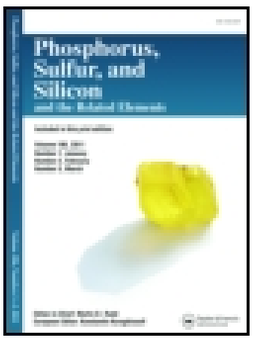

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Synthesis and Biological Activity of Novel Sulfone Derivatives Containing a [1,2,4]Triazolo[4,3-a]pyridine Moiety

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ABSTRACT:

A series of novel sulfone derivatives containing a [1,2,4]triazolo[4,3-a]pyridine moiety was synthesized and characterized via ^{1}H NMR, ^{13}C NMR, IR and elemental analyses. Bioassay results indicated some of the derivatives displayed good antifungal activities and insecticidal activity. The inhibition rates of 8-chloro-3-((2,6-difluorobenzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine against *Rhizotonia erealis* and *Helminthosporium maydis* were 78.6% and 76.4% activities at 50 μg mL^{-1}, respectively. And compound 8-chloro-3-(((6-chloropyridin-3-yl)methyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine showed >

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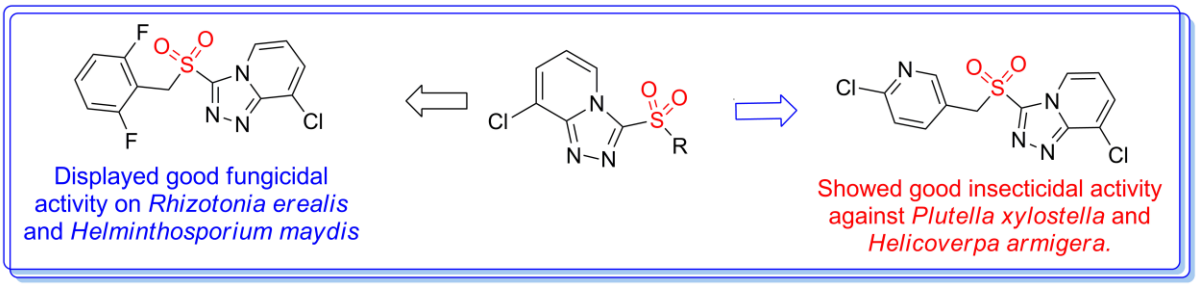
95% mortality at 500 μg mL^{-1} and > 65% mortality at 200 μg mL^{-1} against *Plutella xylostella*, respectively. As well as 8-chloro-3-(((6-chloropyridin-3-yl)methyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine displayed > 90% mortality at 500 μg mL^{-1} against *Helicoverpa armigera*. A preliminary structure activity relationship (SAR) is discussed.

Graphical Abstract



Keywords

Sulfone; [1,2,4]Triazolo[4,3-a]pyridine; Synthesis; Antifungal activity; Insecticidal activity

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INTRODUCTION

Food safety is one of the serious problems humans will be facing in the future, and threats from crop diseases, weeds and insects are still considerable. In recent years, scientists dedicate in developing active molecules with new mechanisms and eco-friendly properties, and we believe the discovery of high efficient pesticide with low mammalian toxicity and low-residue can make a significant contribution to the lifestyle in the future.

Sulfone derivatives are an important class of bioactive compounds with a wide spectrum of activities. They are employed as anti-inflammatory [1, 2], anti-cancer [3-7], anti-HIV-1[8, 9] agents for pharmaceutical application or insecticides [10], herbicides [11], fungicide[11-14] and anti-bacterial agents [15-19] for crop protection. Especially, in the field of pesticides, several sulfone derivatives were discovered and commercialized, such as flubendiamide (Fig. 1), the first ryanodine receptor inhibitor, was discovered and commercialized by Japanese Pesticide Co., Ltd and Bayer Crop Science. In recent years, Song and co-workers [14-19] reported several series of sulfone derivatives displayed excellent anti-fungal and anti-bacteria activities, such as “jiahuangxianjunzuo (A)”, “erlv’ezuoling (B)” and “fubian’ezuofeng (C)” (Figure 1). These three sulfone derivatives, containing an 1,3,4-oxadiazole moiety, were developed and are under the process of commercialization.

The [1,2,4]triazolo[4,3-a]pyridines, an important class of fused heterocycle, possess a broad spectrum of biological and pharmaceutical activities[20-25], which have proven attractive because of their good herbicidal activity [23,] antifungal activity [24-26], anticonvulsant activity [27], and antibacterial activity [28, 29].

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Keeping the above aspects in the mind, a series of new sulfone derivatives containing a [1,2,4]triazolo[4,3-a]pyridine moiety was designed and synthesized. The antifungal activity against *Rhizotonia erealis*, *Rhizoctonia solani*, *Helminthosporium maydis* and *Fusarium graminearum*, as well as the insecticidal insecticidal activities against *Plutella xylostella* and *Helicoverpa armigera*. of these target compounds were evaluated and reported in this paper. To the best of our knowledge, this is the first report on antifungal and insecticidal activities of sulfones derivatives with scaffold of [1,2,4]triazolo[4,3-a]pyridine to date.

