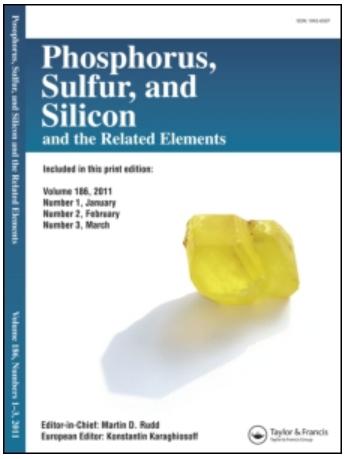

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis and Biological Activity of Novel Symmetrical Bis-2-phenyliminothiazolidine Derivatives

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To cite this Article Li, Gang-Yue , Qian, Xu-Hong , Yan, Sheng-Gang , Cui, Jing-Nan , Huang, Qing-Chun , Zhang, Rong , Liu, Feng-Yu and Cui, Da-Wei(2006) 'Synthesis and Biological Activity of Novel Symmetrical Bis-2-phenyliminothiazolidine Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 12, 2851 — 2861

To link to this Article: DOI: 10.1080/10426500600865103

URL: http://dx.doi.org/10.1080/10426500600865103

Phosphorus, Sulfur, and Silicon, 181:2851–2861, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500600865103

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Received February 26, 2006; accepted May 4, 2006.
This project was supported by the National Key Project for Basic Research (2003CB114400) and the National Natural Science Foundation of China.
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A series of novel symmetrical bis-2-phenyliminothiazolidine derivatives were designed and synthesized. The structures of all the title compounds were characterized by ^{1}H NMR and, in some cases, by ^{13}C NMR, IR, and high-resolution mass spectra. Herbicidal activities were examined, and some of these compounds showed selectively herbicidal activity against Triticum aestivum*. The type of linker between the two 2-phenyliminothiazolidines was crucial for the biological activities.*

Keywords Bis-2-phenyliminothiazolidine; herbicidal activity; selectivity; synthesis

INTRODUCTION

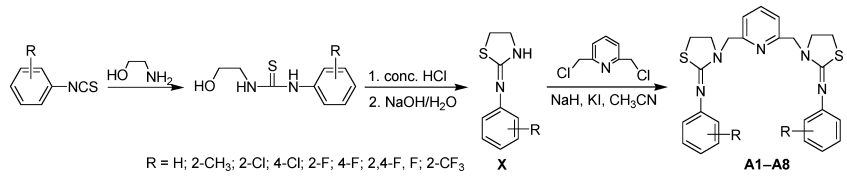
With the occurrence of herbicide-resistant weeds,[1] it is necessary to develop efficient herbicides with novel structures or modes of action. Heterocycle compounds play a very important role in drug design and synthesis, owing to their unique bioactivities. Nitrogen- and sulfur-containing heterocycle compounds, 2-iminothiazolidine derivatives, have gained much interest as potent inhibitors of indoleethylamine N-methyltransferase,[2–3] octopaminergic-agonists,[4–5] anthelmintics,[6–7] diuretic agents,[8] trehalase inhibitors,[9–11] and insecticidal agents.[12] However, few 2-iminothiazolidine derivatives with herbicidal activity were reported, and these mainly involved 2-acyliminothiazolidines, 2-sulfonyliminothiazolidines, and 2-phenyliminothiazolidines.[13] It was presumed that this class of compounds probably possesses herbicidal activities.

Linking two pharmacophores to obtain high bioactivity or selectivity is a common method in the design of new pharmaceuticals and agrochemicals.[14–18] Herein, we designed and synthesized a series of novel symmetrical bis-2-phenyliminothiazolidine derivatives by adopting 2,6-dimethylenepyridine and a di-thiourea group containing a benzene ring as the linker between two 2-phenyliminothiazolidines. The results of the bioassay showed that some of these compounds exhibited selective herbicidal activity against *Triticum aestivum*.

