A facile one-pot synthesis of novel 1,2,4-triazolo[4,3-*a*]pyridine derivatives containing the trifluoromethyl moiety using microwave irradiation

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A series of novel substituted 8-chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridines are synthesised from 2,3-dichloro-5-(trifluoromethyl)pyridine, hydrazine hydrate as starting materials by multi-step reactions under microwave irradiation. Their chemical structures can be characterised by ^{1}H NMR, MS and elemental analysis. The title compounds exhibit weak antifungal activity.

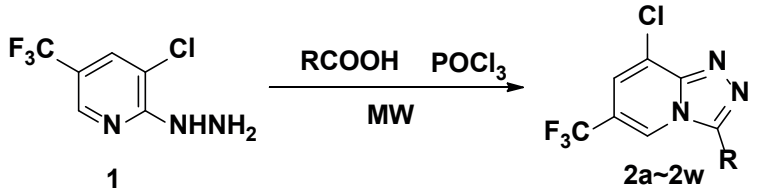
Keywords: 1,2,4-triazolo[4,3-*a*]pyridine, microwave irradiation, synthesis, antifungal activity

In synthetic chemistry, green methods are attracting interest because of their environmental benefits.[1] Such methods include catalyst free,[2] supercritical fluids,[3] water-phase reactions,[4] ionic liquids,[5] solvent-free reactions,[6] metal-free[7] and ultrasound[8] or microwaves irradiation.[9] Nitrogen-containing heterocycles have also proved attractive andthey have been widely used in the medicinal, agricultural and industrial fields.[10] The 1,2,4-triazoles and their fused heterocycles have received considerable attention because of their synthetic and effective biological importance. Reported methods of synthesising substituted 1,2,4-triazolo[4,3-*a*]pyridines, include solution-phase synthesis,[11] catalysed synthesis,[12] iodine mediated synthesis,[13] solvent-free synthesis,[14] microwave synthesis.[15] For example, the patent EP430385[16] described in 1991, that some interesting substituted 1,2,4-triazolo[4,3-*a*]pyridine derivatives were obtained using the key intermediates, substituted N-(2-pyridyl)hydrazones. Another patent CN102002040[17] also described that triazolopyridines could be prepared from substituted 2-hydrazinopyridines and substituted benzaldehydes as starting materials. More recently, triazolopyridines were synthesised from substituted 2-hydrazinopyridines and substituted carboxylic acids using microwave or ultrasonic methods.[18,19] In our previous work, 8-chloro-[1,2,4] triazolo[4,3-*a*]pyridines were synthesised using microwave irradiation[20] and showed antifungal activity. We now desribe a series of novel 1,2,4-triazolo[4,3-*a*]pyridines containing the trifluoromethyl moiety that were synthesised using microwave irradiation.

From the hydrazine **1** the synthetic procedure leading to compounds **2** is shown in Scheme 1. Generally, 1,2,4-triazolo-[4,3-*a*]pyridines are synthesised using two steps as described in the literature.[21,22] First, the key intermediate (hydrazide or hydrazone) is synthesised and then the fused 1,2,4-triazole heterocycles are prepared using different conditions. Here, a one-pot synthesis of novel 1,2,4-triazolo[4,3-*a*]pyridines using a hydrazine and a carboxylic acid in $POCl_3$ is reported under conditions of microwave irradiation. After the reaction was completed, the purification of these compounds is easy. We found that the yields of the title compounds were lower than that of our previous work where the CF_3 group is absent. The reactivity of hydrazine may be reduced by the presence of the electron withdrawing CF_3 group.

The products **2** were identified by ^{1}H NMR and MS spectra. In the ^{1}H NMR spectra of the title compounds, the CH proton signals of the pyridine moiety of title compounds were recognised as singlets. The mass spectra of the 1,2,4-triazolo[4,3-*a*]pyridines **2** showed molecular ion peaks. The measured elemental analyses were also consistent with the corresponding calculated ones. Hence an efficient route is established using a one-pot reaction to afford interesting trifluoro-substituted 1,2,4-triazolo[4,3-*a*]pyridines

The fungicidal activities of the title compounds **2a–w** against *Gibberella zeae* and *Alternaria alternate* were determined. The results are listed in Table 1. At a dose of 50 μg mL^{-1}, all compounds display weak fungicidal activity against *Gibberella zeae* and *Alternaria alternate*.



