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Synthesis and fungicidal activity of novel imidazo[4, 5-*b*]pyridine derivatives

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Abstract: A series of novel imidazo[4,5-*b*]pyridine derivatives were synthesized and their structures were characterized by NMR spectroscopy, mass spectrometry and elemental analysis. The results of bioassays showed that some compounds exhibit good fungicidal activity against *Puccinia polysora*. In particular, compound **7b** showed an EC_{50} value of 4.00 mg/L, which was comparable with that of tebuconazole. Besides, preliminary structure-activity relationship was discussed.

Keywords: fungicidal activity; imidazo[4,5-*b*]pyridine; structure-activity relationship; synthesis.

Introduction

The fungicide market has been dominated by strobilurins, triazoles and amides for a long time. As a result, pathogen resistance to these fungicides has become a serious problem [1]. Agrochemicals have been one of the most effective tools for increasing both crop quality and quantity while reducing labor costs [2-5].

Imidazo[4,5-*b*]pyridines are an important family of heterocyclic compounds, and their derivatives possess various pharmacological properties [6-11]. Examples of pharmacologically active compounds containing an imidazo[4,5-*b*]pyridine skeleton are shown in Figure 1. However, no commercial agrochemicals containing an imidazo[4,5-*b*] pyridine moiety have so far been found. In addition, few references about imidazo[4,5-b]pyridines with fungicidal activity have been published. Therefore, it is important to study imidazo[4,5-*b*]pyridines as potential fungicides.

In our previous work, we have discovered that compound **Ia** containing a nitropyridine core (Figure 2) displays remarkable insecticidal activities [12, 13]. In this report we tried to optimize the lead compound by synthesis of a series of novel imidazo[4,5-*b*]pyridine compounds (Figure 2).

Results and discussion

Target compounds **2a**,**h** and **4a**,**b** were prepared by reacting 3-nitropyridine-2-amines **1** or **3** and aryl aldehyde in the presence of saturated sodium dithionite. Compounds **7a**,**b** were synthesized by cyclization of the corresponding amide **6**. An attempted preparation of compound **7b** directly by treatment of the corresponding pyridine-2,3-diamine **5** with acid was only partially successful providing the product in low yield.

The chemical formula, mass-spectral data and fungicidal activity are shown in Table 1. Bioassays show that this series of compounds have good fungicidal activity against *P. polysora* at the concentration of 500 mg/L. For example, compounds **2g** and **7b** induce the mortality over 90% at the concentration of 500 mg/L. Compounds **2e**, **2h**, **4a**, **4b** and **7a** displayed 74%, 82%, 85%, 72% and 75% fungicidal activity against *P. polysora* at the same concentration, respectively. With the in-depth screening, only compound **7b** exhibits good fungicidal activity against

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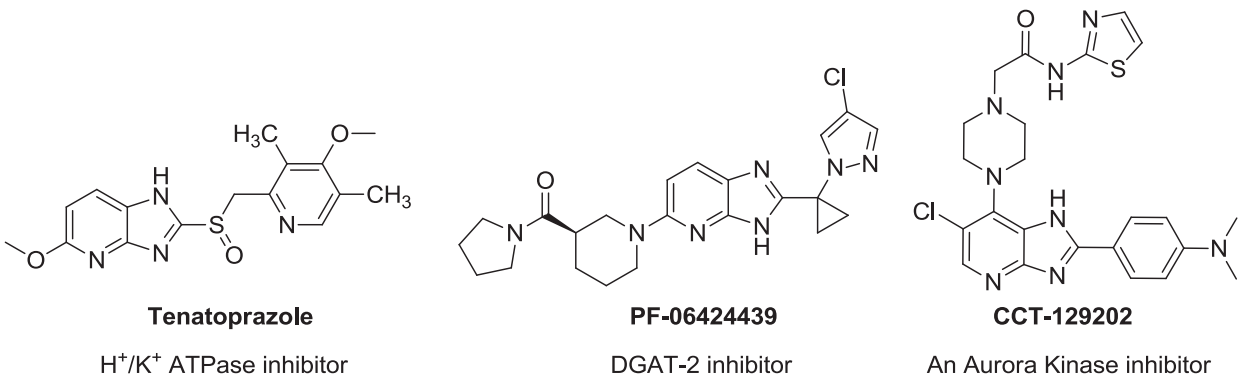


Figure 1 Examples of pharmacologically active compounds containing an imidazo[4,5-*b*]pyridine skeleton[9-11].

