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# Novel hydrazone derivatives containing pyridine amide moiety: Design, synthesis, and insecticidal activity

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ABSTRACT

A series of novel hydrazone derivatives containing pyridine amide moiety were designed, synthesized, and evaluated for their insecticidal activity. Bioassays indicated that some of the target compounds exhibited good insecticidal activities against *Nilaparvata lugens* (*N. lugens*), *Plutella xylostella* (*P. xylostella*), *Mythimna separata* (*M. separata*), *Helicoverpa armigera* (*H. armigera*), *Pyrausta nubilalis* (*P. nubilalis*), and *Culex pipiens pallens* (*C. pipiens pallens*). In particular, compound **5j** revealed excellent insecticidal activity against *C. pipiens pallens*, with the 50% lethal concentration ($LC_{50}$) and the 95% lethal concentration ($LC_{95}$) values of 2.44 and 5.76 mg/L, respectively, which were similar to those of chlorpyrifos (3.26 and 6.98 mg/L, respectively), tebufenozide (1.22 and 2.49 mg/L, respectively), and RH-5849 (2.61 and 6.37 mg/L, respectively). These results indicated that hydrazone derivatives containing pyridine amide moiety could be developed as novel and promising insecticides.



For years, crop damage from harmful pests has become more common and the continued application of traditional pesticides can often lead to the development of more resistant pests, thus bringing about enormous losses in crop production.[1,2] Nowadays, some of insecticides (flubendiamide, chlorpyrifos, tebufenozide, RH-5849, chlorantraniliprole, etc.) were used to control pests in agricultural production.[3,4] However, these insecticides could not effectively control crop pests and prevent resistant pests. Therefore, development of novel and promising insecticides with a new mode of action is an urgent task.

Hydrazone, a highly efficient pharmacophore and widely used in drug design, demonstrated significant fungicidal,[5–7] antibacterial,[7–9] antioxidant,[10] anti-tumor,[11] anticonvulsant,[12–14] anti-inflammatory,[15,16] antimalarial,[17] and anti-tuberculosis[18–22] activities. However, in pesticide areas, several studies documented that hydrazone derivatives exhibited good insecticidal activities,[23–26] examples of such two pesticides are hydramethylnon, the first insecticide containing a hydrazone moiety and commercialized in 1980,[27] and metaflumizone, which was discovered by Badische Anilin Soda Fabrik AG (BASF) and commercialized in 2007.[28] Meanwhile, pyridine amide and their derivatives, an important class of heterocyclic derivatives, represented a key moiety in heterocyclic chemistry and occupied a prime place in pharmaceuticals and pesticides chemistry due to their competence to exhibit a wide range of pharmaceuticals and pesticides activities including antifungal,[29,30] antibacterial,[9,31,32] anti-cancer,[33,34] antioxidant,[35] and insecticidal[36] activities. In our previous work, we have reported a series of hydrazone derivatives containing pyridine amide moiety, shown in Figure 1, which exhibited good antibacterial activity against tobacco bacterial wilt caused by *Ralstonia solanacearum* (*R. solanacearum*).[10]

Based on the above of findings and in continuation of our investigation, to continue our efforts in developing highly active and readily available insecticidal inhibitors, we aim to introduce a pyridine amide group to a hydrazone skeleton to build a novel family of bioactive molecules. In this work, a series of novel hydrazone derivatives containing pyridine amide moiety were designed, synthesized, and evaluated their insecticidal activities against *Nilaparvata lugens* (*N. lugens*), *Plutella xylostella* (*P. xylostella*), *Mythimna separata* (*M. separata*), *Helicoverpa armigera* (*H. armigera*), *Pyrausta nubilalis* (*P. nubilalis*), and *Culex pipiens pallens* (*C. pipiens pallens*). To the best of our knowledge, it is the

*Abbreviations: N. lugens*, *Nilaparvata lugens*; *P. xylostella*, *Plutella xylostella*; *M. separata*, *Mythimna separate*; *H. armigera*, *Helicoverpa armigera*; *P. nubilalis*, *Pyrausta nubilalis*; *C. pipiens pallens*, *Culex pipiens pallens*; *R. solanacearum*, *Ralstonia solanacearum*; $LC_{50}$, 50% lethal concentration; $LC_{95}$, 95% lethal concentration; BASF, Badische Anilin Soda Fabrik AG; THF, tetrahydrofuran; $^1$H NMR, $^1$H nuclear magnetic resonance; $^{13}$C NMR, $^{13}$C nuclear magnetic resonance; SAR, structure–activity relationships.