1 **2a~2w**

2a, R=4-MeOC$_6$H$_4$; 2b, R=2-MeC$_6$H$_4$; 2c, R=3-NO$_2$C$_6$H$_4$; 2d, R=(CH$_3$)$_2$CH;
2e, R=4-MeC$_6$H$_4$; 2f, R=2-MeOC$_6$H$_4$; 2g, R=4-*n*-PrC$_6$H$_4$; 2h, R=3-MeC$_6$H$_4$;
2i, R=3-FC$_6$H$_4$; 2j, R=4-FC$_6$H$_4$; 2k, R=4-NO$_2$C$_6$H$_4$;2l, R=4-IC$_6$H$_4$;
2m, R=4-ClC$_6$H$_4$OCH$_2$;2n, R=3-ClC$_6$H$_4$; 2o, R=4-*t*-BuC$_6$H$_4$; 2p, R=4-NH$_2$C$_6$H$_4$;
2q, R=4-*n*-BuC$_6$H$_4$;2r, R=4-(2-butanoic acid)C$_6$H$_4$; 2s, R=H; 2t, R=Me;
2u, R=2,4-Cl$_2$C$_6$H$_3$; 2v, R=CH$_3$CH$_2$CH$_2$; 2w, R=2-chloropyridin-3-yl

Scheme 1 The synthetic route to the title compounds.

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Table 1 The antifungal activity of the title compounds at 50 μg mL^{-1}

Compound	*Alternaria solani*	*Gibberella zeae*
2a	23.8	18.2
2b	23.8	16.4
2c	23.8	13.5
2d	19.0	11.8
2e	14.3	18.2
2f	17.6	10.3
2g	23.5	10.3
2h	23.5	27.6
2i	23.5	24.1
2j	17.6	27.6
2k	17.6	13.8
2l	23.5	10.3
2m	17.6	10.3
2n	17.6	6.9
2o	17.6	13.8
2p	17.6	10.3
2q	5.9	10.3
2r	23.5	22.6
2s	23.5	25.8
2t	29.4	22.6
2u	29.4	16.1
2v	35.3	15.2
2w	23.5	27.3
Chlorothalonil	63.6	73.1

Experimental

All reagents are analytical grade. Melting points were determined using a X-4 apparatus and were uncorrected. ^{1}H NMR spectra were measured on a Bruker Avance 400 MHz spectrometer using TMS as an internal standard and $CDCl_3$ as solvent. A CEM Discover Focused Synthesiser was used for microwave reaction. Elemental analysis was performed by a PerkinElmer 240C analyser.

Synthesis of **2a**; *general procedure*

A CEM-designed 10-mL pressure-rated vial was charged with $POCl_3$ (2 mL), 3-chloro-2-hydrazinyl-5-(trifluoromethyl)pyridine (211 mg, 1mmol), 4-methoxylbenzoic acid or analogous acid (1mmol). The mixture was irradiated in a CEM Discover Focused Synthesiser (150 W, 140°C, 200 psi, 15min). The mixture was cooled to room temperature by passing compressed air through the microwave cavity for 2 min. It was poured into cold ice (40 mL) and the formed precipitate filtered. The crude solid was recrystallised from EtOH to give the title compound **2a** and others. All the other compounds were synthesised according to the same procedure.

*8-Chloro-3-(4-methoxyphenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2a**): Light yellow solid; yield 68%; m.p. 123–127°C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 3.91 (s, 3H, –CH_3), 7.02 (d, *J*=8.1 Hz, 2H, PhH), 7.47 (s, H, PyH), 7.90 (m, 2H, PhH), 8.84 (s, H, PyH); ESI-MS: 329.0 [M+H]$^+$. Anal. calcd for $C_{14}H_9ClF_3N_3O$: C, 51.31; H, 2.77; N, 12.82; found: C, 51.43; H, 2.54; N, 12.77%.

*8-Chloro-3-(*o*-tolyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2b**): Light yellow solid; yield 41%; m.p. 96–97°C ; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 2.81 (d, *J*=8.1 Hz, 3H, –CH_3,), 7.28 (d, *J*=4.5 Hz, H, PhH), 7.37(t, *J*=7.8 Hz, H, PhH), 7.40(t, *J*=5.0 Hz, H, PhH), 7.48 (d, *J*=7.9 Hz, H, PhH), 8.05（s, H, PyH）, 8.07（s, H, PyH）; ESI-MS: 313.0 [M+H]$^+$. Anal. calcd for $C_{14}H_9ClF_3N_3$ C, 53.95; H, 2.91; N, 13.48; found: C, 53.99; H, 3.01; N, 13.32%.

