl isothiocyanates and simply washed with Et_2O and water without further purification. Cyclization of **3** with hydrochloric acid provided the required 2-phenyliminothiazolidine derivatives **4**. The overall yields of these two steps ranged from 61 to 86%. The structures of the target compounds **4** were well characterized by ^{1}H NMR and, in some cases, by ^{13}C NMR, IR, and HRMS. The IR spectra of compounds **4** showed C=N and C–S stretching bands at 1608–1633 and 1213–1244 cm^{-1}. The ^{1}H NMR spectra of compounds **4** showed a singlet at $\delta =$ 4.69–4.90 ppm attributed to CH_2 linking to the thiazolidine ring. The two groups of triplets at $\delta = 3.09$–3.24 and 3.46–3.75 ppm were due to two conjoint CH_2 of the thiazolidine ring.

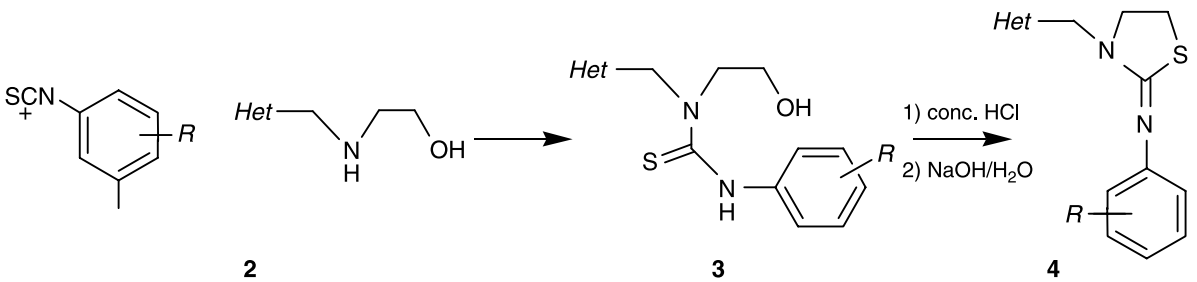


Scheme 2

Herbicidal Activity

In order to analyse the structure-activity relationship of 2-phenyliminothiazilidines, compounds **4a-8** to **4a-16**, **4a-1**, and **4a-6** reported previously [17] are also listed in Tables 1–3.

From the results, only compounds **4a** and **4b** exhibited inhibitory activities against both dicotyledonous and monocotyledonous weeds, but showed



a: *Het*=3-pyridyl
b: *Het*=2-pyridyl
c: *Het*=2-chloro-5-pyridyl

Scheme 3

Table 1. Inhibitory activities of compounds **4**[a] at 50 $\mu g/cm^3$

Comp.	*R*	Growth inhibitory rates/%						Symptoms
		E. crusgalli	*S. vulgare*	*D. sanguinnalis*	*E. prostrasta*	*C. sativus*	*B. campestris*	
4a-1	H	50/50[b]	50/10	70/30	70/80	70/80	10/10	–
4a-2	2-NO_2	30/20	–/–	60/10	80/80	10/20	–/–	*D. sanguinnalis* abnormality
4a-4	4-NO_2	10/20	10/10	20/10	30/20	40/30	–/–	*E. crusgalli* & *D. sanguinnalis* albinism
4a-6	2-CH_3	60/40	20/10	70/60	60/80	60/60	–/–	–
4a-7	2,6-CH_3,CH_3	50/20	30/–	60/20	60/70	60/20	–/–	–
4a-8	2-CF_3	50/10	10/–	60/30	60/60	10/–	–/–	–
4a-9	3-CF_3	40/20	40/–	60/10	70/80	50/40	–/–	–
4a-10	2-F	80/20	–/–	90/90	80/80	40/20	60/20	–
4a-11	4-F	65/80	80/50	80/90	80/85	80/80	10/10	–
4a-12	2,4-F,F	60/30	20/–	70/70	80/90	30/30	–/–	–
4a-13	2,6-F,F	60/10	–/–	60/–	50/80	30/20	10/10	*D. sanguinnalis* abnormality
4a-14	2-Cl	40/–	40/–	50/–	65/80	75/60	–/–	*D. sanguinnalis* abnormality
4a-15	4-Cl	60/40	20/10	90/90	85/90	80/75	20/–	*E. crusgalli* abnormality
4a-16	2,6-Cl,Cl	20/20	–/–	60/–	–/–	–/–	–/–	
4b-1	H	–/–	–/–	–/–	40/30	–/–	–/–	*E. crusgalli* & *D. sanguinnalis* albinism
4b-6	2-CH_3	–/–	–/–	20/60	–/–	50/60	–/–	*D. sanguinnalis* albinism
4b-7	2,6-CH_3,CH_3	–/–	–/–	10/–	30/40	20/20	–/–	–
4b-8	2-CF_3	–/–	–/–	10/–	–/–	20/10	20/–	–
4b-9	3-CF_3	–/–	–/–	10/–	–/–	–/–	–/–	*D. sanguinnalis* albinism
4b-10	2-F	10/50	–/–	30/70	30/40	20/20	–/50	*E. crusgalli, D. sanguinnalis* & *B. campestris* albinism
4b-11	4-F	10/40	40/30	10/30	70/70	70/40	–/–	*D. sanguinnalis* albinism
4b-12	2,4-F,F	20/10	10/10	–/–	10/50	–/–	–/–	Albinism except for *E. prostrasta*
4b-14	2-Cl	–/10	–/–	20/10	30/30	–/–	–/20	–
4b-16	4-CH_3	–/–	–/–	–/–	–/–	60/50	–/–	–

[a] The results of effective compounds were listed; [b] Numerator and denominator stand for the herbicidal activity of the aerial parts and the roots

weak inhibitory activities against *S. vulgare* and *B. campestris*.

Firstly, we investigated the influences resulting from the structural changes of target compounds on biological activities. From results of the bioassay we found that their herbicidal activities descended in the order **4a** > **4b** > inactive **4c**. This indicated that the introduction of chlorine into the pyridine ring led to a loss of biological activities. 3-Pyridinemethyl derivatives **4a** showed higher herbicidal activities than the 2-pyridinemethyl derivatives **4b**.

We further focused on the relationship between the type of substituent *R* on phenyl ring and the biological activities. The compounds with weakly electron-donating or weakly electron-withdrawing group (CH_3, H, Cl, F) at the phenyl ring showed good biological activities. But the introduction of strongly electron-donating group such as the *N,N*-dimethylamino group into the phenyl ring resulted in a complete loss of activity (**4a**-**5**, **4b**-**5**).

Although we have no information about the mode of action of these compounds, it was presumed that their mode of action is possibly concerned with a photoinduced process according to the symptoms of the abnormality or albinism of some weeds and further study of this aspect is underway.