RESULTS AND DISCUSSION

Synthesis

The synthetic route of the sulfone derivatives containing a [1,2,4]triazolo[4,3-a]pyridine moiety is shown in **Scheme 1**. Firstly, 3-chloro-2-hydrazinylpyridine (**2**) was prepared by treatment of 2,3-dichloropyridine (**1**) with hydrazine hydrate (80%) in good yield. Then, 8-chloro-[1,2,4]triazolo[4,3-a]pyridine-3-thiol (**3**) was synthesized via ring-closure reaction of 3-chloro-2-hydrazinylpyridine **2** with CS_2 in the present of NaOH [30]. Subsequently, thioetherification of 8-chloro-[1,2,4]triazolo[4,3-a]pyridine-3-thiol were carried out by treatment of intermediate **3** with different halogenated hydrocarbon in the presence of K_2CO_3 in excellent yields. Finally, the title compounds **5a** to **5s** were synthesized in moderate to good yields via oxidation reaction using H_2O_2 as an oxidizing agent and ammonium molybdate as the catalyst as described in our previous work [31,32].

The structures of the synthesized compounds (**5a** to **5s**) were established on the basis of the spectroscopic data. Using **5d** as an example, as indicated by ^{1}H NMR, the proton at *o*-position of

"N" atom was at δ 8.34 ppm as a doublet with a coupling constant of 6.9 Hz. The proton adjacent to the "Cl" atom was at δ 7.52 ppm, with a coupling constant of 7.2 Hz; resonance frequencies of the proton at *m*-position of "Cl" atom appeared at δ 6.91 ppm as a triplet with "J = 7.1 Hz"; and the protons at benzene ring were near 7.34 -- 7.27 ppm. The main characteristic of the ^{1}H NMR spectra for the compounds was the presence of a singlet at 4.99 ppm for -CH_2-$S(O)_2$- protons. In the ^{13}C NMR spectra of compounds containing the "F", the carbons were split into a multiplet. For instance, in ^{13}C NMR spectra of compounds **4i** and **5j**, the resonance frequencies of the carbons of "-CF_3" near 126.5 ppm appear as a quartet with the coupling constant ($^{1}J_{C\text{-}F}$) of 114.3 Hz. In the ^{13}C NMR spectra of compounds that contain two fluorine atoms (**5k**, **5l** and **5m**), the carbon resonance frequencies were near δ_C 150-163 ppm as doublets with coupling constants ($^{1}J_{C\text{-}F}$) ranging from 241 to 257 Hz.

Antifungal activity

The antifungal activities of the synthesized compounds on *R. erealis, H. maydis, Rhizoctonia solani, F. graminearum* were tested and shown in **Table S 1** (see Supplemental Materials). The results indicated the synthesized compounds exhibited weak to good antifungal activities against the tested fungus at 50 μg/mL; compounds **5c**, **5d**, **5j**, **5k**, **5l**, **5m**, **5n**, **5o**, and **5q** showed > 50% activities against both *R. erealis* and *H. maydis.* Moreover, The EC_{50} of **5l** and **5m** against *R. erealis, H. maydis, R. solani* were further evaluated (**Table S 2**), which indicated that **5l** and **5m** showed range from 39.3 to 53.6 mg/L.

Insecticidal activity

The insecticidal activities of the synthesized compounds against *P. xylostella* and *H. armigera* are presented in **Table S 3** and **Table S 4**. Most of the title compounds displayed weak insecticidal activity against the *P. xylostella*. However, some of the compounds displayed good insecticidal activities. More detail can be found in Supplemental Information.

A preliminary structure activity relationship (SAR) was analyzed based on these insecticidal activity data against both *P. xylostella* and *H. armigera*. The results indicated these compounds containing a pyridine (**5d**) showed good insecticidal activities; and the introduction of a trifluoromethyl at **2** position of benzene could offer a big increase to insecticidal activity, which can be concluded from the t the fact that the activity of **5j** was much higher than that of **5i** and **5r.** And interestingly, in contrast to the above antifungal activity, the insecticidal activity could be decreased by introducing two fluorines at benzene, and the introduction of different halogens at benzene ring (*eg*: **5n**, **5p**) was disadvantageous to enhance their insecticidal activities. Moreover, just as with the antifungal activity, the introduction of alkyl and substituted alkene could not improve the insecticidal activity.

CONCLUSION

In conclusion, a series of novel sulfone derivatives containing a [1,2,4]triazolo[4,3-a]pyridine moiety was synthesized, characterized, and bio-assayed for their antifungal and insecticidal activities. Results of bioassays indicated that the synthesized compounds showed weak to good antifungal activity against *R. erealis, H. maydis, R. solani, F. graminearum,* such as compound **5m** exhibited 78.6% and 76.4% activities against *R. erealis* and *H. maydis*, respectively. And

compounds **5d** and **5j** displayed good insecticidal activities against both *P. xylostella* and *H. armigera*, The preliminary SAR study indicated that antifungal activities could be enhanced by introducing two fluorine atoms at benzene ring, and the introduction of heterocyclic rings was favorable to the insecticidal activity. Moreover, the introduction of alkyl and substituted alkene could not improve both the antifungal activity and insecticidal activities. This is the first study of the synthesis, fungicidal and insecticidal activities of sulfone derivatives containing a [1,2,4]triazolo[4,3-a]pyridine moiety, and the structural modification are underway to explore the more potential of this kind of sulfone derivatives containing a [1,2,4]triazolo[4,3-a]pyridine moiety.