*8-Chloro-3-(3-nitrophenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2c**): Light yellow solid; yield 33%; m.p. 148–151°C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.85 (s, H, PyH), 7.86 (m, 2H, PhH), 8.48 (m, 2H, PhH), 8.73 (s, H, PyH); ESI-MS: 344.0 [M+H]$^+$. Anal. calcd for $C_{13}H_6ClF_3N_4O_2$: C, 45.57; H, 1.76; N, 16.35; found: C,45.58; H, 1.98; N, 16.61%.

*8-Chloro-3-isopropyl-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridin*e (**2d**): Light yellow solid; yield 76%; m.p. 53–55°C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.30 (d, *J*=8.0 Hz, 6H, –CH_3), 2.17 (m, H, –CH–), 8.02 (d, *J*=8.1 Hz, 2H, PyH), 8.53 (s, H, PyH); ESI-MS: 265.0 [M+H]$^+$. Anal. calcd for $C_{10}H_9ClF_3N_3$: C, 45.56; H, 3.44; N, 15.94; found: C, 45.78; H, 3.24; N, 16.02%.

*8-Chloro-3-(*p*-tolyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2e**): Light yellow solid; yield 61%; m.p. 92–94°C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 2.47（t, *J*=8.0 Hz, 3H, –CH_3), 7.27 (d, *J*=4.0 Hz, 2H, PhH), 7.31 (d, *J*=8.0 Hz, 2H, PhH), 8.00 (s, H, PyH), 8.02 (s, H, PyH); ESI-MS: 313.0 [M+H]$^+$. Anal. calcd for $C_{14}H_9ClF_3N_3$: C, 53.95; H, 2.91; N, 13.48; found: C, 53.89; H, 3.18; N, 13.52%.

*8-Chloro-3-(2-methoxyphenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2f**): Light yellow solid; yield 34%, m.p.129–132°C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 3.90 (s, 3H, –CH_3), 7.13 (m, 2H, PhH), 7.57 (m, 2H, PhH), 7.77 (s, H, PyH), 8.03 (s, H, PyH); ESI-MS: 329.0 [M+H]$^+$. Anal. calcd for $C_{14}H_9ClF_3N_3O$: C, 51.31; H, 2.77; N, 12.82; found: C, 51.25; H, 2.65; N, 12.99%.

*8-Chloro-3-(4-propylphenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2g**): Light yellow solid; yield 58%; m.p. 87–89°C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.96 (m, 3H, –CH_3), 1.69 (m, 2H, CH_2), 2.68 (m, 2H, –CH_2–), 7.34 (d, *J*=8.0 Hz, 2H, PhH), 7.76 (d, *J*=4.8 Hz, 2H, PhH), 8.07 (s, H, PyH), 8.52 (s, H, PyH); ESI-MS: 341.1 [M+H]$^+$. Anal. calcd for $C_{16}H_{13}ClF_3N_3$: C, 56.56; H, 3.86; N, 12.37; found: C, 56.76; H, 3.98; N, 12.54%.

*8-Chloro-3-(*m*-tolyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2h**): Light yellow solid; yield 53%; m.p. 52–55°C; ^{1}H NMR ($CDCl_3$,400MHz), δ 2.47(t, *J*=12.0 Hz, 3H, –CH_3), 7.48 (m, 4H, PhH), 7.95 (s, H, PyH), 8.50 (s, H, PyH); ESI-MS: 313.0 [M+H]$^+$. Anal. calcd for $C_{14}H_9ClF_3N_3$: C, 53.95; H, 2.91; N, 13.48; found: C, 53.78; H, 2.79; N, 13.64%.

*8-Chloro-3-(3-fluorophenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2i**): Light yellow solid; yield 48%; m.p. 147–149°C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.52 (s, H, PyH), 7.61 (m, 4H, PhH), 8.51 (s, H, PyH); ESI-MS: 317.0 [M+H]$^+$. Anal. calcd for $C_{13}H_6ClF_4N_3$: C, 49.47; H, 1.92; N, 13.31; found: C, 49.66; H, 2.03; N, 13.45%.