Quantitative Structure-Activity Relationship

The compounds **4** showed different herbicidal activities against different tested weeds. Results of the multiple regression analysis between structural parameters and their herbicidal activity are given below along with the statistical values (n = number of com-

Table 2. Herbicidal activity of compounds **4**

Comp.	*R*	Herbicidal activity (*HA*)					
		E. crusgalli	*S. vulgare*	*D. sanguinnalis*	*E. prostrasta*	*C. sativus*	*B. campestris*
4a-1	H	2.430/2.430	2.430/1.476	2.798/2.062	2.798/3.032	2.798/3.032	1.476/1.476
4a-2	2-NO_2	2.129/1.895	–/–	2.673/1.543	3.099/3.099	1.543/1.895	–/–
4a-4	4-NO_2	1.543/1.895	1.543/1.543	1.895/1.543	2.129/1.895	2.321/2.129	–/–
4a-6	2-CH_3	2.628/2.276	1.850/1.498	2.820/2.628	2.628/3.054	2.628/2.628	–/–
4a-7	2,6-CH_3,CH_3	2.473/1.871	2.105/–	2.649/1.871	2.649/2.841	2.649/1.871	–/–
4a-8	2-CF_3	2.528/1.573	1.573/–	2.704/2.160	2.704/2.704	1.573/–	–/–
4a-9	3-CF_3	2.352/1.926	2.352/–	2.704/1.573	2.900/3.130	2.528/2.352	–/–
4a-10	2-F	3.060/1.856	–/–	3.412/3.412	3.060/3.060	2.282/1.856	2.643/1.856
4a-11	4-F	2.727/3.060	3.060/2.458	3.060/3.412	3.060/3.211	3.060/3.060	1.504/1.504
4a-12	2,4-F,F	2.660/2.116	1.882/–	2.852/2.852	3.086/3.439	2.116/2.116	–/–
4a-13	2,6-F,F	2.660/1.530	–/–	2.660/–	2.484/3.086	2.116/1.882	1.530/1.530
4a-14	2-Cl	2.305/–	2.305/–	2.481/–	2.750/3.084	2.959/2.658	–/–
4a-15	4-Cl	2.658/2.305	1.879/1.527	3.436/3.436	3.235/3.436	3.084/2.959	1.879/–
4a-16	2,6-Cl,Cl	1.926/1.926	–/–	2.704/–	–/–	–/–	–/–
4b-1	H	–/–	–/–	–/–	2.254/2.062	–/–	–/–
4b-6	2-CH_3	–/–	–/–	1.850/2.628	–/–	2.452/2.628	–/–
4b-7	2,6-CH_3,CH_3	–/–	–/–	1.519/–	2.105/2.297	1.871/1.871	–/–
4b-8	2-CF_3	–/–	–/–	1.573/–	–/–	1.926/1.573	1.926/–
4b-9	3-CF_3	–/–	–/–	1.573/–	–/–	–/–	–/–
4b-10	2-F	1.504/2.458	–/–	2.090/2.826	2.090/2.282	1.856/1.856	–/2.458
4b-11	4-F	1.504/2.282	2.282/2.090	1.504/2.090	2.826/2.826	2.826/2.282	–/–
4b-12	2,4-F,F	1.882/1.530	1.530/1.530	–/–	1.530/2.484	–/–	–/–
4b-14	2-Cl	–/1.527	–/–	1.879/1.527	2.113/2.113	–/–	–/1.879
4b-16	4-CH_3	–/–	–/–	–/–	–/–	2.628/2.452	–/–

Table 3. Molecular parameters of compounds **4**

Compound	Descriptor variable							
	lg *P*	E_T/a.u.	Q_{N1}	Q_{N2}	Q_S	Q_{C1}	Q_{C2}	V/Å^3
4a-1	1.27	−98.3806	0.0406	−0.1307	0.0368	0.0121	−0.1664	790.99
4a-2	−1.47	−125.2497	0.0638	−0.1960	0.0483	0.0076	−0.1634	820.82
4a-4	−1.47	−125.2588	0.0514	−0.1501	0.0414	0.0090	−0.1617	850.36
4a-6	1.43	−103.8766	0.0379	−0.1230	0.0367	0.0130	−0.1674	812.74
4a-7	1.58	−109.3730	0.0371	−0.1194	0.0369	0.0133	−0.1672	855.85
4a-8	1.84	−150.7380	0.0573	−0.1595	0.0391	0.0086	−0.1619	834.50
4a-9	1.84	−150.7461	0.0477	−0.1416	0.0370	0.0106	−0.1634	870.37
4a-10	0.67	−113.9899	0.0468	−0.1320	0.0330	0.0113	−0.1652	793.45
4a-11	0.67	−113.9925	0.0438	−0.1348	0.0367	0.0113	−0.1647	799.40
4a-12	0.07	−129.6009	0.0499	−0.1358	0.0330	0.0105	−0.1636	801.88
4a-13	0.07	−129.5989	0.0540	−0.1351	0.0321	0.0094	−0.1616	800.93
4a-14	1.05	−109.4550	0.0468	−0.1349	0.0357	0.0112	−0.1651	812.20
4a-15	1.05	−109.4575	0.0434	−0.1352	0.0378	0.0113	−0.1651	834.66
4a-16	0.83	−120.5302	0.0537	−0.1415	0.0362	0.0092	−0.1622	850.81
4b-1	1.24	−98.3831	0.0602	−0.1457	0.0299	−0.0167	−0.1654	794.99
4b-6	1.39	−103.8785	0.0624	−0.1406	0.0303	−0.0087	−0.1657	821.44
4b-7	1.55	−109.3747	0.0618	−0.1373	0.0309	−0.0075	−0.1656	863.60
4b-8	1.81	−150.7414	0.0831	−0.1774	0.0311	−0.0146	−0.1607	840.60
4b-9	1.81	−150.7488	0.0682	−0.1560	0.0300	−0.0171	−0.1623	873.65
4b-10	0.64	−113.9926	0.0671	−0.1461	0.0263	−0.0164	−0.1636	797.98
4b-11	0.64	−113.9950	0.0637	−0.1498	0.0299	−0.0175	−0.1637	803.08
4b-12	0.04	−129.6039	0.0705	−0.1499	0.0263	−0.0174	−0.1619	806.09
4b-14	1.02	−109.4570	0.0697	−0.1504	0.0297	−0.0116	−0.1633	819.35
4b-16	1.39	−103.8835	0.0597	−0.1439	0.0297	−0.0163	−0.1657	848.39

pounds; r = correlation coefficient; s = standard deviation; F = significance index with respect to the equation). The figures in parentheses are the confidence intervals of the regression coefficient and intercept. Equations (1)–(4) are significant at the 99% level on the basis of results of the statistical F-test. The following regression model turned out to be the best:

$$HA = 0.052 \lg P - 0.285 (\lg P)^2 + 30.947 Q_{C1} \quad (0.0776) \quad (0.0711) \quad (6.1967)$$
$$- 207.662 Q_{C2} - 0.027 E_T - 34.842 \quad (72.3607) \quad (0.0086) \quad (12.6854) \quad (1)$$
$$n = 17, \quad r = 0.914, \quad F = 11.102, \quad s = 0.231$$

$$HA = 0.332 \lg P - 0.307 (\lg P)^2 - 28.572 Q_{N1} \quad (0.0966) \quad (0.0736) \quad (16.9312)$$
$$- 24.139 Q_{N2} + 35.196 Q_{C1} + 0.618 \quad (8.4711) \quad (12.1392) \quad (0.7503) \quad (2)$$
$$n = 21, \quad r = 0.932, \quad F = 19.925, \quad s = 0.254$$

$$HA = 0.390 \lg P - 0.465 (\lg P)^2 - 69.432 Q_{N1} \quad (0.0938) \quad (0.1135) \quad (8.6095)$$
$$- 45.642 Q_{N2} + 0.007 V - 5.788 \quad (7.4865) \quad (0.0036) \quad (3.2449) \quad (3)$$
$$n = 19, \quad r = 0.917, \quad F = 13.793, \quad s = 0.214$$

$$HA = 0.290 \lg P - 0.553 (\lg P)^2 - 0.028 E_T \quad (0.0756) \quad (0.0554) \quad (0.0050)$$
$$- 201.451 Q_{C2} + 88.715 Q_S - 36.152 \quad (49.4537) \quad (12.6766) \quad (8.3703) \quad (4)$$
$$n = 19, \quad r = 0.960, \quad F = 30.671, \quad s = 0.155$$

Equation (1) explains that the aerial parts activity against *E. crusgalli* of the tested compounds mainly depend on the molecular electronic properties (Q_{C1}, Q_{C2}, E_T) and the hydrophobicity (lg P). It was found that the effects of these parameters on the activity descended in the order $Q_{C1} > Q_{C2} > \lg P > E_T$. The higher the value of Q_{C1}, the better the activity. The lower the values of Q_{C2} and E_T, the higher the activity. Equation (2) explains that the aerial parts activity against *D. sanguinnalis* of the tested compounds was mainly dependent on the electronic parameter (Q_{C1}, Q_{N1}, Q_{N2}) and the hydrophobicity (lg P). The effects of the parameters on the activity descended in the order $Q_{C1} > Q_{N1} > Q_{N2} > \lg P$. The higher the values of Q_{C1}, the better the activity. The lower the value of Q_{N1} and Q_{N2}, the higher the activity. Equation (3) explains that the aerial parts activity against *E. prostrasta* of the tested compounds depend on the hydrophobicity (lg P), the electronic parameter (Q_{N1}, Q_{N2}), and the spatial parameter (V). The effects of the parameters on the activity descended in the order $Q_{N1} > \lg P > V > Q_{N2}$. The lower the value of Q_{N1} and Q_{N2}, the higher the activity. The higher the value of V, the better the activity. Equation (4) explains that the roots activity against *E. prostrasta* of the tested compounds depends on the hydrophobicity (lg P) and the electronic parameter (E_T, Q_{C2}, Q_S). It was found that the effects of the parameters on the activity descended in the order $Q_S > Q_{C2} > E_T > \lg P$. The higher the value of Q_S, the better the activity. The lower the value of E_T and Q_{C2}, the higher the activity. In addition, Eq. (1)–(4) imply that there is an optimum value of lg P. The activity against other tested weeds in terms of *HA* gave poor correlations and their equations were not listed.

In conclusion, we have demonstrated that novel 2-phenyliminothiazolidine derivatives containing a pyridinemethyl moiety presented efficient herbicidal activities. Significant relationships were found between the parameters hydrophobicity, spatial parameter, and electronic parameter and the herbicidal activity against some tested weeds. These strong correlations imply that electronic effects may play an important role in binding to the receptor. These equations also imply that there are optimum values of lg P. In general, 3-pyridinemethyl derivatives **4a** showed better herbicidal activities than 2-pyridinemethyl derivatives **4b**, as the former have more net-charge on the C1 and S atom, and less net-charge on N1 atom.

Experimental

Melting points were obtained with an X-6 micro-melting point apparatus. The infrared (IR) spectra were recorded on a Nicolet 20DXB FT-IR spectrometer using KBr pellets or films. The ^{1}H NMR spectra were measured on a Varian INOVA-400 spectrometer with chemical shifts reported as parts per million (in $CDCl_3$, *TMS* as internal standard). The ^{13}C NMR spectra were measured on a Bruker AVANCE-500 spectrometer (in $CDCl_3$, *TMS* as internal standard). High-resolution mass spectra (HRMS) were obtained on an HPLC-Q-Tof MS (Mcrio) spectrometer. Flash chromatography was performed on silica gel. All the solvents were of analytical grade. All chemicals or reagents were purchased from standard commercial suppliers.

*General Synthesis Procedure for Intermediates **2a** and **2b***
Ethanolamine (20 mmol) and 20 mmol pyridylaldehyde in 50 cm^3 methanol were stirred for 36 h at room temperature. Then, 20 mmol $NaBH_4$ were added portionwise and the mixture was stirred at 50°C for 4 h. Methanol was distilled off under reduced pressure and the residue was purified by column chromatography on silica gel by using dichloromethane/methanol/triethylamine as eluent to give a yellowish oil **2** (**2a**: dichloromethane/methanol/triethylamine = 150/20/1, *v*/*v*, 93% yield; **2b**: dichloromethane/methanol/triethylamine = 150/20/1, *v*/*v*, 90% yield).

*General Synthesis Procedure for Intermediate **2c***
2-Chloro-5-chloromethylpyridine (10 mmol) dissolved in 100 cm^3 acetonitrile was added dropwise to a K_2CO_3-containing (10 mmol) ethanolamine (10 mmol) solution in 25 cm^3 acetonitrile over a period of 2 h at room temperature. The resulting mixture was refluxed for 3–5 h. Then, the solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel by using 10% methanol/chloroform as eluent to give yellowish oil **2c** in 70% yield.

*General Synthesis Procedure for the Target Compounds **4***
To a solution of 1.0 mmol **2** in 50 cm^3 ethanol was added 1.0 mmol of the corresponding phenyl isothiocyanate over a 10-min period and the mixture was stirred at room temperature for 30–60 min. Then, the solvent was evaporated under vacuum and the residue was washed with diethyl ether and H_2O to afford **3**, which was used directly without further purification.

The appropriate thiourea **3** (10 mmol) was dissolved in 10 cm^3 conc. HCl and heated at 90°C for 45 min. The cooled mixture was basified with 10 *M* NaOH in an ice bath. The precipitated gummy residue was extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give crude **4**, which was purified by column chromatography on silica gel by using petroleum ether and acetone as eluents. The overall yields of these two steps ranged from 61 to 86%.