EXPERIMENTAL

Synthesis

All solvents were purified according to standard procedures. All reactants and starting materials were purchased from Accela ChemBio Co., Ltd (Shanghai, China). The ^{1}H and ^{13}C NMR spectra (solvent $CDCl_3$) were measured with a JEOL-ECX 500 NMR spectrometer operating at room temperature with tetramethylsilane (TMS) as an internal standard, and chemical shifts are expressed in δ (ppm). The melting points of the synthesized compounds were recorded on a WRX-4 monocular microscope (Shanghai Yice Apparatus & Equipment Co., Ltd, China) and were not corrected. Elemental analysis was carried out on an Elemental Vario-III CHN analyzer (Elementar, Hanau, German). The progress of the reaction was monitored by TLC. The Supplemental Materials file contains sample ^{1}H and ^{13}C NMR spectra of products 5 (Figures S 1 -- S 38).

Preparation of intermediate 2 [33]: To a solution of 2,3-dichloropyridine (50.0 g) in EtOH (40 mL), 25 g hydrazine hydrate (80%) was added and refluxed for 24 h. The resulting mixture was cooled to room temperature, which was filtered and dried to get white needle crystal (41.5 g), yield: 85.6%, m.p. 163-164 °C.

Preparation of intermediates 3 [30]**:** 3-chloro-2-hydrazinylpyridine (12.0 g, 83.58 mmol) was reacted with carbon disulfide (7.64 g, 100 mmol) in the presence of NaOH in ethanol (100 mL) at room temperature for 24 h, After complication of the reaction, and the residues were poured into water (50 mL), then acidified to pH = 4-5 to obtain intermediates 3 (10.31 g), yield, 66.5%, m.p. 298-299 °C (ref. [30], 300-302 °C).

Synthetic procedures for intermediates 4: To a solution of intermediates **3** (1 mmol) and K_2CO_3 (0.5 mmol) in acetonitrile (20 mL), the corresponding halides (1.1 mmol) were slowly added, and the resulting mixture was refluxed for 2 h. After filtration to remove excess K_2CO_3, the residue was concentrated in vacuum and recrystallized from ether to obtain the sulfide derivatives with [1,2,4]triazolo[4,3-a]pyridine moiety.

General synthetic procedures for compounds 5a--5s: Sulfide derivatives **4** (1 mmol) were dissolved in ethanol (20 mL) and stirred at room temperature. Ammonium molybdate (0.20 mmol) was added as catalyst, and then 30% H_2O_2 (2 mmol) was added. The mixture was stirred at room temperature and monitored by TLC, until completion of the reaction; the ethanol was removed under reduced pressure to yield the crude products, which were purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether (5/1) to afford the desired products.

8-chloro-3-((2,4-dichlorobenzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine(5a)*:* yield 84%; Light yellow solid; m.p. 176.8-177.9°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, *J* = 6.9 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 7.52 (d, *J* = 7.2 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 7.34 -- 7.27 (m, 2H, Ph-H), 7.19 (d, *J* = 8.3 Hz, 1H, Ph-H), 6.91 (t, *J* = 7.1 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 4.99 (s, 3H, -CH_2-). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 143.9, 136.8, 136.4, 133.9, 130.1, 128.6, 127.9, 123.2, 122.9, 116.2, 59.3; IR (KBr)/cm^{-1}: 3047.7 (Ar-H), 2922.8, 2916.9, 2878.4 (-CH_2-), 1560.8, 1544.5, 1428.2 (aromatic ring); Anal. Calc. for $C_{13}H_8Cl_3N_3O_2S$: C 41.46%, H 2.14%, N 11.16%. Found: C 41.42%, H 2.16%, N 11.17%.

8-chloro-3-((4-fluorobenzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (5b):yield 85%; Light yellow solid; m.p. 166.6-167.5°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.0 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 7.46 (d, *J* = 7.3 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 7.12 (dd, *J* = 7.4, 5.3 Hz, 2H, Ph-H), 6.89 (t, *J* = 8.0 Hz, 2H, [1,2,4]triazolo[4,3-a]pyridine-H), 6.82 (dd, *J* = 7.2, 6.5 Hz, 1H, Ph-H), 4.78 (s, 2H -CH_2-). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 163.4 (d, $^{1}J_{C\text{-}F}$ = 250.6 Hz), 162.4, 149.1, 143.8, 133.1 (d, $^{2}J_{C\text{-}F}$ = 18.5 Hz), 128.5, 122.9, 121.9, 116.3, 116.0 (d, $^{2}J_{C\text{-}F}$ = 19.7 Hz), 62.3; IR (KBr)/cm^{-1}: 3046.9 (Ar-H), 2924.8, 2918.3, 2882.1 (-CH_2-), 1566.7, 1548.5, 1428.1(aromatic ring); Anal. Calc. for $C_{13}H_9ClFN_3O_2S$: C 47.93%, H 2.78%, N 12.90%. Found: C 47.95%, H 2.74%, N 12.93%.

