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Synthesis and antifungal activity of imidazo[1,2-b]pyridazine derivatives against phytopathogenic fungi

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Abstract: A series of 3,6-disubstituted imidazo[1,2-b]pyridazine derivatives have been synthesized and characterized with spectroscopic analyses. The antifungal activities of these compounds against nine phytopathogenic fungi were evaluated by the mycelium growth rate method. The in *vitro* antifungal bioassays indicated that most of compounds displayed excellent and broad-spectrum antifungal activities. Especially, compounds **4a**, **4c**, **4d**, **4l** and **4r** exhibited 1.9-25.5 fold more potent than the commercially available fungicide hymexazol against *Corn Curvalaria Leaf Spot* (CL), *Alternaria alternate* (AA), *Pyricularia oryzae* (PO) and *Alternaria brassicae* (AB) strains. Structure-activity relationship analysis showed that the enhanced antifungal activity is significantly affected by the substituents on the benzene ring and pyridazine ring.

Keywords: imidazo[1,2-b]pyridazine, pathogenic fungi, synthesis, antifungal activity

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Phytopathogenic fungi present a serious problem of agricultural production worldwide, since they often quickly infect many crops and cause significant yield reduction[1]. Particularly, many phytopathogenic fungi produce mycotoxins that are harmful to animal and human health if they enter the food chain[2]. Therefore, many commercial fungicides with high activity and broad antifungal spectrum have been extensively used to ensure agricultural production and food safety while controlling a variety of plant diseases [3]. However, the continuing use of commercial fungicides has led to the cross-resistance of phytopathogenic fungi to fungicides[4]. Thus, it is necessary to develop new fungicides with novel molecular frameworks to efficiently control these agricultural fungi.

Pyridazines are important heterocycle scaffolds that display diverse biologiacl activites in the fields of medicine[5-11] and agriculture[12]. For example (Fig. 1), Minaprine is a psychotropic drug which has proved to be effective in the treatment of various depressive states[13]; pyridazomy is an antifungal and antibiotic compound, which is the first pyridazine derivative isolated from a natural source[14]; pyridaben is widely used as an acaricide with a long residual action; and chloridazone has been used as a herbicide with a long history[15]. Furthermore, imidazole is an important class of nitrogen containing heterocycle, and some heterocycle-linked imidazole derivatives exhibited potential antimicrobial and antifungal activities, such as imidazo[1,2-a]pyrazines[16], imidazo[1,2-a]pyridine[17], imidazo[1,2-a]pyrimidine[18] and pyrazolo[1,5-a]pyrimidine[19] derivatives showed significant antifungal activity against human pathogenic microorganisms, and [1,2,4]triazolo[1,5-a]pyrimidines[20]

derivatives exhibited certain inhibition activity against phytopathogenic fungi (Fig. 1). Consequently, in the continuation of our research aimed at the discovery and development of novel antifungal candidates[21-24], here we selected imidazo[1,2-b]pyridazine[25] skeleton composed of imidazole and pyridazine rings as the lead compound, a series of 3,6-disubstituted imidazo[1,2-b]pyridazine derivatives (Fig. 2) were designed, synthesized and evaluated for their antifungal activities against nine phytopathogenic fungi.