RESULTS AND DISCUSSION

Synthesis

2-Phenyliminothiazolidines intermediates **X** were prepared, as shown in Scheme 1, according to the reported procedure.[19] The reaction of ethanolamine with aryl isothiocyanates gave thioureas, which were directly used in the next step. The cyclization of thioureas and concentrated HCl and then the neutralization with aqueous 10 M NaOH gave the required 2-phenyliminothiazolidines **X** in the range of 85–99%



SCHEME 1 The synthetic scheme for compounds **A**.

yields, which were also used directly in the next step without further purification.

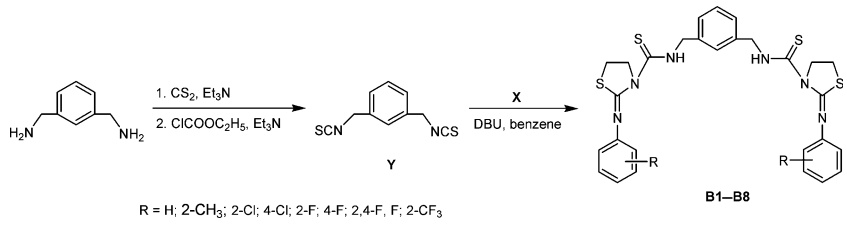
Target compounds **A** were prepared by the reaction of 2,6-dichloromethylpyridine with the anion of 2-phenyliminothiazolidines, which were generated by a treatment of 2-phenyliminothiazolidines with sodium hydride in dry acetonitrile (Scheme 1).

Syntheses of target compounds **B** needed the key intermediate *m*-xylylenediisothiocyanate **Y**, which was commonly prepared by the reaction of carbon disulfide and dicyclohexylcarbodiimine in Et_2O, but with a low yield. Therefore, we adopted a different method as shown in Scheme 2. The reaction of *m*-xylylenediamine with carbon disulfide in the presence of triethylamine gave the corresponding triethylammonium dithiocarbamate salt. After slowly adding ethyl chloroformate with an ice-bath cooling, *m*-xylylenediisothiocyanate **Y** was obtained in an 81% yield.

The target compounds **B** were prepared as shown in Scheme 2. The reaction of *m*-xylylenediisothiocyanate **Y** with the corresponding 2-phenyliminothiazolidines **X** using DBU as a catalyst gave compounds **B** in a 66–99% yield. The structures of all the target compounds were well characterized by ^{1}H NMR and, in some cases, by ^{13}C NMR, IR, and high-resolution mass spectra (HRMS) (Tables I and II).

Biological Activity

Herbicidal activities against *Setaria viridis*, *Eclipta prostrasta*, *Cucumis sativus*, *Chenopodum serotinum*, *T. aestivum* and *Amaranthus*



SCHEME 2 The synthetic scheme for compounds **B**.