8-chloro-3-((4-methoxybenzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (5c)： yield 65%; white solid; m.p. 157.6-159.4°C; ^{1}H NMR (500 MHz, $CDCl_3$) 8.15 (d, *J* = 6.6 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 7.42 (d, *J* = 7.0 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 6.99 (d, *J* = 8.3 Hz, 2H, Ph-H), 6.77 -- 6.71 (m, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 6.67 (d, *J* = 8.3

Hz, 2H,, Ph-H), 4.71 (s, 2H, -CH_2-), 3.69 (s, 3H, -OCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 144.0, 132.4, 128.3, 123.1, 122.7, 117.7, 115.6, 114.5, 62.7, 55.4; IR (KBr)/cm^{-1}: 3085.3 (Ar-H), 2925.2, 2913.5, 2878.4 (-CH_2-), 1547.5, 1536.5, 1456.4 (aromatic ring); Anal. Calc. for $C_{14}H_{12}ClN_3O_3S$: C 49.78%, H 3.58%, N 12.44%. Found: C 49.75%, H 3.55%, N 12.47%.

8-chloro-3-(((6-chloropyridin-3-yl)methyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (5d): yield 82%; White solid; m.p. 185.5-187.1°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 6.9 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 8.31 (s, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 7.60 (dd, *J* = 8.2, 2.2 Hz, pyridine-H)), 7.53 (d, *J* = 7.3 Hz, 1H, Pyridine-H), 7.24 (d, *J* = 6.9 Hz, 1H [1,2,4]triazolo[4,3-a]pyridine-H)), 6.96 (t, *J* = 7.1 Hz, 1H, Pyridine-H), 4.89 (s, 2H, -CH_2-); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 151.8, 143.6, 141.2, 128.8, 124.7, 122.9, 121.4, 116.5, 59.2; IR (KBr)/cm^{-1}: 3075.2 (Ar-H), 2926.1, 2917.9, 2880.3 (-CH_2-), 1547.8, 1532.1, 1452.1 (aromatic ring); Anal. Calc. for $C_{12}H_8Cl_2N_4O_2S$: C 42.00%, H 2.35%, N 16.33%. Found: C 42.03%, H 2.31%, N 16.30%.

8-chloro-3-(methylsulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (5e): yield 69%; White solid; m.p. 149.1-150.0°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 6.9 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 7.55 (d, *J* = 7.4 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 7.07 (t, *J* = 7.1 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 3.58 (s, 3H, -CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 145.5, 128.5, 123.4, 123.2, 116.3, 44.2; IR (KBr)/cm^{-1}: 3075.2 (Ar-H), 2925.4, 2915.3, 2883.2 (--CH_3); Anal. Calc. for $C_7H_6ClN_3O_2S$: C 36.29%, H 2.61%, N 18.14%. Found: C 36.31%, H 2.62%, N 18.13%.

8-chloro-3-(ethylsulfonyl)-[1,2,4]triazolo[4,3-a]pyridine(5f): yield 74%; Light yellow solid; m.p. 126.6-127.4°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 6.9, 0.8 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.54 (dd, *J* = 7.4, 0.8 Hz, 1H, [1,2,4]triazolo[4,3-a]pyridine-H), 7.06 (t, *J* = 7.1 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 3.67 (q, *J* = 7.4 Hz, 2H, -CH_2-), 1.45 (t, *J* = 7.4 Hz, 3H, -CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 144.4, 128.4, 123.5, 123.3, 116.2, 51.1, 6.9; IR (KBr)/cm^{-1}: 3097.2 (Ar-H), 2934.2, 2911.3, 2873.2 (-CH_2CH_3); Anal. Calc. for $C_8H_8ClN_3O_2S$: C 39.11%, H 3.28%, N 17.10%. Found: C 39.12%, H 3.27%, N 17.14%.

8-chloro-3-((2-methylbenzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine(5g): yield 80%; Light yellow solid; m.p. 140.6-141.4°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 6.9 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.42 (d, *J* = 7.3 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.12 (q, *J* = 7.6 Hz, 2H, [1,2,4]triazolo[4,3-a] pyridine-H), 6.87 (t, *J* = 7.1 Hz, 1H, Ar-H), 6.77 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.71 (t, *J* = 7.1 Hz, 1H, Ar-H), 4.84 (s, 2H, -CH_2), 2.32 (s, 3H, -CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 144.2, 139.1, 131.7, 131.3, 129.8, 128.5, 126.4, 124.3, 122.9, 122.6, 115.8, 60.6, 19.7; IR (KBr)/cm^{-1}: 3102.2 (Ar-H), 2937.5, 2913.3, 2873.2 (-CH_2-), 1609.2, 1549.3, 1456.2 (aromatic ring); Anal. Calc. for $C_{14}H_{12}ClN_3O_2S$: C 52.26%, H 3.76%, N 13.06%. Found: C 52.28%, H 3.74%, N 13.02%.