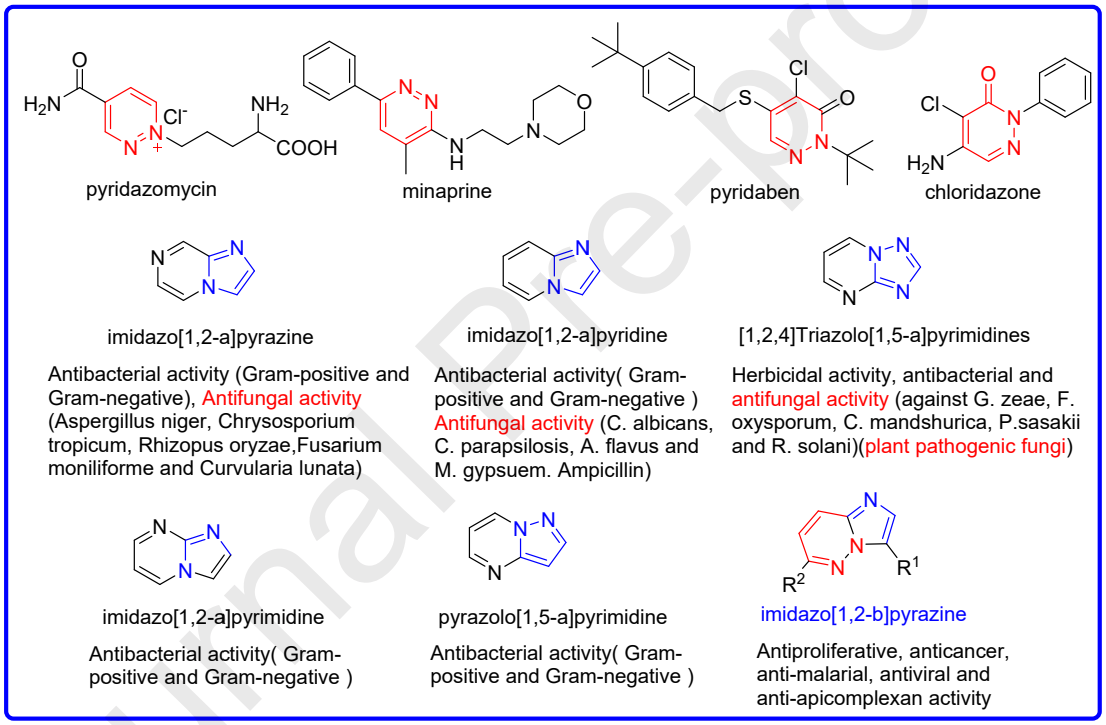
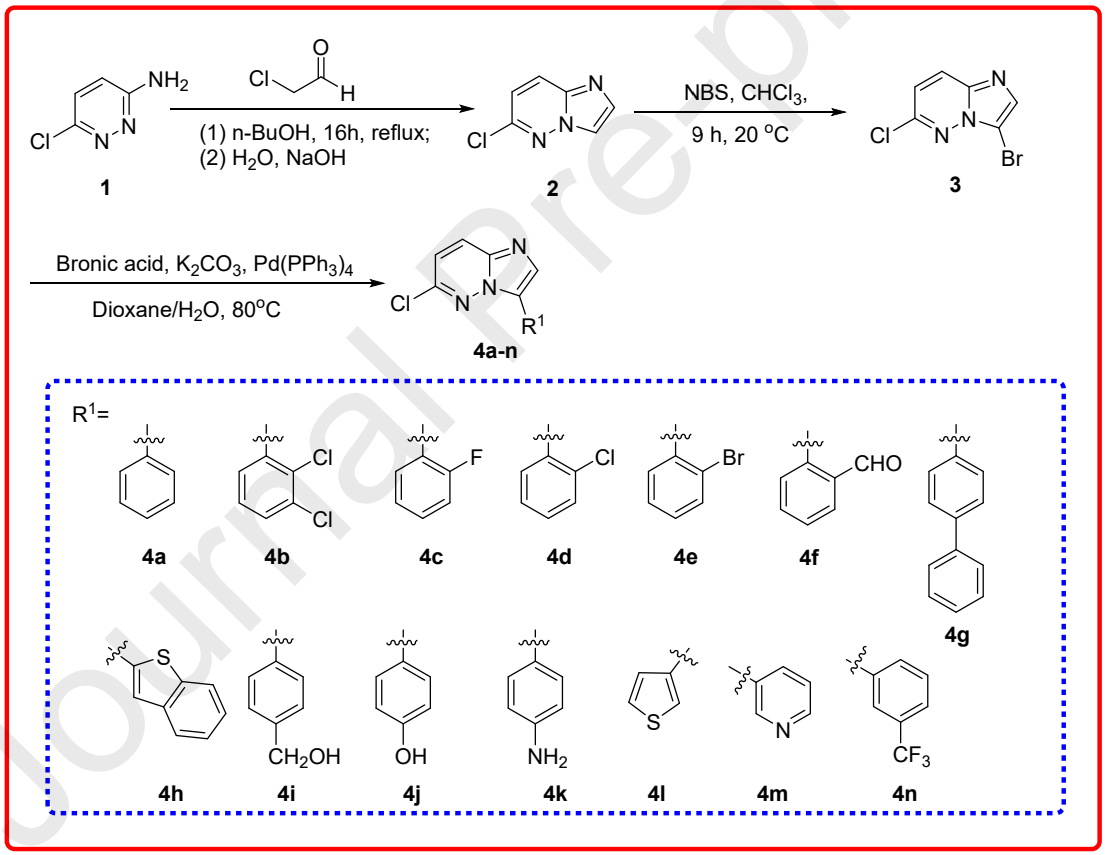