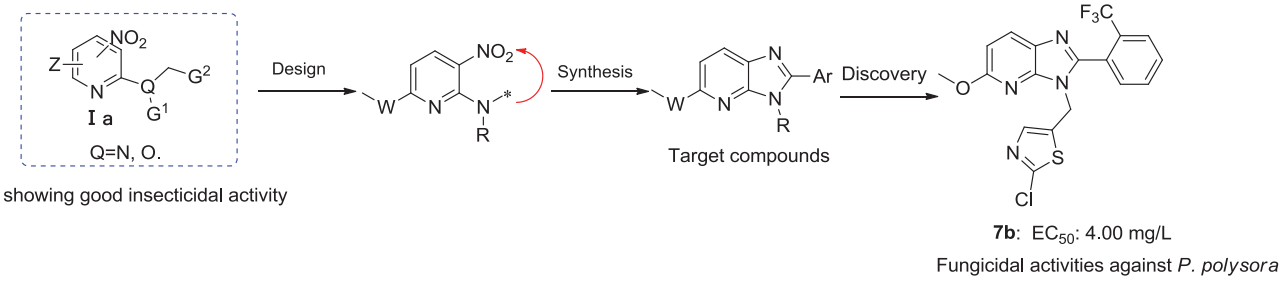


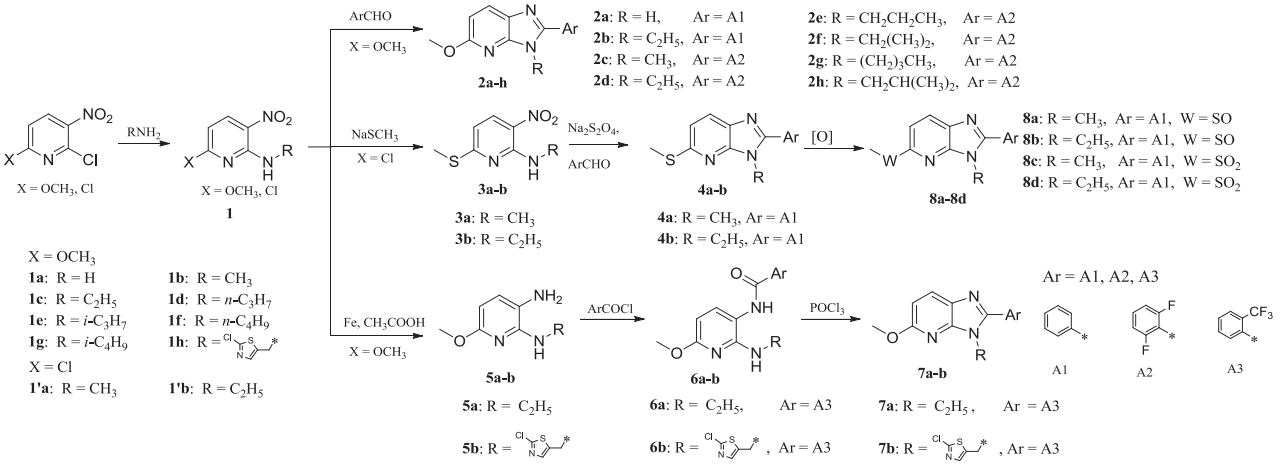
Figure 2 Design strategy of the target compounds containing imidazo[4,5-*b*]pyridine core.

Table 1 Chemical formula, MS data and fungicidal activity (%) against *P. polysora* at 500 mg/L of the compounds.

No.	Formula	MS	Fungicidal activity at 500 mg/L
2a	$C_{13}H_{11}N_3O$	225	20.10
2b	$C_{15}H_{15}N_3O$	253	21.50
2c	$C_{14}H_{11}F_2N_3O$	275	27.60
2d	$C_{15}H_{13}F_2N_3O$	289	0.00
2e	$C_{16}H_{15}F_2N_3O$	303	73.90
2f	$C_{16}H_{15}F_2N_3O$	303	29.90
2g	$C_{17}H_{17}F_2N_3O$	317	90.10
2h	$C_{17}H_{17}F_2N_3O$	317	82.30
4a	$C_{14}H_{13}N_3S$	255	85.00
4b	$C_{15}H_{15}N_3S$	269	72.00
7a	$C_{16}H_{14}F_3N_3O$	321	75.00
7b	$C_{18}H_{12}ClF_3N_4OS$	424	100.00
8a	$C_{14}H_{13}N_3OS$	271	50.00
8b	$C_{15}H_{15}N_3OS$	285	33.60
8c	$C_{14}H_{13}N_3O_2S$	287	0.00
8d	$C_{15}H_{15}N_3O_2S$	301	32.50

P. polysora. Its EC_{50} value is 4.00 mg/L, which is comparable with that of tebuconazole (2.00 mg/L).

For the preliminary structure-activity relationship analysis, the groups W, Ar and R were varied (Scheme 1). When W and Ar are kept constant, the fungicidal activity against *P. polysora* of target compounds is influenced by the nature of the R group. The R group is modified from H to a C1–C4 alkyl or thiazol-5-ylmethyl group. As the chain length increases, the fungicidal activity of the resultant compounds increases: **2g**, **2h** > **2e** > **2d**, **2c**; **7b** > **7a**; **8d** > **8c**. When R and Ar groups are kept constant, the fungicidal activity of the synthesized compounds is influenced by the nature of the W group. Modification of the W group from an oxygen to sulfur atom, sulfoxyl, or sulfuryl groups affects the different level of fungicidal activity against *P. polysora*, as exemplified by the following order: **4a** > **8a** >> **8c**; **4b** > **8b** > **8d** > **2b**. When W and R are kept constant, the fungicidal activity of target compounds is influenced by the nature of the Ar group. Modification of the Ar group from substituted phenyl to substituted phenyl showed the different level of fungicidal activity against P. polysora. The fungicidal activity is correlated as follows: **7a** > **2b** > **2d**. In general, the structure–activity relationships of target compounds can be summarized as follows. Activity order of R: 2-chlorothiazol-5-yl-methyl > *n*-C_4H_9, *i*-C_4H_9



Scheme 1 General synthetic route for the target compounds.

> n-C_3H_7, i-C_3H_7 > C_2H_5, CH_3, H; activity order of W: S > SO > SO_2 > O; activity order of Ar: 2-trifluoromethylphenyl > phenyl > 2,6-difluorophenyl.

Conclusions

A series of imidazo[4,5-*b*]pyridine derivatives were synthesized in the search for a new fungicide. Most of the synthesized compounds showed antifungal activity. In particular, compound **7b** shows the mortality of 100.00% against *P. polysora* at 500 mg/L and its EC_{50} value is 4.00 mg/L, which is comparable with that of tebuconazole (2.00 mg/L).