*8-Chloro-3-(4-fluorophenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2j**): Light yellow solid; yield 57%; m.p. 112–114°C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.16 (m, 2H, PhH), 7.50 (s, H, PyH), 8.13 (m, 2H, PhH), 8.45 (s, H, PyH); ESI-MS: 317.0 [M+H]$^+$. Anal. calcd for $C_{13}H_6ClF_4N_3$: C, 49.47; H, 1.92; N, 13.31; found: C, 49.66; H, 1.88; N, 13.34%.

*8-Chloro-3-(4-nitrophenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2k**): Light yellow solid; yield 49%; m.p. 117–120°C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.57 (s, H, PyH), 8.09 (m, 2H, PhH), 8.33 (m, 2H, PhH), 8.54 (s, H, PyH); ESI-MS: 344.0 [M+H]$^+$. Anal. calcd for $C_{13}H_6ClF_3N_4O_2$: C, 45.57; H, 1.76; N, 16.35; found: C, 45.44; H, 1.58; N, 16.47%.

*8-Chloro-3-(4-iodophenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2l**): Light yellow solid; yield 44%; m.p. 127–130°C ; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 8.54 (s, H, PyH), 8.00 (d, *J*=8.0 Hz, H, PyH) 7.85(t, *J*=7.8 Hz, 2H, PhH), 7.55 (d, *J*=7.5 Hz, H, PhH), 7.37 (d, *J*=7.3 Hz, H, PhH); ESI-MS: 424.9 [M+H]$^+$. Anal. calcd for $C_{13}H_6ClF_3IN_3$: C, 36.86; H, 1.43; N, 9.92; found: C, 36.99; H, 1.57; N, 10.03%.

*8-Chloro-3-(4-chlorophenoxy)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2m**): Light yellow solid; yield 79%; m.p. 82–83°C ; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 8.76 (s, H, PyH), 8.57 (d, *J*=8.5 Hz, H, PyH), 7.00(t, *J*=7.0 Hz, 2H, PhH), 6.88(t, *J*=6.8 Hz, 2H, PhH); ESI-MS: 385.1 [M+H]$^+$. Anal. calcd for $C_{13}H_6Cl_2F_3N_3O$: C, 44.85; H, 1.74; N, 12.07; found: C, 44.79; H, 1.86; N, 12.32%.

*8-Chloro-3-(3-chlorophenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2n**): Light yellow solid; yield 75%; m.p. 83–85°C ; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 8.48 (s, H, PyH), 8.80 (d, *J*=8.1 Hz, H, PyH), 7.84 (d, *J*=7.8 Hz, H, PhH), 7.60(t, *J*=7.6 Hz, H, PhH) 7.52 (s, H, PhH), 7.42 (m, H, PhH); ESI-MS: 332.9 [M+H]$^+$. Anal. calcd for $C_{13}H_6Cl_2F_3N_3$: C, 47.01; H, 1.82; N, 12.65; found: C, 47.22; H, 1.97; N, 12.43%.

*8-Chloro-3-(4-(tert-butyl)phenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2o**): Light yellow solid; yield 69%; m.p. 122–124°C ; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.48 (d, *J*=7.4 Hz, 2H, PhH), 7.78 (s, H, PyH), 7.81 (d, *J*=7.8 Hz, 2H, PhH), 9.38 (s, H, PyH); ESI-MS: 385.1 $[M+H]^+$. Anal. calcd for $C_{17}H_{15}ClF_3N_3$: C, 57.72; H, 4.27; N, 11.88; found: C, 57.83; H, 4.55; N, 12.03%.

*4-(8-Chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)aniline* (**2p**): Light yellow solid; yield 45%; m.p. 91–92°C ; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.28 (s, 2H, $–NH_2$), 7.55 (m, 2H, PhH), 7.83 (m, 2H, PhH), 8.30 (s, H, PyH), 8.54 (s, H, PyH); ESI-MS: 314.0 $[M+H]^+$. Anal. calcd for $C_{13}H_8ClF_3N_4$: C, 49.94; H, 2.58; N, 17.92; found: C, 50.23; H, 2.81; N, 18.23%.