TABLE I Experimental Data of Target Compounds

Compound	R	Yield (%)[a]	M.P. (°C)	Molecular Formula	HRMS[M + H$^+$] Calculated	HRMS[M + H$^+$] Found
A1	H	37	96.5–97.9	$C_{25}H_{25}N_5S_2$	460.1630	460.1640
A2	2-CH_3	33	109.5–110.5	$C_{27}H_{29}N_5S_2$	488.1943	488.1939
A3	2-Cl	33	161.0–162.2	$C_{25}H_{23}Cl_2N_5S_2$	528.0850	528.0864
A4	4-Cl	35	145.5–146.9	$C_{25}H_{23}Cl_2N_5S_2$	528.0850	528.0841
A5	2-F	34	133.5–135.0	$C_{25}H_{23}F_2N_5S_2$	496.1441	496.1452
A6	4-F	30	133.9–135.3	$C_{25}H_{23}F_2N_5S_2$	496.1441	496.1454
A7	2,4-F, F	34	109.2–110.5	$C_{25}H_{21}F_4N_5S_2$	532.1253	532.1245
A8	2-CF_3	29	114.3–115.5	$C_{27}H_{24}F_6N_5S_2$	596.1377	596.1371
B1	H	84	147.9–149.0	$C_{28}H_{28}N_6S_4$	577.1337	577.1341
B2	2-CH_3	87	116.5–118.0	$C_{30}H_{32}N_6S_4$	605.1650	605.1642
B3	2-Cl	99	129.0–130.4	$C_{28}H_{26}Cl_2N_6S_4$	645.0557	645.0545
B4	4-Cl	71	138.0–139.4	$C_{28}H_{26}Cl_2N_6S_4$	645.0557	645.0563
B5	2-F	97	164.7–166.7	$C_{28}H_{26}F_2N_6S_4$	613.1148	613.1130
B6	4-F	99	168.7–170.3	$C_{28}H_{26}F_2N_6S_4$	613.1148	613.1130
B7	2,4-F, F	89	167.4–168.9	$C_{28}H_{24}F_4N_6S_4$	649.0926	649.0942
B8	2-CF_3	66	146.3–147.8	$C_{30}H_{27}F_6N_6S_4$	713.1084	713.1065

[a]Yield determined by isolation based on **X**.

mangostanus were measured according to the method described in the experimental section. Among all the compounds, **A3**, **A4**, **A5**, and **A6** possessed selective herbicidal activities against *T. aestivum* instead of *S. viridis*, *E. prostrasta*, *C. sativus*, *C. serotinum*, and *A. mangostanus*. The herbicidal activity of **A5** against *T. aestivum* reached 86% at 500 mg L^{-1}.

From these results, it was found that the type of linker between the two 2-phenyliminothiazolidines was crucial for biological activities. In study on pharmaceuticals and agrochemicals, the introduction of pyridine into a parent compound may improve biological activities of the compounds.[20–22] Most compounds **A** with the pyridine linker exhibited selective herbicidal activity against *T. aestivum*, but compounds **B** exhibited a loss of bioactivity owing to an increase in the length and rigidity of the linker.

In addition, we studied on the relationship between the type of substituent R on a phenyl ring and biological activities. Compounds with a halogen-substituted phenyl ring showed good biological activities (**A3**, **A4**, **A5**, and **A6**), but the compounds with a poly-fluorine–substituted phenyl ring showed a loss of biological activities (**A7**). This is probably because the fluorine atom is a lipophilic group, and the introduction of poly-fluorine excessively decreases the hydrophilicity of the molecule and furthers the bioactivities. Further research on the modification of the structure is proceeding.