Experimental

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were acquired with a Varian INOVA-300 spectrometer using tetramethylsilane (TMS) as the internal standard and $CDCl_3$ as the solvent. Mass spectra were obtained using a Agilent 5973-6890 gas chromatography-mass spectrometer (GC-MS) and a Agilent 1100 series liquid chromatography-mass spectrometer (LC-MS). The uncorrected melting points were taken in the WRS-1B digital melting points apparatus (Shanghai Physical Optics). The column chromatography was performed using a 200–300 mesh silica gel. Elemental analysis data were obtained with a Vario EL III from Elementar. Reagents and solvents were used by commercial suppliers unless otherwise noted.

The general synthetic methods for the target compounds are shown in Scheme 1. Representative procedures are given as follows. Yields were not optimized. All reactions were carried out under a protective atmosphere of dry nitrogen or utilizing a calcium chloride tube.

N-butyl-6-methoxy-3-nitropyridin-2-amine (1f)

A mixture of 2-methoxyl-6-chloro-3-nitropyridine (4.30 g, 22.8 mmol) and triethylamine (2.31 g, 22.8 mmol) in *N, N*-dimethylformamide (40 mL) was stirred for 0.5 h at room temperature under nitrogen atmosphere. Butylamine (1.67 g, 22.8 mmol) in 10 mL of dry *N, N*-dimethylformamide was slowly added dropwise. The mixture was stirred at room temperature for 2–3 h then poured into water. The resultant precipitate was collected by filtration, washed with water and dried to give a yellow solid; yield 4.63 g (90%). Without further purification, compound **1f** was used in the subsequent reaction.

N-ethyl-6-(methylthio)-3-nitropyridin-2-amine (3b)

N-ethyl-6-chloro-3-nitropyridin-2-amine (11.02 g, 54.7 mmol) in tetrahydrofuran (30 mL) was added dropwise to a solution of sodium methanethiolate (21.14 g, 20%, 60.3 mmol) in water (20 mL) at room temperature. After 3 h of stirring, the mixture was poured into water and the resulting precipitate was filtered and dried to yield **3b** as a yellow solid; yield 11.68 g (97%).

N^2-[(2-Chlorothiazol-5-yl)methyl]-6-methoxypyridine-2, 3-diamine (5b)

N-[(2-chlorothiazol-5-yl)methyl]-6-methoxy-3-nitropyridin-2-amine (3.01 g, 10.0 mmol), and iron dust (1.68 g, 30.1 mmol) were successively added to 60 mL of acetic acid at room temperature for 2–3 h. The mixture was filtered. After the solvent was removed under reduced pressure, the residue was dissolved in dichloromethane, and the solution was washed with water, dried over Na_2SO_4 and

concentrated under reduced pressure to yield **5b** as a black solid; yield 2.46 g (91%).

N-{2-[((2-Chlorothiazol-5-yl)methyl)amino]-6-methoxypyridin-3-yl}-2-(trifluoromethyl)benzamide (6b)

A solution of compound **5b** (2.97 g, 11.0 mmol) in dichloromethane (30 mL) was added dropwise to a solution of 2-(trifluoromethyl)benzoyl chloride (3.43 g, 16.5 mmol) in dichloromethane (20 mL) at 0˚C. After 3 h of stirring, the mixture was poured into water and the aqueous phase was extracted with dichloromethane. The extract was washed twice with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield **6b** as a gray solid; yield 3.01 g (62%).

3-Ethyl-2-(2,6-difluorophenyl)-5-methoxy-3*H*-imidazo[4,5-*b*]pyridine (2g)

A solution of $Na_2S_2O_4$ (6.06 g, 34.8 mmol) in water (20 mL) was added dropwise to a solution of *n*-butyl-6-methoxy-3-nitropyridin-2-amine (1.73 g, 7.7 mmol) and 2,6-difluorobenzaldehyde (1.09 g, 7.7 mmol) in ethanol (80 mL). After 16 h of heating under reflux, the mixture was poured into water and the resulting precipitate was filtered and crystallized from ethyl acetate/petroleum ether to yield **2g** as a yellowish solid; yield 1.44 g (59%).

5-Chloro-2-[(5-methoxy-2-(2-(trifluoromethyl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]thiazole (7b)

Compound **6b** (2.59 g, 5.8 mmol) was added to 15 mL of phosphorus oxychloride. After 3 h of heating under reflux, the solvent was removed under reduced pressure. The residue was treated with 200 mL of ethyl acetate and Na_2CO_3 aqueous solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate, 5:1 to afford compound **7b** as a white solid; yield 0.89 g (36%).

3-Ethyl-5-(methylsulfinyl)-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (8b)

Compound **4b** (1.54 g, 5.7 mmol) in dichloromethane (40 mL) was added dropwise to a solution of 3-chloroperbenzoic acid (1.18 g, 85%, 5.8 mmol) in dichloromethane (20 mL) at 0˚C. After 2 h of stirring, the reaction was poured into water and the aqueous phase was extracted with EA, washed twice with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, and the residue was purified by silica-gel column chromatography to afford compound **8b** as a white solid (0.69 g, 2.3 mmol, yield: 40%).

3-Ethyl-2-(2,6-difluorophenyl)-5-(methylsulfonyl)-3*H*-imidazo[4,5-*b*]pyridine (8d)

Compound **4b** (0.58 g, 2.2 mmol) in dichloromethane (40 mL) was added dropwise to a solution of 3-chloroperbenzoic acid (0.98 g, 85%, 4.8 mmol) in dichloromethane (20 mL) at room temperature. After 2 h of stirring, the reaction was poured into water and the aqueous phase was extracted with dichloromethane. The combined organic layer was washed twice with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by silica-gel column chromatography to afford compound **8d** as a white solid (0.42 g, 1.4 mmol, yield: 64%).

The preparations of other intermediates compounds and final products were conducted in a similar way.