*8-Chloro-3-(4-butylphenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2q**): Light yellow solid; yield 62%; m.p. 75–78°C ; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 0.90 (s, 3H, $–CH_3$), 1.31 (m, 2H, $–CH_2–$), 1.67(q, *J*=1.6, 2H, $–CH_2–$), 2.67(q, *J*=2.6 Hz, 2H, $–CH_2–$), 7.34 (d, *J*=7.3 Hz, 2H, PhH), 7.78 (d, *J*=7.8 Hz, H, PyH), 8.04 (d, *J*=8.0 Hz, 2H, PhH), 9.24 (s, H, PyH); ESI-MS: 355.1 $[M+H]^+$. Anal. calcd for $C_{17}H_{15}ClF_3N_3$: C, 57.72; H, 4.27; N, 11.88; found: C, 57.35; H, 4.54; N, 11.66%.

*2-(4-(8-Chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)phenyl)butanoic acid* (**2r**): Light yellow solid; yield 44%; m.p. 160–163°C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.05 (m, 3H, $–CH_3$), 2.31 (m, H, $–CH_2–$), 2.64 (m, H, $–CH_2–$), 4.16 (m, H, –CH–), 7.29 (m, 5H, PhH), 7.36 (s, H, PyH), 7.93 (s, H, PyH); ESI-MS: 385.1 $[M+H]^+$. Anal. calcd for $C_{17}H_{13}ClF_3N_3O_2$: C, 53.21; H, 3.41; N, 10.95; found: C, 53.34; H, 3.56; N, 11.21%.

*8-Chloro-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2s**): Light yellow solid; yield 23%; m.p. 122–125°C, ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.49 (s, H, PyH), 8.51 (s, H, PyH), 9.02 (s, H, Tr-H); ESI-MS: 223.0 $[M+H]^+$. Anal. calcd for $C_7H_3ClF_3N_3$: C, 37.95; H, 1.36; N, 18.96; found: C, 38.12; H, 1.39; N, 19.22%.

*8-Chloro-3-methyl-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2t**): Light yellow solid; yield 39%; m.p. 146–149°C ; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.60 (s, 3H, $–CH_3$), 8.51 (s, H, PyH), 9.02 (s, H, PyH); ESI-MS: 237.0 $[M+H]^+$. Anal. calcd for $C_8H_5ClF_3N_3$: C, 40.78; H, 2.14; N, 17.84; found: C, 40.98; H, 2.32; N, 17.68%.

*8-Chloro-3-(2,4-dichlorophenyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2u**): Light yellow solid; yield 25%; m.p. 126–128°C ; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.43 (s, H, PhH), 7.52 (d, *J*=7.5 Hz, H, PhH), 7.67 (d, *J*=7.6 Hz, H, PhH), 7.85 (s, H, PyH), 8.08 (s, H, PyH); ESI-MS: 366.9 $[M+H]^+$. Anal. calcd for $C_{13}H_5Cl_3F_3N_3$: C, 42.60; H, 1.37; 11.46; found: C, 42.77; H, 1.56; N, 11.71%.

*8-Chloro-3-propyl-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2v**): Light yellow solid; yield 76%; m.p. 97–99°C ; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 4.72(t, *J*=4.7 Hz, 2H, $–CH_2–$), 5.78 (s, 3H, $–CH_3$), 6.88 (d, *J*=6.9 Hz, 2H, $–CH_2–$), 7.53 (s, H, PyH), 8.87 (s, H, PyH); ESI-MS: 265.0 $[M+H]^+$. Anal. calcd for $C_{10}H_9ClF_3N_3$: C, 45.56; H, 3.44; N, 15.94; found: C, 45.67; H, 3.51; N, 16.13%.

*8-Chloro-3-(2-chloropyridin-3-yl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-*a*]pyridine* (**2w**): Light yellow solid; yield 56%; m.p. 136–138°C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.57 (s, H, PyH), 8.34 (m, 3H, PyH), 8.72 (s, H, PyH); ESI-MS: 333.9 $[M+H]^+$. Anal. calcd for $C_{12}H_5Cl_2F_3N_4$: C, 43.27; H, 1.51; N, 16.82; found: C, 43.58; H, 1.45; N, 16.98%.

Antifungal activity

The antifungal activities of the title compounds against *Gibberella zeae* and *Alternaria alternata* were evaluated, chlorothalonil was selected as a positive control. Culture plates were cultivated at 24±1 ºC. The relative inhibition rate of the circle mycelium compared to a blank assay was calculated as follows: Relative ratio % = $(N_S - N_C)/N_C \times 100\%$, where N_S is the extended diameter of the circle mycelium during the blank assay and N_C is the extended diameter of the circle mycelium during testing.

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