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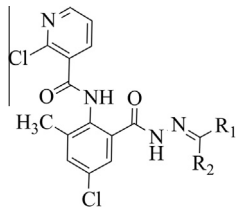


**Figure 1.** Compounds previously reported against tobacco bacterial wilt.

first report on the insecticidal activity of hydrazone derivatives containing pyridine amide moiety.

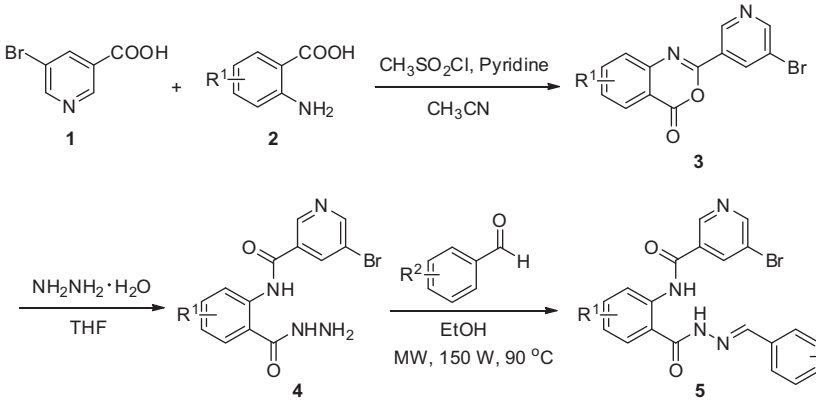
The synthetic route of the target compounds **5a–5t** was depicted in Scheme 1. 5-Bromonicotinic acid **1** and substituted anthranilic acid **2**, using as the starting materials, were reacted with methanesulfonyl chloride to obtain intermediate **3**. Then, intermediate **3** and 80% hydrazine hydrate were reacted in tetrahydrofuran (THF) at room temperature to produce the key intermediate **4**. Finally, the title compounds **5a–5t** were obtained under microwave irradiation reaction at 90 °C and 150 W for 10 min with the yields of 75.1–84.2%, and confirmed their structures by IR, $^1$H NMR, $^{13}$C NMR, and elemental analysis. The physical characteristics, IR, $^1$H NMR, $^{13}$C NMR, and elemental analysis data for all synthesized compounds are reported in the Supplementary data, and the data for compound **5j** were shown below.

*5-Bromo-N-(2-(2-(2,4-dichlorobenzylidene)hydrazinecarbonyl)-5-chloro-3-methylphenyl)pyridine amide* (**5j**): White solid; mp 285–287 °C; yield 82.3%; $^1$H NMR (500 MHz, DMSO-$d_6$, ppm) $\delta$: 12.16 (s, 1H, pyridine—CO*NH*), 10.30 (s, 1H, Ar—CO*NH*), 9.03 (s, 1H, pyridine—H), 8.92 (s, 1H, pyridine—H), 8.66 (s, 1H, pyridine—H), 8.48 (s, 1H, —*CH*=N), 7.96 (d, 1H, $J$ = 8.60 Hz, Ar—H), 7.72–7.43 (m, 4H, Ar—H), 2.28 (s, 3H, —$CH_3$); $^{13}$C NMR (125 MHz, DMSO-$d_6$, ppm) $\delta$: 168.92, 162.76, 161.66, 157.43, 154.08, 148.32, 147.21, 138.87, 138.33, 135.64, 134.65, 133.96, 132.77, 131.73, 130.59, 129.84, 129.52, 127.83, 124.81, 119.88, 17.95; IR (KBr, cm$^{-1}$) $v$: 3444.87, 3222.84, 1674.21, 1653.00, 1635.64, 1627.92, 1589.34, 1558.48, 1525.69, 1506.41, 1471.69, 1458.18, 1429.25, 1411.89, 1367.53, 1330.88, 1303.88, 1246.02, 1219.01, 1199.72; Anal. Calcd for $C_{21}H_{14}BrCl_3N_4O_2$: C, 46.65; H, 2.61; N, 10.36. Found: C, 46.84; H, 2.92; N, 10.48.