5-Methoxy-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (2a)

White solid, mp: 208.5 - 210.2˚C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (s, 3H, CH_3), 6.68 (d, *J* = 8.7 Hz, 1H, Ar H), 7.41-7.49 (m, 3H, Ar H), 7.87 (d, *J* = 8.7 Hz, 1H, Ar H), 8.00-8.07 (m, 2H, Ar H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 53.8, 106.6, 126.3, 127.9, 129.0, 129.6, 130.2, 150.4, 153.2, 155.4, 161.8; GC-MS: *m/z* 225, M^+, base peak at *m/z* 225; Elemental analysis: Calcd: C, 69.32; H, 4.92; N, 18.66; Found: C, 69.40; H, 4.93; N, 18.63.

3-Ethyl-5-methoxy-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (2b)

Gray solid; mp 118.3 - 118.7˚C; ^{1}H NMR: δ 1.46 (t, *J* = 7.2 Hz, 3H, CH_3), 4.02 (s, 3H, CH_3), 4.34 (q, *J* = 7.2 Hz, 2H, CH_2), 6.7 (d, *J* = 8.4 Hz, 1H, Ar H), 7.49 - 7.57 (m, 3H, Ar H), 7.72 - 7.77 (m, 2H, Ar H), 7.94 (d, *J* = 8.4 Hz, 1H, Ar H); ^{13}C NMR: δ 15.1, 38.6, 53.6, 106.0, 128.7, 128.8, 129.5, 130.0, 130.8, 145.9, 151.4, 161.2; GC-MS: *m/z* 253, M^+, base peak at *m/z* 253. Anal. Calcd: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.08; H, 5.99; N, 16.64.

2-(2,6-Difluorophenyl)-5-methoxy-3-methyl-3*H*-imidazo[4,5-*b*]pyridine (2c)

White solid, mp 158.5 - 159.8˚C; ^{1}H NMR: δ 3.73 (s, 3H, CH_3), 4.03 (s, 3H, CH_3), 6.73 (d, *J* = 8.4 Hz, 1H, Ar H), 7.05-7.14 (m, 2H, Ar H), 7.46 - 7.56 (m, 1H, Ar H), 7.98 (d, *J* = 8.4 Hz, 1H, Ar H); ^{13}C NMR: δ 29.0, 53.6, 106.5, 111.7 (d, *J* = 6.9 Hz), 112.0 (d, *J* = 6.9 Hz), 130.5, 132.0 (t, *J* = 10.3 Hz), 141.0, 145.6, 159.4, 159.5, 161.7, 162.7, 162.8; GC-MS:

m/z 275, M^+, base peak at *m/z* 275. Anal. Calcd: C, 61.09; H, 4.03; N, 15.27. Found: C, 61.05; H, 4.02; N, 15.28.

2-(2,6-Difluorophenyl)-3-ethyl-5-methoxy-3*H*-imidazo[4,5-*b*]pyridine (2d)

Gray solid; mp 123.9 - 126.5˚C; ^{1}H NMR: δ 1.37 (t, *J* = 7.2 Hz, 3H, CH_3), 4.02 (s, 3H, CH_3), 4.13 (q, *J* = 7.5 Hz, 2H, CH_2), 6.73 (d, *J* = 8.7 Hz, 1H, Ar H), 7.06 - 7.12 (m, 2H, Ar H), 7.49 - 7.52 (m, 1H, Ar H), 7.97 (d, *J* = 8.4 Hz, 1H, Ar H); ^{13}C NMR: δ 14.7, 38.5, 53.6, 106.5, 111.7, 112.0, 130.5, 132.1 (t, *J* = 9.8 Hz), 140.3, 145.1, 159.5, 159.6, 161.5, 162.8, 162.9; GC-MS: *m/z* 289, M^+, base peak at *m/z* 289. Anal. Calcd: C, 62.28; H, 4.53; N, 14.53. Found: C, 62.25; H, 4.52; N, 14.50.

2-(2,6-Difluorophenyl)-5-methoxy-3-propyl-3*H*-imidazo[4,5-*b*]pyridine (2e)

White solid; mp 108.0 - 108.3˚C; ^{1}H NMR: δ 0.77 (t, *J* = 7.5 Hz, 3H, CH_3), 1.76 - 1.84 (m, 2H, CH_2), 4.02 (s, 3H, CH_3), 4.08 (q, *J* = 6.9 Hz, 2H, CH_2), 6.73 (d, *J* = 8.7 Hz, 1H, Ar H), 7.06 - 7.12 (m, 2H, Ar H), 7.49 - 7.55 (m, 1H, Ar H), 7.98 (d, *J* = 8.7 Hz, 1H, Ar H); ^{13}C NMR: δ 11.0, 22.5, 44.9, 53.6, 106.4, 111.6, 112.0, 130.5, 132.0 (t, *J* = 10.0 Hz), 140.6, 145.4, 159.4, 159.5, 161.5, 162.7, 162.8; GC-MS: *m/z* 303, M^+, base peak at *m/z* 303. Anal. Calcd: C, 63.38; H, 5.02; N, 13.80. Found: C, 63.36; H, 5.01; N, 13.85.

2-(2,6-Difluorophenyl)-3-isopropyl-5-methoxy-3*H*-imidazo[4,5-*b*]pyridine (2f)

White solid; mp 120.4 - 122.9˚C; ^{1}H NMR: δ 1.70 (d, *J* = 6.9 Hz, 6H, $2CH_3$), 4.01 (s, 3H, CH_3), 4.34 - 4.39 (m, 1H, CH), 6.71 (d, *J* = 8.7 Hz, 1H, Ar H), 7.05 - 7.10 (m, 2H, Ar H), 7.48 - 7.53 (m, 1H, Ar H), 7.95 (d, *J* = 8.4 Hz, 1H, Ar H); ^{13}C NMR: δ 20.8, 49.4, 53.4, 106.1, 111.4, 111.7, 130.3, 131.9 (t, *J* = 10.0 Hz), 139.9, 144.8, 159.4, 159.5, 160.5, 162.7, 162.8; GC-MS: *m/z* 303, M^+, base peak at *m/z* 303. Anal. Calcd: 63.36; H, 4.98; N, 13.85. Found: C, 63.30; H, 4.97; N, 13.87.