8-chloro-3-((4-(trifluoromethoxy)benzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (5h): yield 52%; Light yellow solid; m.p. 154.6-155.5°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 6.9, 0.9 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.45 (dd, *J* = 7.3, 1.0 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.17 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.04 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.79 (td, *J* = 7.2, 1.0 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 4.81 (s, 2H, -CH_2); ^{13}C NMR (126 MHz,, $CDCl_3$) δ

150.1, 149.1, 143.7, 132.8, 128.6, 124.8, 122.9, 122.8, 121.5, 116.0, 62.3; IR (KBr)/cm^{-1}: 3105.1 (Ar-H), 2923.2, 2885.3 (-CH_2-), 1548.8, 1532.4, 1446.3 (aromatic ring); Anal. Calc. for $C_{14}H_9ClF_3N_3O_3S$: C 42.92%, H 2.32%, N 10.73%. Found: C 42.91%, H 2.33%, N 10.72%.

8-chloro-3-((4-(trifluoromethyl)benzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine(5i): yield 40%; Light yellow solid; m.p. 166.5-167.4°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 6.8 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.50 -- 7.45 (m, 4H, [1,2,4]triazolo[4,3-a] pyridine-H + Ar-H), 7.31 (d, *J* = 8.1 Hz, 2H, Ar-H), 6.82 (t, *J* = 7.2 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 4.89 (s, 2H, -CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 131.7, 130.0, 128.6, 126.5 (q, $^1J_{C-F}$ = 114.3 Hz), 123.1, 122.8, 116.1, 62.5, 29.8; IR (KBr)/cm^{-1}: 3098.2 (Ar-H), 2943.2, 2895.4 (-CH_2-), 1548.6, 1532.3, 1448.3 (aromatic ring); Anal. Calc. for $C_{14}H_9ClF_3N_3O_2S$: C 44.75%, H 2.41%, N 11.18%. Found: C 44.72%, H 2.44%, N 11.16%..

8-chloro-3-((2-(trifluoromethyl)benzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (5j): yield 78%; Light yellow solid; m.p. 140.6-141.6°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 7.0 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.70 -- 7.66 (m, 1H, Ar-H), 7.50 (dt, *J* = 11.6, 5.3 Hz, 4H, Ar-H), 6.94 (t, *J* = 7.1 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 5.06 (s, 2H, -CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.3, 144.4, 133.6, 132.3, 129.9, 128.6, 127.2, 127.2, 124.2 (q, $^1J_{C-F}$ = 114.3 Hz), 123.2, 123.2, 116.2, 59.5; IR (KBr)/cm^{-1}: 3087. (Ar-H), 2953.1, 2885.9 (-CH_2-), 1549.7, 1533.7, 1449.3 (aromatic ring). Anal. Calc. for $C_{14}H_9ClF_3N_3O_2S$: C 44.75%, H 2.41%, N 11.18%. Found: C 44.73%, H 2.45%, N 11.15%.

8-chloro-3-((2,4-difluorobenzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine(5k). yield 83%; Light yellow solid; m.p. 171.4-172.3°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.0 Hz, 1H,

[1,2,4]triazolo[4,3-a] pyridine-H), 7.52 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.19 (dd, *J* = 11.5, 5.3 Hz, 1H,, [1,2,4]triazolo[4,3-a] pyridine-H), 6.93 (t, *J* = 7.1 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 6.80 -- 6.71 (m, 2H, Ar-H), 4.87 (s, 2H, -CH_2-); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9 (d, $^1J_{C-F}$ = 241.9 Hz), 160.9 (d, $^1J_{C-F}$ = 244.9 Hz),149.3, 143.8, 133.8 (dd, $^2J_{C-F}$ = 10.1, 3.9 Hz), 128.6, 123.1 (d, $^2J_{C-F}$ = 18.4 Hz), 116.2 (s), 112.3 (dd, $^2J_{C-F}$ = 21.8Hz), 109.8, 104.9, 104.7, 104.5, 55.8; IR (KBr)/cm^{-1}: 3121.2 (Ar-H), 2943.8, 2883.2 (-CH_2-), 1545.8, 1532.3, 1447.4 (aromatic ring); Anal. Calc. for $C_{13}H_8ClF_2N_3O_2S$: C 45.42%, H 2.35%, N 12.22%. Found: C 45.43%, H 2.34%, N 12.21%.

8-chloro-3-((2,5-difluorobenzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (5l): yield 79%; White solid; m.p. 160.0-160.7°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 6.9, 0.9 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.45 (dd, *J* = 7.3, 1.0 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.17 (d, *J* = 7.9 Hz, 2H, Ar-H), 7.04 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.79 (td, *J* = 7.2, 1.0 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 4.81 (s, 2H, -CH_2-); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6 (d, $^1J_{C-F}$ = 241.9 Hz), 149.3 (d, $^1J_{C-F}$ = 244.9 Hz), 143.9, 128.6, 123.3, 123.0, 119.3 (d, $^2J_{C-F}$ = 17.3 Hz), 119.1 (d, $^2J_{C-F}$ = 17.3 Hz), 118.5 (d, $^2J_{C-F}$ = 23.9 Hz), 117.2 (d, $^2J_{C-F}$ = 24.5 Hz), 116.2, 115.1, 55.9; IR (KBr)/cm^{-1}: 3118.3 (Ar-H), 2946.7, 2889.2 (-CH_2-), 1548.2, 1536.7, 1448.8 (aromatic ring); Anal. Calc. for $C_{13}H_8ClF_2N_3O_2S$: C 45.42%, H 2.35%, N 12.22%. Found: C 45.41%, H 2.33%, N 12.23%.