2-[(2-Nitrophenyl)imino]-3-(3-pyridylmethyl)thiazolidine
(**4a-2**, $C_{15}H_{14}N_4O_2S$)
Yield 71%; mp 93.0–93.5°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.20$ (t, $J = 7.0$ Hz, 2H), 3.59 (t, $J = 7.0$ Hz, 2H), 4.74 (s, 2H), 7.07 (dd, $J = 1.2$, 8.2 Hz, 1H), 7.12 (ddd, $J = 1.2$, 7.4, 8.2 Hz, 1H), 7.34 (dd, $J = 5.0$, 7.6 Hz, 1H), 7.48 (ddd, $J = 1.2$, 7.4, 8.2 Hz, 1H), 7.81–7.86 (m, 1H), 7.89 (dd, $J = 1.2$, 8.2 Hz, 1H), 8.57 (dd, $J = 1.2$, 5.0 Hz, 1H), 8.59 (d, $J = 2.0$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1623$, 1595, 1517, 1234, 756 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{15}N_4O_2S$ [M + H^+] 315.0916, found 315.0926.

2-[(3-Nitrophenyl)imino]-3-(3-pyridylmethyl)thiazolidine
(**4a-3**, $C_{15}H_{14}N_4O_2S$)
Yield 75%; mp 66.5–67.5°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.21$ (t, $J = 7.0$ Hz, 2H), 3.59 (t, $J = 7.0$ Hz, 2H), 4.75 (s, 2H), 7.25–7.31 (m, 1H), 7.34 (dd, $J = 4.8$, 8.0 Hz, 1H), 7.43 (t, $J = 8.0$ Hz, 1H), 7.75 (d, $J = 8.0$ Hz, 1H), 7.84 (t, $J = 2.0$ Hz, 1H), 7.87–7.92 (m, 1H), 8.58 (dd, $J = 1.6$, 4.8 Hz, 1H), 8.63 (d, $J = 1.6$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1618$, 1595, 1521, 1234, 742, 710 cm^{-1}; HRMS calculated for $C_{15}H_{15}N_4O_2S$ [M + H^+] 315.0916, found 315.0924.

2-[(4-Nitrophenyl)imino]-3-(3-pyridylmethyl)thiazolidine
(**4a-4**, $C_{15}H_{14}N_4O_2S$)
Yield 72%; mp 102.6–103.1°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.22$ (t, $J = 7.0$ Hz, 2H), 3.60 (t, $J = 7.0$ Hz, 2H), 4.75 (s, 2H), 7.02–7.08 (m, 2H), 7.32 (dd, $J = 4.8$, 8.0 Hz, 1H), 7.69–7.75 (m, 1H), 8.14–8.20 (m, 2H), 8.58 (dd, $J = 1.2$, 4.8 Hz, 1H), 8.62 (d, $J = 1.6$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} =$ 1621, 1578, 1492, 1233, 853 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{15}N_4O_2S$ [M + H^+] 315.0916, found 315.0911.

2-[[4-(Dimethylamino)phenyl]imino]-3-(3-pyridylmethyl)-thiazolidine (**4a-5**, $C_{17}H_{20}N_4S$)
Yield 68%; mp 80.7–81.4°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.91$ (s, 6H), 3.11 (t, $J = 6.8$ Hz, 2H), 3.47 (t, $J = 6.8$ Hz, 2H), 4.73 (s, 2H), 6.73 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J =$ 8.8 Hz, 2H), 7.29 (dd, $J = 4.8$, 7.6 Hz, 1H), 7.76 (d, $J =$ 7.6 Hz, 1H), 8.55 (dd, $J = 1.6$, 4.8 Hz, 1H), 8.61 (d, $J = 1.6$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1619$, 1512, 1239, 820 cm^{-1}; HRMS calculated for $C_{17}H_{21}N_4S$ [M + H^+] 313.1487, found 313.1497.

2-[(2,6-Dimethylphenyl)imino]-3-(3-pyridylmethyl)-thiazolidine (**4a-7**, $C_{17}H_{19}N_3S$)
Yield 80%; mp 74.6–76.0°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.14$ (s, 6H), 3.12 (t, $J = 7.0$ Hz, 2H), 3.56 (t, $J = 7.0$ Hz, 2H), 4.78 (s, 2H), 6.88 (t, $J = 7.4$ Hz, 1H), 7.01 (d, $J =$ 7.4 Hz, 2H), 7.30 (dd, $J = 5.2$, 7.6 Hz, 1H), 7.79 (d, $J =$ 7.6 Hz, 1H), 8.56 (d, $J = 5.2$ Hz, 1H), 8.65 (s, 1H) ppm; IR (KBr): $\bar{\nu} = 1625$, 1588, 1228, 768 cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{20}N_3S$ [M + H^+] 298.1378, found 298.1364.

2-(Phenylimino)-3-(2-pyridylmethyl)thiazolidine
(**4b-1**, $C_{15}H_{15}N_3S$)
Yield 85%; mp 84.1–86.1°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.15$ (t, $J = 7.0$ Hz, 2H), 3.64 (t, $J = 7.0$ Hz, 2H), 4.85 (s, 2H), 6.96 (d, $J = 8.0$ Hz, 2H), 7.03 (t, $J = 7.4$ Hz, 1H), 7.20 (dd, $J = 5.2$, 7.6 Hz, 1H), 7.23–7.31 (m, 2H), 7.45 (d, $J =$ 7.8 Hz, 1H), 7.68 (ddd, $J = 1.6$, 7.6, 7.8 Hz, 1H), 8.56 (dd, $J = 1.6$, 5.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 26.93$, 50.74, 52.04, 121.94, 122.34, 122.52, 122.98, 128.80, 136.74, 149.18, 152.12, 157.33, 158.69 ppm; IR (KBr): $\bar{\nu} = 1614$, 1587, 1236, 761, 697 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{16}N_3S$ [M + H^+] 270.1065, found 270.1076.

2-[(2-Nitrophenyl)imino]-3-(2-pyridylmethyl)thiazolidine
(**4b-2**, $C_{15}H_{14}N_4O_2S$)
Yield 74%; mp 62.4–63.1°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.22$ (t, $J = 7.0$ Hz, 2H), 3.74 (t, $J = 7.0$ Hz, 2H), 4.84

(s, 2H), 7.03–7.12 (m, 2H), 7.22 (dd, $J = 5.2$, 7.4 Hz, 1H), 7.46 (ddd, $J = 1.2$, 7.6, 7.8 Hz, 1H), 7.54 (d, $J = 7.8$ Hz, 1H), 7.74 (ddd, $J = 1.6$, 7.4, 7.8 Hz, 1H), 7.86 (dd, $J = 1.2$, 8.0 Hz, 1H), 8.55 (dd, $J = 1.6$, 5.2 Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1625$, 1596, 1516, 1236, 757 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{15}N_4O_2S$ $[M + H^+]$ 315.0916, found 315.0927.