3-Butyl-2-(2,6-difluorophenyl)-5-methoxy-3*H*-imidazo[4,5-*b*]pyridine (2g)

Yellowish solid; mp 66.3 - 66.9˚C; ^{1}H NMR: δ 0.80 (t, *J* = 7.5 Hz, 3H, CH_3), 1.17 - 1.24 (m, 2H, CH_2), 1.71 (t, *J* = 7.2 Hz, 2H, CH_2), 4.02 (s, 3H, CH_3), 4.12 (t, *J* = 7.2 Hz, 2H, CH_2), 6.72 (d, *J* = 8.7 Hz, 1H, Ar H), 7.06 - 7.11 (m, 2H, Ar H), 7.48 - 7.54 (m, 1H, Ar H), 7.97 (d, *J* = 8.7 Hz, 1H, Ar H); ^{13}C NMR: δ 13.3, 19.4, 31.2, 42.8, 53.6, 106.4, 111.6 (d, J = 2.3 Hz), 111.9 (d, J = 1.7 Hz), 130.4, 132.1 (t, J = 10.4 Hz), 140.6, 145.2, 159.3, 159.4, 161.4, 162.6, 162.7.; GC-MS: *m/z* 317, M^+, base peak at *m/z* 317. Anal. Calcd: C, 64.34; H, 5.40; N, 13.24. Found: C, 64.31; H, 5.39; N, 13.20.

3-(sec-Butyl)-2-(2,6-difluorophenyl)-5-methoxy-3*H*-imidazo[4,5-*b*]pyridine (2h)

Yellow solid; mp: 102.7 - 103.2˚C; ^{1}H NMR: δ 0.77 (d, *J* = 6.9 Hz, 6H, $2CH_3$), 2.15 - 2.19 (m, 1H, CH), 3.94 (d, *J* = 7.5 Hz, 2H, CH_2), 4.01 (s, 3H, CH_3), 6.72 (d, *J* = 8.7 Hz, 1H, Ar H), 7.05 - 7.11 (m, 2H, Ar H), 7.48 - 7.54 (m, 1H, Ar H), 7.97 (d, *J* = 8.7 Hz, 1H, Ar H); ^{13}C NMR: δ 19.8, 28.4, 50.5, 53.6, 106.4, 111.6, 111.9, 130.0, 132.0 (t, *J* = 10.0 Hz), 140.9, 145.5, 159.2, 159.3, 161.4, 162.6, 162.7; GC-MS: *m/z* 317, M^+, base peak at *m/z* 261. Anal. Calcd: C, 64.34; H, 5.40; N, 13.24. Found: C, 64.38; H, 5.38; N, 13.21.

3-Methyl-5-(methylthio)-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (4a)

White solid, mp: 150.3 - 150.6˚C; ^{1}H NMR: δ 2.68 (s, 3H, CH_3), 3.97 (s, 3H, CH_3), 7.14 (d, *J* = 8.4 Hz, 1H, Ar H), 7.52 - 7.57 (m, 3H, Ar H), 7.81 - 7.86 (m, 2H, Ar H), 7.89 (d, *J* = 8.1 Hz, 1H, Ar H); ^{13}C NMR: δ 13.8, 30.4, 116.7, 127.2, 128.7, 128.9, 129.8, 129.9, 131.9, 148.9, 152.8, 153.9; HPLC-MS Pos $[M+1]^+$ = 256. Anal. Calcd: C, 65.86; H, 5.13; N, 16.46. Found: C, 65.90; H, 5.10; N, 16.49.

3-Ethyl-5-(methylthio)-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (4b)

White solid; mp 127.9 - 130.0˚C; ^{1}H NMR: δ 1.48 (t, *J* = 7.5 Hz, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.39 (q, *J* = 7.5 Hz, 2H, CH_2), 7.13 (d, *J* = 8.4 Hz, 1H, Ar H), 7.52 - 7.58 (m, 3H, Ar H), 7.74 - 7.79 (m, 2H, Ar H), 7.87 (d, *J* = 8.1 Hz, 1H, Ar H); ^{13}C NMR: δ 13.7, 15.0, 38.6, 116.7, 127.1, 128.7, 128.8, 129.8, 130.3, 132.1, 148.4, 152.5, 153.7; GC-MS: *m/z* 269, M^+, base peak at *m/z* 236. Anal. Calcd: C, 66.88; H, 5.61; N, 15.60. Found: C, 66.92; H, 5.62; N, 15.57.

3-Ethyl-5-methoxy-2-(2-(trifluoromethyl)phenyl)-3*H*-imidazo[4,5-*b*]pyridine (7a)

Yellow solid; mp 83.3 - 85.5˚C; ^{1}H NMR: δ 2.25 (s, 3H, CH_3), 4.14 (s, 3H, CH_3), 4.78 (dd, *J* = 5.1, 0.6 Hz, 2H, CH_2), 7.21 (s, 1H, thiazole-H), 7.43 - 7.48 (m, 3H, Ar H), 7.58 (bs, 1H, NH), 7.92 - 7.97 (m, 2H, Ar H); ^{13}C NMR: δ 14.5, 38.2, 53.6, 106.1, 117.0 (q, *J* = 272 Hz), 126.6 (q, *J* = 4.6 Hz), 128.8, 129.3, 129.6 (q, *J* = 34 Hz), 130.3, 130.6, 131.5, 132.0, 144.9, 148.1, 161.4; GC-MS: *m/z* 321, M^+, base peak at *m/z* 321. Anal. Calcd: C, 59.81; H, 4.39; N, 13.08; Found: C, 59.87; H, 4.38; N, 13.10.