8-chloro-3-((2,6-difluorobenzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (5m): yield 64%; White solid; m.p. 190.0-192.8°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 7.0, 0.6 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.53 (dd, *J* = 12.3, 5.7 Hz, 1H, [1,2,4]triazolo[4,3-a]

pyridine-H), 7.34 (ddd, *J* = 13.0, 8.4, 6.5 Hz, 1H, Ar-H), 6.92 (t, *J* = 7.2 Hz, 1H, Ar), 6.86 (dd, *J* = 14.9, 7.0 Hz, 2H, Ar-H), 4.90 (s, 2H, -CH_2-);^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7 (d, $^1J_{C\text{-}F}$ = 253.7 Hz), 160.7 (d, *J* = 253.2 Hz), 149.3, 144.0, 132.3, 128.5, 122.9 (t, *J* = 19.0 Hz), 116.2 (d, $^2J_{C\text{-}F}$ = 20.4 Hz), 111.9 (d, $^2J_{C\text{-}F}$ = 20.3 Hz), 51.2; IR (KBr)/cm^{-1}: 3082.2 (Ar-H), 2913.8, 2899.q (-CH_2-), 1565.2, 1546.3, 1447.2 (aromatic ring); Anal. Calc. for $C_{13}H_8ClF_2N_3O_2S$: C 45.42%, H 2.35%, N 12.22%. Found: C 45.42%, H 2.32%, N 12.24%.

3-((2-bromo-4-fluorobenzyl)sulfonyl)-8-chloro-[1,2,4]triazolo[4,3-a]pyridine (5n):yield 63%; Light yellow solid; m.p. 177.3-178.3°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 7.0 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.53 (d, *J* = 7.2 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H),), 7.22 -- 7.16 (m, 2H, Ar-H), 7.09 (t, *J* = 7.8 Hz, 1H, Ar-H), 6.94 (t, *J* = 7.1 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H),), 4.86 (s, 2H);^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, $^1J_{C\text{-}F}$ = 253.7 Hz), 149.3, 143.8, 133.8, 128.7, 128.3, 124.8 (d, $^2J_{C\text{-}F}$ = 9.5 Hz), 123.1, 119.9, 119.7, 116.3, 112.9 (d, $^2J_{C\text{-}F}$ = 15.0 Hz), 55.9; IR (KBr)/cm^{-1}: 3104.1 (Ar-H), 2915.2, 2869.9 (-CH_2-), 1564.7, 1566.2, 1447.3 (aromatic ring); Anal. Calc. for $C_{13}H_8BrClFN_3O_2S$: C 38.59%, H 1.99%, N 10.38%. Found: C 38.61%, H 2.01%, N 10.34%.

8-chloro-3-((2-chloro-4-fluorobenzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (5o): yield 58%; White solid; m.p. 180.5-181.6°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 7.0, 0.6 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.51 (dd, *J* = 7.3, 0.6 Hz, 1H, Ar-H), 7.34 (dd, *J* = 8.6, 5.9 Hz, 1H, Ar-H), 7.06 (dd, *J* = 8.3, 2.6 Hz, 1H, Ar-H), 6.96 -- 6.88 (m, 2H, Ar-H), 4.98 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2 (d, $^1J_{C\text{-}F}$ = 254.6 Hz), 149.4, 143.9, 136.7, 134.5 (d, $^3J_{C\text{-}F}$ = 9.3 Hz), 128.6, 123.2, 122.9, 120.7, 117.7 (d, $^2J_{C\text{-}F}$ = 24.9 Hz), 116.2, 115.1 (d, $^2J_{C\text{-}F}$ = 21.5 Hz), 59.2,

29.8; IR (KBr)/cm^{-1}: 3114.4 (Ar-H), 2912.3, 2869.9 (-CH_2-), 1567.1, 1564.2, 1447.3 (aromatic ring); Anal. Calc. for $C_{13}H_8Cl_2FN_3O_2S$: C 43.35%, H 2.24%, N 11.67%. Found: C 43.32%, H 2.23%, N 11.69%.

8-chloro-3-((3-chloro-2-fluorobenzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (5p): yield 82%; White solid; m.p. 177.4-178.1°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 4.4, 3.5 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.51 (dd, *J* = 7.4, 1.0 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.37 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.08 (t, *J* = 7.0 Hz, 1H, Ar-H), 6.97 (d, *J* = 7.9 Hz, 1H, Ar-H), 6.92 (t, *J* = 7.2 Hz, 1H, Ar-H), 4.92 (s, 2H, -CH_2-).^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2 (d, $^1J_{C\text{-}F}$ = 215.7 Hz), 152.6, 149.3, 143.9, 132.5, 131.1, 128.6, 125.1 (d, $^2J_{C\text{-}F}$ = 14.5 Hz), 123.2, 122.9, 116.2, 115.6, 115.4, 56.9; IR (KBr)/cm^{-1}: 3089.5 (Ar-H), 2902.3, 2879.6 (-CH_2-), 1568.2, 1563.1, 1448.1 (aromatic ring);Anal. Calc. for $C_{13}H_8Cl_2FN_3O_2S$: C 43.35%, H 2.24%, N 11.67%. Found: C 43.37%, H 2.26%, N 11.65%.