2-[(3-Nitrophenyl)imino]-3-(2-pyridylmethyl)thiazolidine (**4b-3**, $C_{15}H_{14}N_4O_2S$)
Yield 78%; oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.22$ (t, $J = 7.0$ Hz, 2H), 3.72 (t, $J = 7.0$ Hz, 2H), 4.85 (s, 2H), 7.23 (dd, $J = 5.2$, 7.6 Hz, 1H), 7.25–7.31 (m, 1H), 7.37–7.43 (m, 2H), 7.71 (dd, $J = 7.6$, 8.0 Hz, 1H), 7.80–7.88 (m, 2H), 8.58 (d, $J = 5.2$ Hz, 1H) ppm; IR (film): $\bar{\nu} = 1622$, 1596, 1521, 1236, 744, 687 cm^{-1}; HRMS calculated for $C_{15}H_{15}N_4O_2S$ $[M + H^+]$ 315.0916, found 315.0918.

2-[(4-Nitrophenyl)imino]-3-(2-pyridylmethyl)thiazolidine (**4b-4**, $C_{15}H_{14}N_4O_2S$)
Yield 80%; mp 72.6–73.2°C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.24$ (t, $J = 7.0$ Hz, 2H), 3.75 (t, $J = 7.0$ Hz, 2H), 4.85 (s, 2H), 7.03 (d, $J = 8.8$ Hz, 2H), 7.20–7.28 (m, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.65–7.74 (m, 1H), 8.16 (d, $J = 8.8$ Hz, 2H), 8.58 (d, $J = 4.4$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1612$, 1575, 1502, 1244, 852 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{15}N_4O_2S$ $[M + H^+]$ 315.0916, found 315.0927.

2-[[4-(Dimethylamino)phenyl]imino]-3-(2-pyridylmethyl)-thiazolidine (**4b-5**, $C_{17}H_{20}N_4S$)
Yield 68%; mp 65.2–66.3°C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.91$ (s, 6H), 3.14 (t, $J = 6.8$ Hz, 2H), 3.61 (t, $J = 6.8$ Hz, 2H), 4.85 (s, 2H), 6.72 (d, $J = 8.6$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 7.20 (dd, $J = 4.8$, 7.6 Hz, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.68 (dd, $J = 7.6$, 8.0 Hz, 1H), 8.56 (d, $J = 4.8$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1618$, 1589, 1514, 1240, 827 cm^{-1}; HRMS calculated for $C_{17}H_{21}N_4S$ $[M + H^+]$ 313.1487, found 313.1475.

2-[(2-Methylphenyl)imino]-3-(2-pyridylmethyl)thiazolidine (**4b-6**, $C_{16}H_{17}N_3S$)
Yield 70%; oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.14$ (s, 3H), 3.11 (t, $J = 6.8$ Hz, 2H), 3.65 (t, $J = 6.8$ Hz, 2H), 4.85 (s, 2H), 6.85 (d, $J = 7.6$ Hz, 1H), 6.94 (t, $J = 7.6$ Hz, 1H), 7.06–7.21 (m, 3H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 8.55 (dd, $J = 0.8$, 4.0 Hz, 1H) ppm; IR (film): $\bar{\nu} = 1628$, 1591, 1236, 761 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{18}N_3S$ $[M + H^+]$ 284.1221, found 284.1216.

2-[(2,6-Dimethylphenyl)imino]-3-(2-pyridylmethyl)-thiazolidine (**4b-7**, $C_{17}H_{19}N_3S$)
Yield 75%; oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.10$ (s, 6H), 3.09 (t, $J = 6.8$ Hz, 2H), 3.69 (t, $J = 6.8$ Hz, 2H), 4.86 (s, 2H), 6.85 (t, $J = 7.6$ Hz, 1H), 6.98 (d, $J = 7.6$ Hz, 2H), 7.14–7.20 (m, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.66 (ddd, $J = 1.6$, 7.6, 8.0 Hz, 1H), 8.55 (dd, $J = 1.6$, 4.8 Hz, 1H) ppm; IR (film): $\bar{\nu} = 1633$, 1588, 1238, 764 cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{20}N_3S$ $[M + H^+]$ 298.1378, found 298.1382.

2-[[2-(Trifluoromethyl)phenyl]imino]-3-(2-pyridylmethyl)-thiazolidine (**4b-8**, $C_{16}H_{14}F_3N_3S$)
Yield 79%; oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.10$ (t, $J = 6.8$ Hz, 2H), 3.64 (t, $J = 6.8$ Hz, 2H), 4.84 (s, 2H), 6.98–7.08 (m, 2H), 7.12–7.18 (m, 1H), 7.39 (t, $J = 7.6$ Hz, 1H), 7.44 (d, $J = 7.6$ Hz, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.64 (t, $J = 7.6$ Hz, 1H), 8.52 (d, $J = 4.0$ Hz, 1H) ppm; IR (film): $\bar{\nu} = 1625$, 1598, 1238, 758 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{15}F_3N_3S$ $[M + H^+]$ 338.0939, found 338.0940.

2-[[3-(Trifluoromethyl)phenyl]imino]-3-(2-pyridylmethyl)-thiazolidine (**4b-9**, $C_{16}H_{14}F_3N_3S$)
Yield 61%; mp 42.2–43.3°C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.20$ (t, $J = 7.0$ Hz, 2H), 3.70 (t, $J = 7.0$ Hz, 2H), 4.85 (s, 2H), 7.13 (d, $J = 8.0$ Hz, 1H), 7.18–7.32 (m, 3H), 7.37 (t, $J = 8.0$ Hz, 1H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.66–7.76 (m, 1H), 8.58 (d, $J = 5.2$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1623$, 1586, 1239, 800, 702 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{15}F_3N_3S$ $[M + H^+]$ 338.0939, found 338.0923.

2-[(2-Fluorophenyl)imino]-3-(2-pyridylmethyl)thiazolidine (**4b-10**, $C_{15}H_{14}FN_3S$)
Yield 83%; mp 46.7–47.8°C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.18$ (t, $J = 7.0$ Hz, 2H), 3.70 (t, $J = 7.0$ Hz, 2H), 4.88 (s, 2H), 6.95–7.09 (m, 4H), 7.21 (dd, $J = 5.2$, 7.6 Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.70 (ddd, $J = 1.6$, 7.6, 7.6 Hz, 1H), 8.55 (dd, $J = 1.6$, 5.2 Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1622$, 1600, 1239, 754 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{15}FN_3S$ $[M + H^+]$ 288.0971, found 288.0971.