5-Chloro-2-[(5-methoxy-2-(2-(trifluoromethyl)phenyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl]thiazole (7b*)*

White solid; mp 136.6 - 137.4 ; ^{1}H NMR: δ 2.24 (s, 3H, CH_3), 4.14 (s, 3H, CH_3), 4.64 (dd, *J* = 5.7, 0.6 Hz, 2H, CH_2), 7.34 (bs, 1H, NH), 7.35 - 7.43 (m, 2H, Ar H), 7.50 - 7.53 (m, 1H, Ar H), 7.53 (s, 1H, thiazole-H), 7.96 - 7.99 (m, 1H, Ar H); ^{13}C NMR: δ 38.7, 53.9, 107.2, 117.8 (q, *J* = 273 Hz), 126.8 (q, *J* = 4.8 Hz), 128.1, 129.2, 129.8 (q, *J* = 30 Hz), 130.8, 130.9, 131.8, 132.2, 134.9, 140.5, 144.2, 147.2, 153.0, 161.7; GC-MS: *m/z* 424, M^+, base peak at *m/z* 132. Anal. Calcd: C, 50.89; H, 2.85; N, 13.19. Found: C, 50.95; H, 2.86; N, 13.14;

3-Methyl-5-(methylsulfinyl)-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (8a)*:*

White solid, mp: 166.5 - 167.3˚C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.92 (s, 3H, CH_3), 4.00 (s, 3H, CH_3), 7.56 - 7.61 (m, 3H, Ar H), 7.83 - 7.88 (m, 2H, Ar H), 7.95 (d, *J* = 8.4 Hz, 1H, Ar H), 8.26 (d, *J* = 8.1 Hz, 1H, Ar H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.6, 41.7, 113.6, 128.2, 128.8, 129.0, 129.2, 130.5, 136.4, 148.7, 156.4, 158.6; GC-MS: *m/z* 271, M^+, base peak at *m/z* 224. Anal. Calcd: C, 61.97; H, 4.83; N, 15.49; Found: C, 61.95; H, 4.82; N, 15.46.

3-Ethyl-5-(methylsulfinyl)-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (8b)

White solid, mp: 165.3 - 165.4˚C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (t, *J* = 7.2 Hz, 3H, CH_3), 2.92 (s, 3H, CH_3), 4.42(q, *J* = 7.2 Hz, 2H, CH_2), 7.56 - 7.61 (m, 3H, Ar H), 7.77 - 7.83 (m, 2H, Ar H), 7.95 (d, *J* = 8.4 Hz, 1H, Ar H), 8.25 (d, *J* = 8.1 Hz, 1H, Ar H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.0, 39.0, 41.7, 113.6, 128.3, 128.9, 129.0, 129.6, 130.5, 136.5, 148.2, 156.2, 158.6; GC-MS: *m/z* 285, M^+, base peak at *m/z* 270; Elemental analysis: Calcd: C, 63.13; H, 5.30; N, 14.73; Found: C, 63.15; H, 5.31; N, 14.76.

3-Methyl-5-(methylsulfonyl)-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (8c)

Yellow solid; mp 183.9 - 186.3˚C; ^{1}H NMR: δ 3.31 (s, 3H, CH_3), 4.08 (s, 3H, CH_3), 7.60 - 7.64 (m, 3H, Ar H), 7.88 - 7.91 (m, 2H, Ar H), 8.11 (d, *J* = 8.1 Hz, 1H, Ar H), 8.28 (d, *J* = 8.1 Hz, 1H, Ar H); ^{13}C NMR: δ 30.9, 40.7, 116.1, 127.8, 128.9, 129.2, 131.0, 138.0, 148.5, 151.0, 158.4; GC-MS: *m/z* 287, M^+, base peak at *m/z* 287; Elemental analysis: Calcd: C, 61.97; H, 4.83; N, 15.49. Found: C, 61.92; H, 4.82; N, 15.47.

3-Ethyl-5-(methylsulfonyl)-2-phenyl-3*H*-imidazo[4,5-*b*]pyridine (8d)

White solid; mp 187.4 - 188.1˚C; ^{1}H NMR: δ 1.50 (t, *J* = 7.5 Hz, 3H, CH_3), 3.31 (s, 3H, CH_3), 4.49 (q, *J* = 7.5 Hz, 2H, CH_2), 7.56 - 7.65 (m, 3H, Ar H), 7.79 - 7.85 (m, 2H, Ar H), 8.09 (d, *J* = 8.1 Hz, 1H, Ar H), 8.24 (d, *J* = 8.4 Hz, 1H, Ar H); ^{13}C NMR: δ 15.0, 39.2, 40.5, 115.9, 127.8, 128.9, 129.2, 130.8, 138.0, 147.9, 150.9, 158.1; GC-MS: *m/z* 300, M^+, base peak at *m/z* 300. Anal. Calcd: C, 52.26; H, 3.29; N, 11.43. Found: C, 52.20; H, 3.30; N, 11.40.

***N*-Methyl-6-(methylthio)-3-nitropyridin-2-amine (3a)**

^{1}H NMR: δ 2.60 (s, 3H, CH_3), 3.21 (d, *J* = 5.1 Hz, 2H, CH_2), 6.50 (d, *J* = 9.0 Hz, 1H, Py H), 8.17 (d, *J* = 9.0 Hz, 1H, Py H), 8.51 (bs, 1H, NH); ^{13}C NMR: δ 13.3, 28.0, 109.8, 123.8, 134.0, 151.8, 168.9; GC-MS: *m/z* 199, M^+, base peak at *m/z* 199.