Fig. 1. Chemical structures of containing pyridazine or imidazole

As shown in Scheme 1, 6-chloroimidazo[1,2-b]pyridazine (**2**) was obtained by the cyclization of 3-amino-6-chloropyridazine (**1**) and chloroacetaldehyde at reflux in butanol for 16 h, followed by N-bromosuccinimide (NBS) bromination to afford 3-bromo-6-chloro-imidazo[1,2-b]pyridazines (**3**). Afterwards, a series of C-3 substituted 6-chloro-imidazo[1,2-b]pyridazine derivatives (**4a–n**) were smoothly

obtained by the Suzuki cross-coupling reaction. In order to investigate the impact of C-6 substituents on the antifungal activity, we selected 6-chloro-3-phenylimidazo[1,2-b]pyridazine (**4a**) with the higher activity as a secondary parent compound and designed a series of its derivatives. As depicted in Scheme 2, several C-6 substituted 3-phenylimidazo[1,2-b]pyridazine derivatives were prepared by fluorination (**4o**), palladium carbon dechlorination (**4p**), Suzuki reaction (**4q**) and etherification (**4r-v**). The structures of all synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS.



Scheme 1. Synthesis of C-3 substituted 6-chloro-imidazo[1,2-b]pyridazines (**4a–n**)

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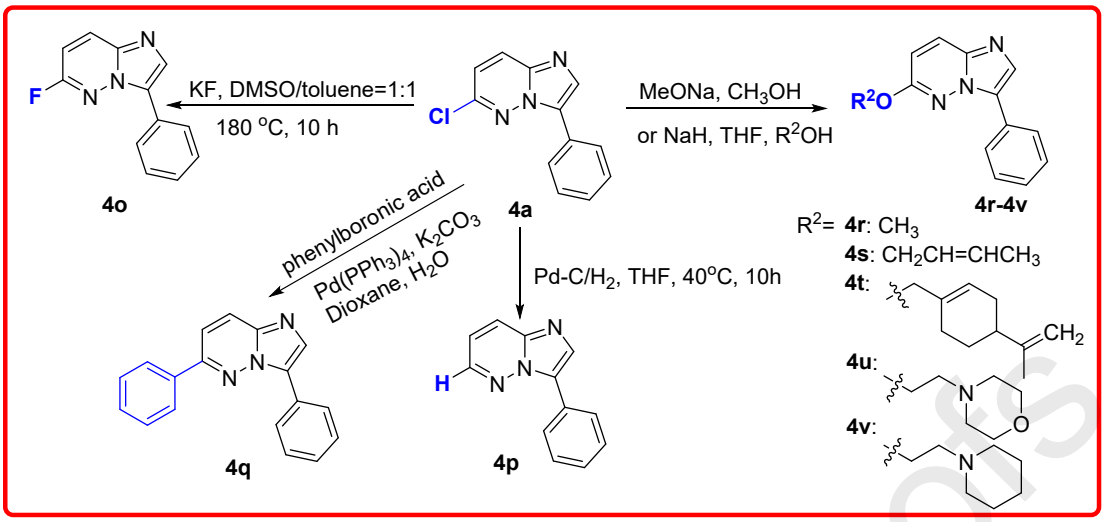