In this study, the insecticidal activities of the target compounds **5a–5t** against *N. lugens*, *P. xylostella*, *M. separata*, *H. armigera*, *P. nubilalis*, and *C. pipiens pallens* were evaluated using the previously reported methods.[37–45] Meanwhile, the commercial insecticides of chlorpyrifos, tebufenozide, and RH-5849 which were commonly used in China, used as the positive controls, were evaluated at the same conditions. The results of the preliminary bioassays, as listed in Table 1, indicated that the target compounds **5a–5t** showed insecticidal activities against *N. lugens*, *P. xylostella*, *M. separata*, *H. armigera*, and *P. nubilalis* at 500 mg/L, with the values of 22.20–96.67%, 3.30–73.33%, 0–90.00%, 15.00–90.00%, and 10.00–80.00%, respectively, which were all lower than those of chlorpyrifos (100.00%), tebufenozide (100.00%), and RH-5849 (100.00%). Meanwhile, Table 1 also showed that compounds **5b**, **5e**, and **5j** exhibited significant insecticidal activity against *C. pipiens pallens*, with a value of 100.00% at the concentrations of 10 and 5 mg/L, which were equally to those of chlorpyrifos (100.00%), tebufenozide (100.00%), and RH-5849 (100.00%). Moreover, compound **5j** revealed the best insecticidal activity against *C. pipiens pallens* at 2.5 mg/L, with a value of 50.00%, which was better than those of chlorpyrifos (20.00%) and RH-5849 (40.00%), but lower than that of tebufenozide (60.00%).

The 50% lethal concentration ($LC_{50}$) and 95% lethal concentration ($LC_{95}$) values of some of the synthesized compounds as well as for the commercial pesticides chlorpyrifos, tebufenozide, and RH-5849 against *C. pipiens pallens* were also determined and presented in Table 2. Table 2 showed that compounds **5a**, **5b**, **5o**, **5p**, **5e**, and **5j** exhibited insecticidal activity against *C. pipiens pallens* with the $LC_{50}$ and $LC_{95}$ values of 2.44–5.75 and 5.76–17.07 mg/L, respectively. Especially, compound **5j** revealed the best insecticidal activity against *C. pipiens pallens*, with the $LC_{50}$ and $LC_{95}$ values of 2.44 and 5.76 mg/L, respectively, which were similar to those of chlorpyrifos (3.26 and 6.98 mg/L, respectively), tebufenozide (1.22 and 2.49 mg/L, respectively), and RH-5849 (2.61 and 6.37 mg/L, respectively).

As an extension of this approach, the structure–activity relationships (SAR) were also discussed on the basis of the insecticidal activity values in Tables 1 and 2. As shown in Tables 1 and 2, when $R^1$ were electron-withdrawing group, the corresponding compound **5h** ($R^1$: 5-Cl, $R^2$: 2,4-di-Cl) possessed better insecticidal activities at 500 μg/mL against *N. lugens*, *M. separate*, *H. armigera*, *P. nubilalis*, and *C. pipiens pallens*, with the values of 86.67%,




**5a**: $R^1$=5-Cl, $R^2$=4-Br
**5b**: $R^1$=5-Cl, $R^2$=4-$CF_3$
**5c**: $R^1$=5-Cl, $R^2$=2-F
**5d**: $R^1$=5-Cl, $R^2$=4-F
**5e**: $R^1$=5-Cl, $R^2$=2-$NO_2$
**5f**: $R^1$=5-Cl, $R^2$=4-$CH_3$
**5g**: $R^1$=5-Cl, $R^2$=4-Cl
**5h**: $R^1$=5-Cl, $R^2$=2,4-di-Cl
**5i**: $R^1$=5-Cl-3-$CH_3$, $R^2$=4-Cl
**5j**: $R^1$=5-Cl-3-$CH_3$, $R^2$=2,4-di-Cl
**5k**: $R^1$=3-$CH_3$, $R^2$=4-Cl
**5l**: $R^1$=3-$CH_3$, $R^2$=2,4-di-Cl
**5m**: $R^1$=H, $R^2$=4-F
**5n**: $R^1$=H, $R^2$=2,4-di-Cl
**5o**: $R^1$=H, $R^2$=4-Br
**5p**: $R^1$=H, $R^2$=2-Br
**5q**: $R^1$=H, $R^2$=2,3-di-Cl
**5r**: $R^1$=H, $R^2$=4-Cl
**5s**: $R^1$=H, $R^2$=2-Cl
**5t**: $R^1$=4-Cl, $R^2$=2,4-di-Cl

**Scheme 1.** Synthetic route of the target compounds **5a–5t**.