TABLE II IR and ^{1}H NMR Data of Target Compounds

Compound	IR ν_{max}(KBr,cm^{-1})	^{1}H NMR or ^{13}C NMR δ (ppm, $CDCl_3$/TMS)
A1	1641, 1589, 1239, 1143, 764, 696	3.18 (t, J = 7.0 Hz, 4H), 3.70 (t, J = 7.0 Hz, 4H), 4.86 (s, 4H), 6.95 (d, J = 8.0 Hz, 4H), 7.04 (t, J = 7.6 Hz, 2H) 7.26–7.34 (m, 6H), 7.68 (t, J = 7.6 Hz, 1H)
A2	1632, 1592, 1232, 1143, 763	2.12 (s, 6H), 3.17 (t, J = 6.8 Hz, 4H), 3.75 (t, J = 6.8 Hz, 4H), 4.87 (s, 4H), 6.85 (d, J = 7.6 Hz, 2H), 6.96 (t, J = 7.6 Hz, 2H), 7.08–7.16 (m, 4H), 7.33 (d, J = 7.6 Hz, 2H), 7.68 (t, J = 7.6 Hz, 1H)
A3	1637, 1578, 1232, 1142, 761	3.21 (t, J = 6.8 Hz, 4H), 3.82 (t, J = 6.8 Hz, 4H), 4.96 (s, 4H), 6.94–7.04 (m, 4H), 7.18 (t, J = 7.2 Hz, 2H), 7.36 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 7.2 Hz, 2H), 7.75 (t, J = 7.2 Hz, 1H)
A4	1608, 1581, 1231, 1131, 831	^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 27.10, 51.19, 51.74, 121.14, 123.07, 123.93, 127.19, 127.45, 129.65, 137.56, 149.12, 156.51, 159.69 3.18 (t, J = 6.8 Hz, 4H), 3.71 (t, J = 6.8 Hz, 4H), 4.83 (s, 4H), 6.87 (d, J = 8.4 Hz, 4H), 7.22 (d, J = 8.4 Hz, 4H), 7.28 (d, J = 7.6 Hz, 2H), 7.68 (t, J = 7.6 Hz, 1H)
A5	1633, 1603, 1244, 1145, 753	3.20 (t, J = 7.0 Hz, 4H), 3.77 (t, J = 7.0 Hz, 4H), 4.89 (s, 4H), 6.90–7.10 (m, 8H), 7.37 (d, J = 7.6 Hz, 2H), 7.70 (t, J = 7.6 Hz, 1H)
A6	1619, 1574, 1232, 1150, 838	3.17 (t, J = 7.0 Hz, 4H), 3.71 (t, J = 7.0 Hz, 4H), 4.83 (s, 4H), 6.84–6.91 (m, 4H), 6.96 (t, J = 8.4 Hz, 4H), 7.29 (d, J = 7.6 Hz, 2H), 7.68 (t, J = 7.6 Hz, 1H)
A7	1624, 1591, 1242, 1138, 846, 816	3.21 (t, J = 7.0 Hz, 4H), 3.77 (t, J = 7.0 Hz, 4H), 4.86 (s, 4H), 6.73–6.85 (m, 4H), 6.86–6.95 (m, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.70 (t, J = 7.6 Hz, 1H)
A8	1640, 1598,1234, 1121, 758	3.20 (t, J = 6.8 Hz, 4H), 3.76 (t, J = 6.8 Hz, 4H), 4.85 (s, 4H), 7.02 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.57 (d, J = 7.6 Hz, 2H), 7.71 (t, J = 7.6 Hz, 1H)
B1	1604, 1584, 1243, 1171, 762, 693	^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 27.09, 50.98, 51.70, 120.98, 122.40, 122.74, 122.80(d, J = 28.75 Hz), 124.23(d, J = 271.25 Hz), 126.28(d, J = 5.0 Hz), 132.35, 137.57, 150.52, 156.49, 158.90 3.12 (t, J = 7.0 Hz, 4H), 4.84 (t, J = 7.0 Hz, 4H), 4.89 (d, J = 4.4 Hz, 4H), 6.89 (d, J = 7.6 Hz, 4H), 7.14 (t, J = 7.6 Hz, 2H), 7.22–7.38 (m, 8H), 12.59 (s, 2H, –NH)
B2	1610, 1594, 1238, 1174, 761	^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 25.08, 49.65, 54.96, 121.28, 125.08, 126.56, 126.71, 129.03, 129.22, 137.58, 148.44, 158.64, 180.17 1.98 (s, 6H), 3.12 (t, J = 7.0 Hz, 4H), 4.83–4.90 (m, 8H), 6.82 (d, J = 8.0 Hz, 2H), 7.04 (t, J = 6.8 Hz, 2H), 7.10–7.17 (m, 4H), 7.22–7.26 (m, 3H), 7.31 (s, 1H), 12.59 (s, 2H, –NH)

(Continued on next page)

TABLE II IR and ^{1}H NMR Data of Target Compounds (*continued*)