Scheme 2. Synthesis of C-6 substituted imidazo[1,2-b]pyridazines (**4m-v**)

According to the mycelium linear growth rate method, a series of compounds **4a–v** were screened *in vitro* for their antifungal activities at 50 μg/mL against nine phytopathogenic fungi [e.g., *Fusarium solani* (FS), *Botryosphaeria berengriana f. sp. Piricola* (BP), *Corn Curvalaria Leaf Spot* (CL), *Fusarium bulbigenum* (FB), *Fusarium graminearum* (FG), *Alternaria alternata* (AA), *Pyricularia oryzae* (PO), *Fusarium oxysporum f. sp. Vasinfectum* (FV) and *Alternaria brassicae* (AB)]. Hymexazol and carbendazim, two commercial agricultural fungicides, were used as the positive control.

Table 1 Antifungal activities of **4a-v** against nine phytopathogenic fungi at 50 μg/mL.

Compounds	Antifungal activities (inhibition % ± SE) [a]								
	FS	*FV*	*FB*	*FG*	CL	*BP*	*AA*	*PO*	*AB*
3	46.2 ± 0.6	41.9 ± 0.7	65.3 ± 2.0	42.5 ± 0.7	12.6 ± 1.5	44.3 ± 0.8	28.1 ± 0.7	11.4 ± 1.4	68.0 ± 1.2
4a	98.9 ± 1.1	74.2 ± 1.4	76.1 ± 2.2	81.3 ± 0.8	97.8 ± 1.8	96.7 ±1.2	91.1 ± 0.8	87.4 ± 1.6	92.8 ± 1.3
4b	11.9 ± 3.3	5.8 ± 3.4	12.3 ± 2.5	9.5 ± 2.2	53.3 ± 0.5	37.7 ± 1.4	49.6 ± 1.3	40.2 ± 3.1	33.3 ± 2.3
4c	87.4 ± 1.3	64.2 ± 1.7	93.6 ± 1.3	78.1 ± 2.2	95.6 ± 0.4	85.2 ± 1.6	89.4 ± 2.6	88.0 ± 4.2	86.9 ± 1.3
4d	84.8 ± 0.6	52.5 ± 4.3	54.7 ± 0.6	68.9 ± 0.7	93.3 ± 0.2	84.2 ± 0.7	91.7 ± 1.3	87.6 ± 2.7	85.5 ± 2.7
4e	8.5 ± 1.7	12.5 ± 0.6	13.0 ±2.2	31.9 ±1.6	72.6 ±1.4	54.1 ±1.6	56.3 ±1.3	41.0 ±2.7	52.9 ± 1.3
4f	20.0 ± 2.2	27.1 ± 0.7	35.9 ± 1.1	16.0 ± 1.5	5.6 ± 1.9	5.5 ± 2.5	11.9 ± 1.9	17.1 ± 1.6	20.3 ± 3.2
4g	12.2 ± 1.1	3.3 ± 3.8	8.0 ± 1.3	29.3 ± 0.7	30.4 ± 1.3	20.2 ± 2.5	57.0 ± 1.3	43.6 ± 2.7	27.5 ± 1.3
4h	18.9 ± 1.9	7.9 ± 1.9	21.7 ± 2.2	18.6 ± 1.4	4.4 ± 2.2	23.5 ± 1.9	10.4 ± 4.3	13.7 ± 1.6	13.0 ± 2.2
4i	37.8 ± 3.8	58.3 ± 2.9	68.8 ± 2.5	32.4 ± 1.6	57.0 ± 1.3	61.2 ± 0.9	49.6 ± 1.3	45.3 ± 1.6	62.3 ± 3.3