2-[(4-Fluorophenyl)imino]-3-(2-pyridylmethyl)thiazolidine (**4b-11**, $C_{15}H_{14}FN_3S$)
Yield 85%; mp 77.8–78.7°C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.16$ (t, $J = 7.0$ Hz, 2H), 3.65 (t, $J = 7.0$ Hz, 2H), 4.83 (s, 2H), 6.86–7.00 (m, 4H), 7.21 (dd, $J = 4.8$, 7.6 Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.69 (ddd, $J = 1.6$, 7.6, 8.0 Hz, 1H), 8.57 (dd, $J = 1.6$, 4.8 Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1614$, 1589, 1213, 842 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{15}FN_3S$ $[M + H^+]$ 288.0971, found 288.0968.

2-[(2,4-Difluorophenyl)imino]-3-(2-pyridylmethyl)-thiazolidine (**4b-12**, $C_{15}H_{13}F_2N_3S$)
Yield 80%; mp 50.6–51.9°C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.19$ (t, $J = 7.0$ Hz, 2H), 3.71 (t, $J = 7.0$ Hz, 2H), 4.86 (s, 2H), 6.74–6.86 (m, 2H), 6.89–6.97 (m, 1H), 7.21 (dd, $J = 4.8$, 7.6 Hz, 1H), 7.49 (d, $J = 8.0$ Hz, 1H), 7.70 (ddd, $J = 1.6$, 7.6, 8.0 Hz, 1H), 8.56 (dd, $J = 1.6$, 4.8 Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1610$, 1588, 1244, 846, 757 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{14}F_2N_3S$ $[M + H^+]$ 306.0877, found 306.0883.

2-[(2,6-Difluorophenyl)imino]-3-(2-pyridylmethyl)-thiazolidine (**4b-13**, $C_{15}H_{13}F_2N_3S$)
Yield 82%; mp 90.1–90.9°C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.21$ (t, $J = 7.0$ Hz, 2H), 3.74(t, $J = 7.0$ Hz, 2H), 4.90 (s,

2H), 6.82–6.98 (m, 3H), 7.21 (dd, $J = 4.8$, 7.2 Hz, 1H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.71 (ddd, $J = 1.6$, 7.2, 8.0 Hz, 1H), 8.55 (dd, $J = 1.6$, 4.8 Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1618$, 1587, 1234, 763, 738 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{14}F_2N_3S$ $[M + H^+]$ 306.0877, found 306.0887.

2-[(2-Chlorophenyl)imino]-3-(2-pyridylmethyl)thiazolidine (**4b-14**, $C_{15}H_{14}ClN_3S$)
Yield 75%; mp 48.0–49.1°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.18$ (t, $J = 7.0$ Hz, 2H), 3.72 (t, $J = 7.0$ Hz, 2H), 4.89 (s, 2H), 6.93–7.02 (m, 2H), 7.14–7.24 (m, 2H), 7.32–7.39 (m, 1H), 7.61 (d, $J = 7.6$ Hz, 1H), 7.70 (t, $J = 7.6$ Hz, 1H), 8.56 (d, $J = 4.8$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1621$, 1582, 1233, 755 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{15}ClN_3S$ $[M + H^+]$ 304.0675, found 304.0672.

2-[(4-Chlorophenyl)imino]-3-(2-pyridylmethyl)thiazolidine (**4b-15**, $C_{15}H_{14}ClN_3S$)
Yield 78%; mp 73.0–74.5°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.17$ (t, $J = 7.0$ Hz, 2H), 3.66 (t, $J = 7.0$ Hz, 2H), 4.83 (s, 2H), 6.84–6.92 (m, 2H), 7.18–7.25 (m, 3H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.69 (ddd, $J = 1.6$, 7.6, 8.0 Hz, 1H), 8.57 (dd, $J = 1.6$, 4.4 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 26.98$, 50.80, 51.98, 122.40, 122.45, 123.33, 128.02, 128.81, 136.77, 149.27, 150.69, 157.11, 159.14 ppm; IR (KBr): $\bar{\nu} = 1613$, 1580, 1238, 843 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{15}ClN_3S$ $[M + H^+]$ 304.0675, found 304.0672.

2-[(4-Methylphenyl)imino]-3-(2-pyridylmethyl)thiazolidine (**4b-16**, $C_{16}H_{17}N_3S$)
Yield 77%; mp 85.9–87.0°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3H), 3.14 (t, $J = 7.0$ Hz, 2H), 3.63 (t, $J = 7.0$ Hz, 2H), 4.84 (s, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.4$ Hz, 2H), 7.20 (dd, $J = 4.8$, 7.6 Hz, 1H), 7.45 (d, $J = 7.8$ Hz, 1H), 7.68 (dd, $J =$ 7.6, 7.8 Hz, 1H), 8.56 (d, $J = 4.8$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1625$, 1597, 1503, 1236, 828 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{18}N_3S$ $[M + H^+]$ 284.1221, found 284.1220.

2-(Phenylimino)-3-[(2-chloro-5-pyridyl)methyl]thiazolidine (**4c-1**, $C_{15}H_{14}ClN_3S$)
Yield 81%; mp 69.0–70.0°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.14$ (t, $J = 6.8$ Hz, 2H), 3.51 (t, $J = 6.8$ Hz, 2H), 4.71 (s, 2H), 6.95 (d, $J = 7.8$ Hz, 2H), 7.06 (t, $J = 7.4$ Hz, 1H), 7.25–7.36 (m, 3H), 7.76 (dd, $J = 2.4$, 8.0 Hz, 1H), 8.39 (d, $J = 2.4$ Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 26.80, 46.87, 50.16, 121.79, 123.25, 124.31, 128.92, 131.86, 139.06, 149.38, 150.67, 151.71, 158.72 ppm; IR (KBr): $\bar{\nu} =$ 1615, 1590, 1238, 764, 693 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{15}ClN_3S$ $[M + H^+]$ 304.0675, found 304.0672.

2-[(2-Nitrophenyl)imino]-3-[(2-chloro-5-pyridyl)-methyl]thiazolidine (**4c-2**, $C_{15}H_{13}ClN_4O_2S$)
Yield 80%; mp 82.3–83.0°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.21$ (t, $J = 7.0$ Hz, 2H), 3.59 (t, $J = 7.0$ Hz, 2H), 4.71 (s, 2H), 7.05 (d, $J = 7.6$ Hz, 1H), 7.14 (t, $J = 7.6$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 8.36 (s, 1H) ppm; IR (KBr): $\bar{\nu} = 1624$, 1599, 1517, 1230, 764 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{14}ClN_4O_2S$ $[M + H^+]$ 349.0526, found 349.0540.