Compound	IR ν_{max}(KBr,cm^{-1})	^{1}H NMR or ^{13}C NMR δ (ppm, $CDCl_3$/TMS)
B3	1614, 1586, 1235, 1176, 749	3.14 (t, J = 7.0 Hz, 4H), 4.82–4.98 (m, 8H), 6.96 (d, J = 7.6 Hz, 2H), 7.04 (t, J = 7.6 Hz, J = 8.0 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H), 7.23–7.28 (m, 3H), 7.32–7.37 (m, 3H), 12.40 (s, 2H, –NH)
B4	1614, 1592, 1244, 1174, 820	3.14 (t, J = 7.0 Hz, 4H), 4.80–4.90 (m, 8H), 6.81 (d, J = 8.8 Hz, 4H), 7.20–7.33 (m, 8H), 12.42 (s, 2H, –NH)
B5	1615, 1555, 1236, 1181, 760	3.16 (t, J = 7.0 Hz, 4H), 4.84–4.92 (m, 8H), 6.92–6.98 (m, 2H), 7.03–7.11 (m, 6H), 7.24–7.28 (m, 3H), 7.34 (s, 1H), 12.47 (s, 2H, –NH)
B6	1603, 1589, 1246, 1180, 837	3.13 (t, J = 7.0 Hz, 4H), 4.78–4.94 (m, 8H), 6.80–6.88 (m, 4H), 6.96–7.04 (m, 4H), 7.21–7.31 (m, 3H), 7.33 (s, 1H), 12.50 (s, 2H, –NH)
B7	1618, 1553, 1240, 1177, 845, 810	3.17 (t, J = 7.0 Hz, 4H), 4.84–4.92 (m, 8H), 6.78–6.95 (m, 4H), 7.22–7.30 (m, 5H), 7.32 (s, 1H), 12.40 (s, 2H, –NH)
B8	1613, 1596, 1247, 1158, 767	3.15 (t, J = 7.0 Hz, 4H), 4.80–4.94 (m, 8H), 7.00 (d, J = 8.0 Hz, 2H), 7.17–7.24 (m, 5H), 7.28 (s, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 12.14 (s, 2H, –NH)

From the results shown in Table IV, it was found that compounds **A** and **B** exhibited different electronic properties, hydrophobicity, and spatial properties owing to the linker's variation and substituents on the phenyl ring. Compounds **A** presented a smaller molecular volume, a bigger dipole moment, higher energy of the lowest unoccupied molecular orbital, higher net charges on the N1 atom, and lower net charges on the N2 atom than compounds **B**, and these might be the reasons that compounds **A** were active but compounds **B** were inactive. In addition, the values of lg P, E_L, Q_{N1}, and Q_{N2} of compounds with bioactivity remained in the range from 2.32 to 3.07,

TABLE III Herbicidal Activities of Compounds[a] at 500 mg L^{-1}

		Average Growth Inhibitory Rate (%)
Compound	R	Triticum aestivum
A3	2-Cl	53
A4	4-Cl	73
A5	2-F	86
A6	4-F	48

[a]The results of effective compounds were listed.