***N*-Ethyl-6-(methylthio)-3-nitropyridin-2-amine (3b):**

^{1}H NMR: δ 1.31 (t, *J* = 7.2 Hz, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.69 – 3.73 (m, 2H, CH_2), 6.48 (d, *J* = 8.7 Hz, 1H, Py H), 8.15 (d, *J* = 8.7 Hz, 1H, Py H), 8.54 (bs, 1H, NH); ^{13}C NMR: δ 13.2, 14.6, 36.0, 109.7, 123.9, 133.9, 151.9, 168.7; GC-MS: *m/z* 213, M^+, base peak at *m/z* 213.

***N*^{2}-Ethyl-6-methoxypyridine-2,3-diamine (5a):**

^{1}H NMR: δ 1.22 (t, *J* = 7.2 Hz, 3H, CH_3), 2.81 (bs, 2H, NH_2), 3.43 (q, *J* = 7.5 Hz, 2H, CH_2), 3.83 (s, 3H, CH_3), 4.37 (bs, 1H, NH), 5.87 (d, *J* = 8.1 Hz, 1H, Py H), 6.86 (d, *J* = 7.8 Hz, 1H, Py H); ^{13}C NMR: δ 15.3, 36.0, 53.3, 95.7, 119.3, 128.0, 135.0, 150.2; GC-MS: *m/z* 167, M^+, base peak at *m/z* 167.

***N*^{2}-((2-Chlorothiazol-5-yl)methyl)-6-methoxypyridine-2,3-diamine (5b)**

^{1}H NMR: δ 3.73 (s, 3H, CH_3), 4.13 (bs, 2H, NH_2), 4.64 (d, *J* = 6.0 Hz, 2H, CH_2), 5.84 (d, *J* = 7.8 Hz, 1H, Py H), 6.32 (t, *J* = 5.7 Hz, 1H, NH), 6.79 (d, *J* = 8.1 Hz, 1H, Py H), 7.59 (s, 1H, Ar H); ^{13}C NMR: δ 37.4, 53.5, 96.6, 120.1, 128.9, 138.4, 140.5, 147.7, 151.1, 158.0; GC-MS: *m/z* 270, M^+, base peak at *m/z* 138.

***N*-(2-(Ethylamino)-6-methoxypyridin-3-yl)-2-(trifluoromethyl)benzamide (6a):**

^{1}H NMR: δ 1.23 (t, *J* = 7.5 Hz, 3H, CH_3), 3.45 – 3.52 (m, 2H, CH_2), 3.89 (s, 3H, CH_3), 6.02 (d, *J* = 8.4 Hz, 1H, Py H), 6.99 (bs, 1H, NH), 7.32 (d, *J* = 8.4 Hz, 1H, Ar H), 7.57 - 7.71 (m, 3H, Ar H), 7.75 (d, *J* = 7.5 Hz, 1H, Py H); ^{13}C NMR: δ 14.8, 36.2, 53.3, 95.8, 108.7, 118.2 (q, *J* = 271 Hz), 126.2 (q, *J* = 4.6 Hz), 126.7, 128.5, 129.6 (q, *J* = 29.8 Hz), 131.3, 132.0, 137.2, 152.6, 162.2, 167.2; GC-MS: *m/z* 339, M^+, base peak at *m/z* 166.

N-{2-[((2-Chlorothiazol-5-yl)methyl)amino]-6-methoxypyridin-3-yl}-2-(trifluoro-methyl)benzamide (6b)

^{1}H NMR: δ 3.93 (s, 3H, CH_3), 4.78 (s, 2H, CH_2), 6.15 (d, J = 8.1 Hz, 1H, Py H), 7.11 (bs, 1H, NH), 7.34 (d, J = 8.4 Hz, 1H, Ar H), 7.44 (s, 1H, Ar H), 7.59 - 7.69 (m, 3H, Ar H), 7.76 (d, J = 7.2 Hz, 1H, Py H); ^{13}C NMR: δ 38.1, 53.7, 98.7, 109.7, 118.5 (q, J = 272 Hz), 126.5 (q, J = 5.1 Hz), 127.0, 128.1, 128.6, 128.9 (q, J = 30 Hz), 130.4, 132.3, 137.6, 138.7, 140.2, 151.2, 158.5, 166.9; GC-MS: m/z 442, M^+, base peak at m/z 173.

Biological Assay

Stock solution of every test compound was prepared in DMF at a concentration of 1000 mg /L and then the solution was diluted to the required test concentration (50-500 mg/L) with water containing Tween 80 (0.40 mg/L) [14-17].

For Fungicidal activity against P. polysora, the corn leaves with *P. polysora* were dipped in the test solutions to wash the spores. After filtration with 2-4 layers of gauze, and spore suspension was prepared. The spore suspension was inoculated, and cultured 24 h under weak light. Each assay contained three replications. After 24 h, mortality was recorded. The test was run three times, and results were averaged.

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References

[1] Liu, A. P.; Wang, X. G.; Liu, X. P.; Li, J. M.; Chen, H. B.; Hu, L.; Yu, W. Q.; He, L.; Liu, W. D.; and Huang, M. Z. Synthesis and fungicidal Activity of Novel 2-heteroatomthiazole-based carboxanilides. *J. Heterocycl. Chem.* **2017**, 54, 1625-1629.

[2] Jeschke, P. The unique role of halogen substituents in the design of modernagrochemicals. *Pest Manage. Sci.* **2010**, 66, 10–27.

[3] Guan, A. Y.; Liu, C. L.; Yang, X. P.; Dekeyser, M. Application of the intermediate derivatization approach in agrochemical discovery. *Chem. Rev.* **2014**, 114, 7079–7107.