2-[(3-Nitrophenyl)imino]-3-[(2-chloro-5-pyridyl)-methyl]thiazolidine (**4c-3**, $C_{15}H_{13}ClN_4O_2S$)
Yield 80%; oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.22$ (t, $J = 6.8$ Hz, 2H), 3.60 (t, $J = 6.8$ Hz, 2H), 4.72 (s, 2H), 7.24–7.30 (m, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.43 (t, $J = 8.0$, 8.0 Hz, 1H), 7.74 (dd, $J = 2.4$, 8.4 Hz, 1H), 7.81 (t, $J = 2.0$ Hz, 1H), 7.84–7.91 (m, 1H), 8.41 (d, $J = 2.4$ Hz, 1H) ppm; IR (film): $\bar{\nu} = 1620$, 1597, 1520, 1236, 744, 688 cm^{-1}; HRMS calculated for $C_{15}H_{14}ClN_4O_2S$ $[M + H^+]$ 349.0526, found 349.0520.

2-[(4-Nitrophenyl)imino]-3-[(2-chloro-5-pyridyl)-methyl]thiazolidine (**4c-4**, $C_{15}H_{13}ClN_4O_2S$)
Yield 75%; mp 117.7–118.3°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.23$ (t, $J = 7.0$ Hz, 2H), 3.60 (t, $J = 7.0$ Hz, 2H), 4.72 (s, 2H), 7.00–7.06 (m, 2H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.71 (dd, $J = 2.4$, 8.4 Hz, 1H), 8.14–8.20 (m, 2H), 8.40 (d, $J = 2.4$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1611$, 1567, 1501, 1239, 854 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{14}ClN_4O_2S$ $[M + H^+]$ 349.0526, found 349.0542.

2-[[4-(Dimethylamino)phenyl]imino]-3-[(2-chloro-5-pyridyl)-methyl]thiazolidine (**4c-5**, $C_{17}H_{19}ClN_4S$)
Yield 68%; oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.91$ (s, 6H), 3.11 (t, $J = 6.8$ Hz, 2H), 3.46 (t, $J = 6.8$ Hz, 2H), 4.69 (s, 2H), 6.72 (d, $J = 9.0$ Hz, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 7.32 (d, $J = 8.2$ Hz, 1H), 7.75 (dd, $J = 2.4$, 8.2 Hz, 1H), 8.38 (d, $J = 2.4$ Hz, 1H) ppm; IR (film): $\bar{\nu} = 1620$, 1512, 1234, 822 cm^{-1}; HRMS calculated for $C_{17}H_{20}ClN_4S$ $[M + H^+]$ 347.1097, found 347.1087.

2-[(2-Methylphenyl)imino]-3-[(2-chloro-5-pyridyl)-methyl]thiazolidine (**4c-6**, $C_{16}H_{16}ClN_3S$)
Yield 80%; mp 113.3–113.9°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.17$ (s, 3H), 3.14 (t, $J = 7.0$ Hz, 2H), 3.53 (t, $J = 7.0$ Hz, 2H), 4.72 (s, 2H), 6.83 (d, $J = 8.0$ Hz, 1H), 6.98 (t, $J = 7.6$ Hz, 1H), 7.08–7.18 (m, 2H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.76 (dd, $J = 2.4$, 8.4 Hz, 1H), 8.40 (d, $J = 2.4$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1620$, 1589, 1237, 768 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{17}ClN_3S$ $[M + H^+]$ 318.0832, found 318.0838.

2-[(2,6-Dimethylphenyl)imino]-3-[(2-chloro-5-pyridyl)-methyl]thiazolidine (**4c-7**, $C_{17}H_{19}ClN_3S$)
Yield 79%; mp 62.6–63.8°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.12$ (s, 6H), 3.12 (t, $J = 7.0$ Hz, 2H), 3.56 (t, $J = 7.0$ Hz, 2H), 4.75 (s, 2H), 6.88 (t, $J = 7.4$ Hz, 1H), 7.01 (d, $J = 7.4$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.79 (dd, $J = 2.0$, 8.4 Hz, 1H), 8.43 (d, $J = 2.0$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1629$, 1588, 1228, 774 cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{19}ClN_3S$ $[M + H^+]$ 332.0988, found 332.0987.

2-[[2-(Trifluoromethyl)phenyl]imino]-3-[(2-chloro-5-pyridyl)-methyl]thiazolidine (**4c-8**, $C_{16}H_{13}ClF_3N_3S$)
Yield 83%; mp 87.1–88.4°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.17$ (t, $J = 7.0$ Hz, 2H), 3.56 (t, $J = 7.0$ Hz, 2H), 4.71 (s, 2H), 7.00 (d, $J = 8.0$ Hz, 1H), 7.10 (t, $J = 7.6$ Hz, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.78 (dd, $J = 2.4$, 8.4 Hz, 1H), 8.36 (d, $J = 2.4$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1618$, 1574, 1232, 761 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{14}ClF_3N_3S$ $[M + H^+]$ 372.0549, found 372.0557.

2-[[3-(Trifluoromethyl)phenyl]imino]-3-[(2-chloro-5-pyridyl)-methyl]thiazolidine (**4c-9**, $C_{16}H_{13}ClF_3N_3S$)
Yield 73%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.16$ (t, $J =$ 6.8 Hz, 2H), 3.53 (t, $J = 6.8$ Hz, 2H), 4.69 (s, 2H), 7.12 (d, $J = 7.6$ Hz, 1H), 7.21 (s, 1H), 7.28 (d, $J = 8.4$ Hz, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.38 (t, $J = 7.6$ Hz, 1H), 7.72 (dd, $J = 2.0$, 8.4 Hz, 1H), 8.39 (d, $J = 2.0$ Hz, 1H) ppm; IR (film): $\bar{\nu} =$ 1623, 1602, 1585, 1236, 799, 700 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{14}ClF_3N_3S$ $[M + H^+]$ 372.0549, found 372.0546.

2-[(2-Fluorophenyl)imino]-3-[(2-chloro-5-pyridyl)methyl]-thiazolidine (**4c-10**, $C_{15}H_{13}ClFN_3S$)
Yield 82%; mp 43.2–44.6°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.17$ (t, $J = 7.0$ Hz, 2H), 3.56 (t, $J = 7.0$ Hz, 2H), 4.73 (s, 2H), 6.94–7.10 (m, 4H), 7.34 (d, $J = 8.2$ Hz, 1H), 7.84 (dd, $J = 2.4$, 8.2 Hz, 1H), 8.39 (d, $J = 2.4$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1621$, 1584, 1236, 767 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{14}ClFN_3S$ $[M + H^+]$ 322.0581, found 322.0580.