TABLE IV The Molecular Parameters of Target Compounds

		Descript parameters								
Compound	R	lg P	V ($Å^3$)	E_T (a.u.)	E_H (eV)	E_L (eV)	Dipole (Db)	Q_S	Q_{N1}	Q_{N2}
A-1	H	3.52	1183.10	−166.2534	−8.4210	−0.3983	6.387	0.0321	−0.0405	−0.1157
A-2	2-CH_3	3.83	1252.67	−177.3462	−8.3594	−0.3631	6.428	0.0314	−0.0389	−0.1093
A-3	2-Cl	3.07	1244.20	−188.4056	−8.4919	−0.4894	6.211	0.0327	−0.0479	−0.1243
A-4	4-Cl	3.07	1269.08	−188.4077	−8.5681	−0.5401	8.102	0.0346	−0.0433	−0.1233
A-5	2-F	2.32	1193.37	−197.4737	−8.4980	−0.5066	6.476	0.0308	−0.0475	−0.1209
A-6	4-F	2.32	1199.40	−197.4777	−8.6139	−0.5652	8.610	0.0337	−0.0437	−0.1234
A-7	2,4-F,F	1.11	1208.77	−228.6941	−8.6661	−0.6859	9.542	0.0324	−0.0501	−0.1277
A-8	2-CF_3	4.66	1299.16	−270.9710	−8.5978	−0.6552	6.465	0.0368	−0.0601	−0.1505
B-1	H	5.11	1343.47	−200.5508	−8.5654	−1.1345	0.7275	0.0405	−0.1613	−0.0426
B-2	2-CH_3	5.42	1422.19	−211.5482	−8.4635	−1.0401	0.6199	0.0368	−0.1406	−0.0507
B-3	2-Cl	4.67	1410.78	−222.7057	−8.5464	−1.1002	1.756	0.0376	−0.1528	−0.0568
B-4	4-Cl	4.67	1421.97	−222.7043	−8.6488	−1.2298	0.8321	0.0421	−0.1719	−0.0479
B-5	2-F	3.91	1355.83	−231.7742	−8.6096	−1.1582	2.844	0.0397	−0.1733	−0.0474
B-6	4-F	3.91	1359.52	−231.7740	−8.7004	−1.2831	0.5196	0.0404	−0.1615	−0.0483
B-7	2,4-F,F	2.71	1370.61	−262.9953	−8.7255	−1.3173	2.224	0.0401	−0.1819	−0.0527
B-8	2-CF_3	6.25	1458.93	−305.7674	−8.5282	−1.1148	4.059	0.0377	−0.1488	−0.0968

from −0.5652 to −0.4894, from −0.0433 to −0.0479, and from −0.1243 to −0.1209, respectively. This indicated that for compounds possessing bioactivity, it was necessary that their electronic parameters and hydrophobicity lie in a suitable range.

CONCLUSIONS

In conclusion, we have demonstrated that the novel symmetrical bis-2-phenyliminothiazolidine derivatives with a pyridine linker presented selective herbicidal activity against *T. aestivum*. It was found that the activity of such compounds against *T. aestivu* could be strongly related to the electronic properties and hydrophobicity. Future structural modification and biological evaluation should be carried out to explore the full potential of this novel class of herbicidal molecules.

EXPERIMENTAL

Melting points were obtained with an X-6 micro-melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 20DXB FT-IR spectrometer using potassium bromide pellets or films. ^{1}H NMR spectra were measured on a Varian INOVA-400 spectrometer with chemical shifts reported as an parts per million (in $CDCl_3$, TMS as an internal standard). ^{13}C NMR spectra were measured on a Bruker AVANCE-500 spectrometer (in $CDCl_3$, TMS as internal standard). Mass spectra were measured on an HP 1100 LC-MSD HRMS were obtained on an HPLC-Q-Tof MS (micro) spectrometer. Flash chromatography was performed on silica gel. All of the solvents were analytical grade. All chemicals or reagents were purchased from standard commercial suppliers.

General Synthetic Procedure for 2-Phenyliminothiazolidines X

To a solution of ethanolamine (0.305 g, 5.0 mmol) in 50 mL of chloroform was added dropwise the corresponding aryl isothiocyanate (5.0 mmol) over a period of 10 min, and the mixture was stirred at r.t. for about 2 h. Then the solvent was evaporated under vacuum, and the residue was washed with diethyl ether and water to afford thiourea, which was used directly in the next step without further purification. The corresponding thiourea (5.0 mmol) was dissolved in hydrochloric acid (10 mL) and heated at 90°C for 45 min. The mixture cooled in an ice bath was basified with 10 M NaOH. The precipitated residue was filtered and washed with water to give a white solid **X** in an 85–99% yield.