[4] Lv, P.; Chen, Y. L.; Zhao, Z.; Shi, T. Z.; Wu, X. W.; Xue, X. W.; Li, Q. X.; Hua, R. M. Design, synthesis, and antifungal activities of 3-acyl thiotetronic acid derivatives: new fatty acid synthase inhibitors. *J. Agric. Food Chem.* **2018**, 66, 1023–1032.

[5] Jian, W. L.; He, D. H.; Xi, P. G.; Li, X. W. Synthesis and biological evaluation of novel fluorine-containing stilbene derivatives as fungicidal agents against phytopathogenic fungi. *J. Agric. Food Chem.* **2015**, 63, 9963–9969.

[6] Krause, M.; Foks, H.; Gobis, K. Pharmacological Potential and Synthetic Approaches of Imidazo[4,5-*b*]pyridine and Imidazo [4,5-*c*]pyridine Derivatives. *Molecules.* **2017**, 22, 399-423.

[7] Ouyang, J. F.; Shao, J. A.; Zou, H. B.; Lou, Y. J.; Yu, Y. P. Hepatic Differentiation of rat mesenchymal Stem Cells by a Small Molecule. *ChemMedChem.* **2012**, 7, 1447-1452.

[8] Lapierre, J. M.; Eathiraj, S.; David, V.; Liu, Y. B.; Bull, C.; Susan, C. K.; Shin, L.; Kelleher, E.; Kizer, D.; Koerner, S.; Makhija, S.; Matsuda, A.; Moussa, M.; Namdev, N.; Savage, R.; Szwaya, J.; Volckova, E.; Westlund, N.; Wu, H.; Schwartz, B. Discovery of 3-(3-(4-(1-Aminocyclobutyl)phenyl)-5-phenyl-3*H*-imidazo[4,5-*b*] pyridin-2-yl)pyridin-2-amine (ARQ 092): an orally bioavailable, selective, and potent allosteric AKT inhibitor. *J. Med. Chem.* **2016**, 59, 6455-6469.

[9] Han, W. B.; Wang, C.; Wang, M. L.; Zhang, K. S. Process for synthesis of 2-mercapto-5-methoxyimidazolo[4,5-*b*]pyridine as intermediate of tenatoprazole. CN Patent Application *CN 102040607 A*, **2011**.

[10] Bader, S. J.; Herr, M.; Aspnes, G. E.; Cabral, S.; Li, Q. F.; Bian, J. W.; Coffey, S. B.; Dowling, M. S.; Fernando, D. P.; Jiao, W. H.; Lavergne, S. Y.; Kung, D. W. Route selection and optimization in the synthesis of two imidazopyridine inhibitors of DGAT-2. *Org. Process Res. Dev.* **2018**, 22, 360–367.

[11] Cheng, C.; Liu, Z. G.; Zhang, H.; Xie, J. D.; Chen, X. G.; Zhao, X. Q.; Wang, F.; Liang, Y. J.; Chen, L. K.; Singh, S.; Chen, J. J.; Talele, T. T.; Chen, Z. S.; Zhong, F. T.; Fu, L. W. Enhancing chemosensitivity in ABCB1- and ABCG2-overexpressing cells and cancer stem-like cells by an aurora kinase inhibitor CCT129202. *Mol. Pharm.* **2012**, 9, 1971-1982.

[12] Wu, D. X.; Liu, M. H.; Liu, A. P.; Huang, M. Z.; Hu, Z. B.; Ren, Y. G.; Liu, X. P.; Tang, M.; Zuo, W. Q. Synthesis and crystal structure of N-((6-chloropyridin-3-yl)methyl)6-eth oxy-*N*-ethyl-3-nitropyridin-2-amine. *Chin. J. Struct. Chem.* **2012**, 31, 621-624.

[13] Liu, A. P.; Yu, W. Q.; Liu, M. H.; Bai, J. J.; Liu, W. D.; Liu, X. P.; Pei, H.; Hu, L.; Huang, M. Z.; Wang, X. G. Synthesis and insecticidal activity of novel nitropyridyl-based dichloropropene ethers. *J. Agric. Food Chem.* **2015**, 63, 7469-7475.

[14] Huang, D. L.; Huang, M. Z.; Liu, W. D.; Liu, A. P.; Liu, X. P.; Chen, X. Y.; Pei, H.; Sun, J.; Yin, D. L.; Wang, X. G. Design, synthesis and biological evaluation of 1*H*-pyrazole-5-carboxamide derivatives as potential fungicidal and insecticidal agents. *Chem. Papers.* **2017**, 71, 2053-2061.

[15] Xue, H. S.; Liu, A. P.; Liu, W. D.; Li, J. M.; Ren, Y. G.; Huang, L.; He, L.; Ou, X. M.; Ye, J.; Huang, M. Z. Syntheses and fungicidal activities of thiazole-5-carboxanilides bearing thioether group. *Chem. Res. Chin. Univ.* **2016**, 32, 781-785.

[16] Yan, Z. Z.; Liu, A. P.; Huang, M. Z.; Liu, M. H.; Pei, H.; Huang, L.; Yi, H. B.; Liu, W. D.; Hu, A. X. Design, synthesis, DFT study and antifungal activity of the derivatives of pyrazolecarboxamide containing thiazole or oxazole ring. *Eur. J. Med. Chem.* **2018**, 149, 170-181.

[17] Liu, A. P.; Wang, X. G.; Ou, X. M.; Huang, M. Z.; Chen, C.; Liu, S. D.; Huang, L.; Liu, X. P.; Zhang, C. L.; Zheng, Y. Q.; Ren, Y. G.; He, L.; Yao, J. R. Synthesis and fungicidal activities of novel bis(trifluoromethyl)phenyl-based strobilurins. *J. Agric. Food. Chem.* **2008**, 56, 6562-6566.