2-[(4-Fluorophenyl)imino]-3-[(2-chloro-5-pyridyl)methyl]-thiazolidine (**4c-11**, $C_{15}H_{13}ClFN_3S$)
Yield 77%; mp 105.0–106.4°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.15$ (t, $J = 7.0$ Hz, 2H), 3.51 (t, $J = 7.0$ Hz, 2H), 4.69 (s, 2H), 6.85–6.93 (m, 2H), 6.93–7.01 (m, 2H), 7.33 (d, $J =$ 8.0 Hz, 1H), 7.73 (dd, $J = 2.4$, 8.0 Hz, 1H), 8.39 (d, $J = 2.4$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1618$, 1587, 1235, 837 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{14}ClFN_3S$ $[M + H^+]$ 322.0581, found 322.0590.

2-[(2,4-Difluorophenyl)imino]-3-[(2-chloro-5-pyridyl)-methyl]thiazolidine (**4c-12**, $C_{15}H_{12}ClF_2N_3S$)
Yield 81%; mp 96.6–98.0°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.18$ (t, $J = 7.0$ Hz, 2H), 3.56 (t, $J = 7.0$ Hz, 2H), 4.72 (s, 2H), 6.76–6.96 (m, 3H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.80 (dd, $J = 2.4$, 8.4 Hz, 1H), 8.39 (d, $J = 2.4$ Hz, 1H) ppm; IR(KBr): $\bar{\nu} = 1617$, 1586, 1237, 846, 812 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{13}ClF_2N_3S$ $[M + H^+]$ 340.0487, found 340.0479.

2-[(2,6-Difluorophenyl)imino]-3-[(2-chloro-5-pyridyl) methyl]thiazolidine (**4c-13**, $C_{15}H_{13}ClF_2N_3S$)
Yield 86%; mp 85.3–85.9°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.20$ (t, $J = 7.0$ Hz, 2H), 3.60 (t, $J = 7.0$ Hz, 2H), 4.76 (s, 2H), 6.84–7.00 (m, 3H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.87 (dd, $J = 2.4$, 8.4 Hz, 1H), 8.39 (d, $J = 2.4$ Hz, 1H) ppm; IR (KBr): $\bar{\nu} = 1614$, 1583, 1233, 750 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{13}ClF_2N_3S$ $[M + H^+]$ 340.0487, found 340.0496.

2-[(2-Chlorophenyl)imino]-3-[(2-chloro-5-pyridyl)methyl]-thiazolidine (**4c-14**, $C_{15}H_{13}Cl_2N_3S$)
Yield 81%; oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.16$ (t, $J = 7.0$ Hz, 2H), 3.56 (t, $J = 7.0$ Hz, 2H), 4.74 (s, 2H), 6.92–7.02 (m, 2H), 7.18 (ddd, $J = 1.2$, 7.6, 7.6 Hz, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.37 (dd, $J = 1.2$, 7.8 Hz, 1H), 7.89 (dd, $J = 2.4$, 8.0 Hz, 1H), 8.42 (d, $J = 2.4$ Hz, 1H) ppm; IR (film): $\bar{\nu} = 1621$, 1581, 1235, 760 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{14}Cl_2N_3S$ $[M + H^+]$ 338.0285, found 338.0290.

2-[(4-Chlorophenyl)imino]-3-[(2-chloro-5-pyridyl)methyl]-thiazolidine (**4c-15**, $C_{15}H_{13}Cl_2N_3S$)
Yield 81%; mp 88.0–88.8°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.16$ (t, $J = 6.8$ Hz, 2H), 3.52 (t, $J = 6.8$ Hz, 2H), 4.69 (s, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 7.24 (d, $J = 8.6$ Hz, 2H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.72 (dd, $J = 2.2$, 8.4 Hz, 1H), 8.38 (d, $J = 2.2$ Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 26.86$, 46.89, 50.23, 123.19, 124.36, 128.36, 128.95, 131.67, 138.98, 149.39, 150.27, 150.80, 159.17 ppm; IR (KBr): $\bar{\nu} = 1608$, 1582, 1237, 835 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{14}Cl_2N_3S$ $[M + H^+]$ 338.0285, found 338.0290.

Biological Assay

The herbicidal activities of compounds **4** were evaluated with a previously reported procedure [17]. Each sample was dissolved in *DMF*, and then the solution was diluted with emulsifier 0201 (a mixture of anionic and nonionic surfactant) containing 0.1 mg/cm^3 H_2O until the required concentration was achieved. The biological tests were carried out in plastic boxes. Nineteen milliliters of 0.9% thawed water agar and 1 cm^3 of diluted solution were added to the plastic boxes and shaken. After the drug-containing agar was cool, the seeds of *Echinochloa crusgalli*, *Sorghum vulgare*, *Digitaria sanguin-*

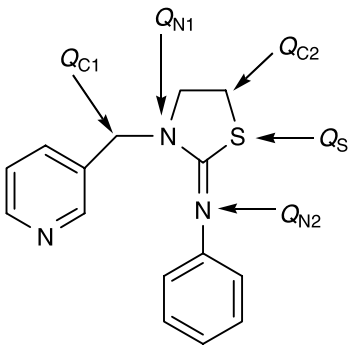


Fig. 1. Demonstration of the net-charge (*e.g.*, compound **4a-1**)

nalis, *Eclipta prostrasta*, *Cucumis sativus*, and *Brassica campestris* were sowed, and then the cultivations were kept at $24 \pm 1°C$ with exposure to light of 3000 $1\times$ for 7 days. The growth inhibitory rates (%) of compounds **4** related to the control were determined (Table 1). The experiments were conducted in three replicates with 150 seeds per plant for each concentration. The herbicidal activity (Table 2) was expressed in terms of *HA* by the formula [18]

$$HA = \lg[a/(100 - a)] + \lg M_w$$

where a indicates the growth inhibitory rates (%) and M_w indicates the molecular weight of the tested compounds.

Descriptor Variables

The molecular total energy (E_T), the net charges on N, S, and C atom (Q_N, Q_S, and Q_C) (Fig. 1), the volume *V,* and the molecular hydrophobicity parameter (lg *P*) were calculated with Hyperchem Software (2002 edition) of Hypercube, Inc. Also, the energy of the highest occupied molecular orbital (E_{HOMO}) and the energy of the lowest unoccupied molecular orbital (E_{LUMO}) were calculated. However, the latter two parameters were not listed here because they gave poor correlations with herbicidal activity. Before all parameters of a compound were calculated, its spatial molecular conformation was also optimized with Hyperchem to acquire its most relaxed conformation. All descriptor data are listed in Table 3. In addition, the molecular shape parameters such as surface area, angle, and length were calculated by using a molecular modeling program, PCMODEL (6th edition) of Serena Software based on the most optimized conformation, which showed poor correlations with herbicidal activity and were not listed.

Multiple Linear Regression (MLR) Analysis

The regression analysis was done with a computer software package Origin (version 7.0) of Microcal Software, Inc. The regression was done in a stepwise manner, with the parameter minimizing the sum of squared deviations being introduced step-by-step and the analysis being stopped when the introduction of the new parameter was no longer statistically significant as evidenced by *F*-test.

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