The Synthesis of M-xylylenediisothiocyanate Y

m-Xylylenediamine (6.8 g, 50 mmol) was dissolved in anhydrous diethyl ether or the minimum amount of benzene and reacted with carbon disulfide (9.12 g, 120 mmol) and triethylamine (10.1 g, 100 mmol) at r.t. After complete precipitation of the triethylammonium dithiocarbamate salt, the mixture was filtered. The solid was washed with anhydrous diethyl ether and air dried for about 10 min. Then the solid was dissolved in chloroform (50 mL), treated with triethylamine (10.1 g, 100 mmol), and cooled to 0°C. To this solution was added ethyl chloroformate (10.8 g, 100 mmol) dropwise over a 15-min period with violent stirring. The mixture was allowed to warm to r.t. and was stirred for about 1 h. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel by using petroleum ether/dichloromethane (5/1, v/v) as an eluent to give **Y** in an 81% yield.

General Synthetic Procedure for the Target Compounds A

2-Phenyliminothiazolidine (10 mmol) was added to a suspension of sodium hydride (0.6 g, 25 mmol) in dry acetonitrile (15 mL) and DMF (0.5 mL). After stirring for 0.5 h at r.t. a solution of 2,6-dichloromethylpyridine (5 mmol) in dry acetonitrile (10 mL) and a little KI as a catalyst were added. The reaction was refluxed for 3–8 h. The solvent was distilled off under reduced pressure, and the residue was purified by silica column with 20% acetone/petroleum ether as an eluent to give white solid **A** in a 29–37% yield.

General Synthetic Procedure for the Target Compounds B

A mixture of *m*-xylylene diisothiocyanate **Y** (0.22 g, 1.0 mmol) and 2-phenyliminothiazolidines **X** (2.0 mmol) in benzene (25 mL) was refluxed for about 1 h with a drop of DBU (1,8-diaza-bicyclo [5.4.0]undec-7-ene) as a catalyst. The excess of benzene was then distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel by using dichloromethane as an eluent to give the white solid **B** in a 66–99% yield.

Biological Assay and Molecular Parameters

The herbicidal activities of the target compounds were measured with the method described as follows. Each sample was dissolved in DMF, and then the solution was diluted with emulsifier 0201 (a mixture of anionic and nonionic surfactant) containing water (0.1 g L^{-1}) until the

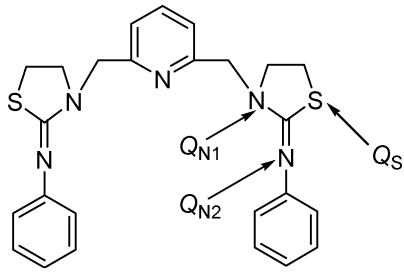


FIGURE 1 The demonstration of the net charge (e.g., compound **A-1**).

required concentration was achieved. The biological tests were carried out in plastic boxes. Nineteen mL of 0.9% thawed water agar and 1 mL of diluted solution were added to the plastic boxes and shaken. After the drug-containing agar was cool, the seeds of *S. viridis, E. prostrasta, C. sativus, C. serotinum, T. aestivum*, and *A. mangostanus* were sowed, and then the cultivations were kept at $24 \pm 1^{\circ}$C with exposure to light of 3000 LX for 7 days. The growth inhibitory rates (%) of the target compounds related to the control were determined. The results of compounds demonstrating activity are listed in Table III.

The molecular total energy (E_T), the energy of the highest occupied molecular orbital (E_{HOMO}), energy of the lowest unoccupied molecular orbital (E_{LUMO}), net charges on the N and S atom (Q_N and Q_S) (Figure 1), dipole moment, volume V, and the molecular hydrophobicity parameter (lg P) were calculated with Hyperchem Software (2002 edition) of Hypercube, Inc. Before all parameters of a compound were calculated, its spatial molecular conformation was also optimized with Hyperchem to acquire its lowest energy conformation. All descriptor data are listed in Table IV.

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