3-((2-bromo-4-fluorobenzyl)sulfonyl)-8-chloro-[1,2,4]triazolo[4,3-a]pyridine (5q):yield 61%; White solid; m.p. 177.3-178.3°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 7.0, 0.8 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.51 (dd, *J* = 7.3, 0.8 Hz, 1H, Ar-H), 7.37 (dd, *J* = 8.6, 5.8 Hz, 1H, Ar-H), 7.23 (dd, *J* = 8.0, 2.6 Hz, 1H, Ar-H), 7.00 (ddd, *J* = 8.6, 7.8, 2.6 Hz, 1H, Ar-H), 6.90 (t, *J* = 7.1 Hz, 1H, Ar-H), 5.01 (s, 2H, -CH_2-); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9 (d, $^1J_{C\text{-}F}$ = 255.4 Hz), 149.4, 143.9, 134.5 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 128.6, 126.3, 123.2, 122.9, 122.5, 120.9 (d, $^2J_{C\text{-}F}$ = 24.6 Hz), 116.2, 115.5 (d, $^2J_{C\text{-}F}$ = 21.6 Hz), 61.4; IR (KBr)/cm^{-1}: 3102.4 (Ar-H), 2909.55, 2889.9 (-CH_2-), 1557.1, 1547.2, 1443.2 (aromatic ring); Anal. Calc. for $C_{13}H_8BrClFN_3O_2S$: C 38.59%, H 1.99%, N 10.38%. Found: C 38.55%, H 1.97%, N 10.35%.

8-chloro-3-((2-fluoro-5-(trifluoromethyl)benzyl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (**5r**): yield 87%; White solid; m.p. 152.8-153.8°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.0 Hz, 1H, [1,2,4]triazolo [4,3-a] pyridine-H), 7.62 -- 7.57 (m, 1H, Ar-H), 7.51 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.41 (d, *J* = 4.7 Hz, 1H, Ar-H), 7.17 (t, *J* = 8.7 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 6.92 (t, *J* = 7.1 Hz, 1H, [1,2,4]triazolo [4,3-a] pyridine-H), 4.94 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.3 (d, $^{1}J_{C-F}$ = 257.8 Hz), 149.3, 143.7, 130.1, 129.2 (q, $^{2}J_{C-F}$ = 9.1 Hz), 128.7, 124.1, 123.4 (q, $^{1}J_{C-F}$ = 94.8 Hz), 122.8, 117.0 (d, $^{1}J_{C-F}$ = 22.9 Hz), 116.4, 115.0 (d, $^{2}J_{C-F}$ = 15.9 Hz), 55.9; IR (KBr)/cm^{-1}: 3078.6 (Ar-H), 2909.1, 2879.2 (-CH_2-), 1558.1, 1554.2, 1448.3 (aromatic ring);Anal. Calc. for $C_{14}H_8ClF_4N_3O_2S$: C 42.71%, H 2.05%, N 10.67%. Found: C 42.72%, H 2.04%, N 10.70%.

8-chloro-3-((3,4,4-trifluorobut-3-en-1-yl)sulfonyl)-[1,2,4]triazolo[4,3-a]pyridine (5s): yield 59%; Light yellow solid; m.p. 86.6-87.4°C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 6.9, 0.8 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.58 (d, *J* = 7.6 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 7.11 (t, *J* = 7.0 Hz, 1H, [1,2,4]triazolo[4,3-a] pyridine-H), 3.91 (t, ^{3}J = 7.2 Hz, 2H, -CH_2-), 3.07 -- 2.96 (m, 2H, -$CH_2CF = CF_2$);^{13}C NMR (126 MHz, $CDCl_3$) δ 153.96 (ddd, $^{1}J_{C-F}$ = 287.8, $^{1}J_{C-F}$ = 274.6, $^{2}J_{C-F}$ = 45.7 Hz), 149.17, 142.21, 127.81 (ddd, $^{1}J_{C-F}$ = 234.9 Hz, *J* = 53.3 Hz, $^{2}J_{C-F}$ = 16.9 Hz), 126.43, 126.09122.92 (s), 121.47, 114.12, 77.40, 77.14, 76.89, 30.22, 26.61 (dd, $^{2}J_{C-F}$ = 21.6, $^{3}J_{C-F}$ = 2.0 Hz). IR (KBr)/cm^{-1}: 3100.2 (Ar-H), 2922.3, 2888.7 (-CH_2-); Anal. Calc. for $C_{10}H_7ClF_3N_3O_2S$: C 36.88%, H 2.17%, N 12.90%. Found: C 36.87%, H 2.13%, N 12.93%.