4j	30.4 ± 3.4	57.5 ± 1.1	61.2 ± 1.0	14.8 ± 2.2	61.4 ± 1.4	51.9 ± 1.9	44.7 ± 0.7	43.6 ± 0.9	56.5 ± 2.2
4k	41.5 ± 3.2	37.9 ±2.3	41.8 ±0.8	29.0 ±1.6	29.6 ±1.9	61.2 ±0.9	35.1 ±1.1	24.8 ±1.6	35.5 ±3.3
4l	98.1 ± 0.6	92.9 ± 1.4	94.3 ± 1.7	73.8 ± 2.2	96.7 ± 0.6	96.6 ± 0.4	98.9 ± 1.3	91.7 ± 2.7	84.1 ± 1.3
4m	30.0 ± 1.1	46.4 ± 1.1	49.7 ± 1.0	25.2 ± 2.2	58.6 ± 2.6	36.6 ± 0.6	31.9 ± 2.1	20.5 ± 1.0	30.4 ± 2.0
4n	62.1 ± 1.1	17.1 ± 1.2	52.6 ± 1.2	72.0 ± 0.7	82.0 ± 1.5	77.0 ± 0.8	84.5 ± 0.7	77.2 ± 1.4	81.4 ± 1.2
4o	68.1 ± 3.4	64.4 ± 0.6	66.7 ± 1.0	62.4 ± 0.8	90.1 ± 1.1	67.2 ± 4.6	76.2 ± 0.6	71.8 ± 2.7	74.6 ± 2.2
4p	56.3 ± 2.4	57.5 ± 1.2	57.6 ± 1.0	69.5 ± 0.8	88.3 ± 1.1	80.3 ± 1.6	63.8 ± 0.8	65.8 ± 1.6	72.5 ± 3.6
4q	31.9 ± 3.3	38.6 ±1.1	39.7 ± 0.5	4.8 ± 1.6	36.4 ± 2.8	31.7 ± 0.8	22.0 ± 1.2	15.4 ± 5.4	28.3 ± 3.2
4r	98.7 ± 1.3	79.8 ± 1.1	84.9 ± 0.7	81.7 ± 1.4	99.7 ± 0.5	81.4 ± 0.9	92.4 ± 1.6	86.3 ± 3.1	94.2 ± 1.3
4s	67.5 ± 1.5	42.2 ± 0.6	39.2 ± 0.2	42.9 ± 1.8	84.3 ± 1.3	62.3 ± 3.3	70.9 ± 2.6	70.7 ± 0.1	73.9 ± 2.2
4t	2.6 ± 2.6	5.4 ± 1.2	2.0 ± 2.0	2.2 ± 2.7	19.3 ± 1.3	30.1 ± 1.4	19.1 ± 0.8	24.4 ± 2.7	17.4 ± 2.8
4u	15.1 ± 1.3	15.6 ± 1.2	10.5 ± 2.3	7.7 ± 1.0	20.0 ± 3.8	26.8 ± 2.5	14.2 ± 1.3	24.4 ± 0.5	8.7 ± 0.6
4v	38.1 ± 2.2	23.1 ± 0.8	14.4 ± 1.1	25.6 ± 2.1	18.5 ± 2.4	25.7 ± 0.9	22.0 ± 3.4	33.3 ± 4.1	3.6 ± 1.3
Hymexazol	63.5 ± 1.4	42.8 ± 2.5	59.3 ± 2.2	42.8 ± 2.2	63.0 ± 3.4	44.8 ±1.9	78.4 ± 1.3	72.4 ± 1.6	74.6 ±2.8
Carbendazim	100 ± 1.0	99.8 ± 0.2	99.6 ± 0.9	99.8 ± 1.2	9.9 ± 2.1	93.4 ± 1.6	1.4 ± 1.2	7.0 ± 0.5	2.2 ± 1.2

[a] Values are the mean ± SE of three replicates;