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Bioassay

Antifungal biological assay

The antifungal activities against *Rhizotonia cerealis, Helminthosporium maydis, Rhizoctonia solani,* and *Fusarium graminearum* were evaluated using the poison plate technique at a concentration of 50 mg/L [34]. All the synthesized compounds (**5a-5s**) were dissolved in DMSO (10 mL) and then mixed with potato dextrose agar (PDA, 90 mL). All fungal species were incubated in PDA at 27 ± 1°C for 120 h to obtain new mycelium for antifungal assay, then mycelia dishes were cut from the culture medium in approximately 4 mm diameter. One of the specimens was picked up with a sterilized inoculation needle and then inoculated in the center of the PDA plate aseptically. The inoculated plates were incubated at 27 ±1°C for 120 h. DMSO in sterile distilled water served as the control, whereas carbendazim and propiconazole acted as the positive control. Three replicates were proformed for each treatment. The radial growth of the fungal colonies was measured on the sixth day and the data were statistically analyzed. The in vitro inhibiting effects of the test compounds on the fungi were calculated by the formula:

$$I(\%) = [(C-T)/(C-0.4)] \times 100$$

Where C represents the diameter of fungal growth on untreated PDA, T represents the diameter of fungi on treated PDA, and I is the inhibitory rate.

Insecticidal bioassays against *Plutella xylostella*.

Previously reported protocol [33, 35] were employed to evluate insecticidal activities against *Plutella xylostella*. Fresh cabbage discs (diameter of 2 cm) were dipped in the prepared solutions

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containing compounds **5a** to **5s** for 10 s, dried in air and placed in a Petri dish (diameter of 9 cm) lined with filter paper. Twenty larvaes of secondinstar of *Plutella xylostella* were carefully transferred to the Petri dishes. Chlorpyrifos was used as postive control; three replicates were performed for each experiment. Mortalities were caculated after 72 h. Evaluations of mortality were caculated in a percentage scale (0 = no activity and 100 = complete eradication) at 5% intervals. The results are summarized in Table S 3 (Supplemental Materials)

Insecticidal activity against *Helicoverpa armigera*

The insecticidal activities of ompounds **5a** to **5s** against *Helicoverpa armigera* were tested by the diet-incorporated method [33, 35]. A quantity of 3 mL of prepared solutions containing the compounds was added to the forage (27 g), subsequently diluted to different concentrations and then placed in a 24-pore plate.One larva was placed in each of the wells on the plate. Mortalities were determined after 72--96 h, Evaluations were based on a percentage scale (0 = no activity and 100 = complete eradication) at 5% intervals. The results are given in Table S 4 (Supplemental Materials)

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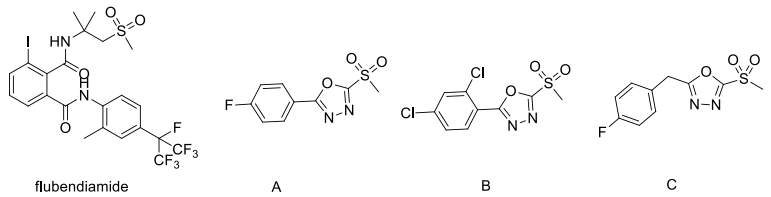

Figure 1. The chemical structures of pesticides containing a sulfone

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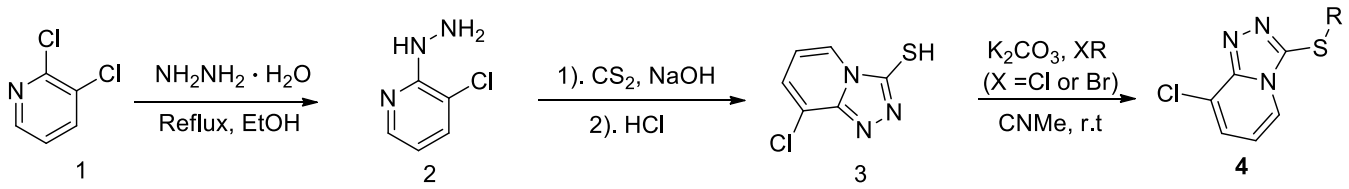

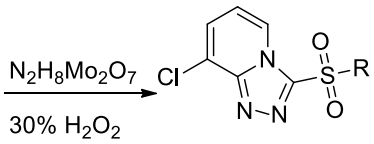

5a: R = 2,4-dichlorobenzyl; **5b**: R = 4-fluorobenzyl;
5c: R = 4-methoxybenzyl; **5d**: R = 6-chloropyridin-3-ylmethyl;
5e: R = Methyl; **5f**: R = Ethyl;
5g: R = 2-methylbenzyl; **5h**: R = 4-(trifluoromethoxy)benzyl;
5i: R = 4-(trifluoromethyl)benzyl; **5j**: R = 2-(trifluoromethyl)benzyl;
5k: R = 2,4-difluorobenzyl; **5l**: R = 2,5-difluorobenzyl;
5m: R = 2,6-difluorobenzyl; **5n**: R = 4-bromo-2-fluorobenzyl;
5o: R = 2-chloro-4-fluorobenzyl; **5p**: R = 3-chloro-2-fluorobenzyl;
5q: R = 2-bromo-4-fluorobenzyl; **5r**: R = 2-fluoro-5-(trifluoromethyl)benzyl;
5s: R = 3,4,4-trifluorobut-3-en-1-yl.

Scheme 1. Synthesis of compounds **5a** to **5s**