As described in Table 1, the results revealed that all the compounds displayed varying degrees of antifungal activity against each of the tested plant pathogens. Among them, the key intermediate compound **3** exhibited certain antifungal activity, especially for the FB and AB strains. Therefore, compounds **4a**-**4n** were synthesized by replacing the bromine atom of compound **3** with aromatic rings and heterocycles. It is noteworthy that compounds **4a**, **4c**, **4d** and **4l** exhibited broad spectrum antifungal activity against nine phytopathogenic fungi than the positive control hymexazol, and also showed remarkable antifungal activity against CL, AA, PO and AB compared with carbendazim. For example, at the concentration of 50 μg/mL, compound **4a** demonstrated over 91.1% inhibition of FS, CL, BP, AA and AB strains; compound **4c** displayed 93.6% and 95.6% inhibition of FB and CL strains, respectively; compound **4d** displayed 93.3% and 91.7% inhibition of CL and AA strains, respectively; and the compound **4l** demonstrated over 91.7% inhibition of FS,

FV, FB, CL, BP, AA and AB strains. Additionally, compounds **4i**, **4j**, **4k** and **4n** showed similar activities as hymexazol. Unfortunately, compounds **4b**, **4e**, **4f**, **4g** and **4h** exhibited weak antifungal activity to some tested fungi. Subsequently, in order to further explore the influence of C-6 substituents on the antifungal activity, compounds **4o-4v** were synthesized by derivatization from compound **4a**. To our delight, compound **4r** possessed significant antifungal activity compared with other compounds and the two positive control compounds. Meanwhile, compounds **4o**, **4p** and **4s** showed more activity than the positive control hymexazol and more potent than carbendazim against CL, AA, PO and AB, but compounds **4q**, **4t**, **4u** and **4v** displayed weak antifungal activity against nine strains of phytopathogenic fungi.

Based on the bioassay results in Table 1, some interesting structure-activity relationships was observed. Firstly, compared with the intermediate compound **3**, introduction of phenyl ring (**4a**) and thiofuran ring (**4l**) on the C-3 position significantly improved the antifungal activity. For example, compound **3** showed less than 68.0% inhibition against nine phytopathogenic fungi, but compounds **4a** and **4l** displayed more than 73.8% inhibition at the concentration of 50 μg/mL.

Secondly, compared with the unsubstituted phenyl ring compound **4a**, introduction of either electron-donating or electron-withdrawing groups on the phenyl ring invariably reduced the antifungal activity. Generally, some of the title compounds bearing halogen atoms (F, Cl, CF_3) on the phenyl ring, such as compounds **4c**, **4d** and **4n**, displayed better antifungal activity than those bearing hydrogen bond donor groups of CH_2OH, OH and NH_2 (**4i**, **4j** and **4k**). Whereas,

compounds **4b** and **4e** (containing the 2,3-dichloro and 2-bromo groups on the phenyl ring) exhibited weak antifungal activity to four phytopathogenic fungi (FS, FV, FB and FG). The ortho formyl and para pheny substitution on the C3 phenyl ring abrogated the antifungal activity, such as compounds **4f** and **4g**.

Unlike thiofuran group (**4l**), introducing 2-benzthiophenyl group (**4h**) and 3-pyridyl group (**4m**) at R^1 position overall decreased the antifungal effects. For example, compound **4l** showed more than 73.8% inhibition against nine phytopathogenic fungi, but compounds **4h** and **4m** displayed less than 58.6% inhibition at the concentration of 50 μg/mL.

Substitution of chlorine atom of compound **4a** with hydrogen, a benzene ring or alkoxy substituent resulted in loss of activity, except the small methoxy substituent bearing compound **4r** retained the antifungal activity. For instance, the removal of chlorine atom from the C-6 position of compound **4a** afforded the moderate potent compound **4p** (56.3% < inhibition rate < 88.3%), which suggested that the chlorine atoms was essential for the antifungal activities. Meanwhile, introduction of fluorine atom on the C-6 position afforded the slightly more potent compound **4o** (62.4% < inhibition rate < 90.1%) and introduction of $OCH_2CH{=}CHCH_3$ group afforded the slightly less potent compound **4f** (39.2% < inhibition rate < 84.3%) than compound **4p**. However, introduction of the methoxy group on the 6-position of compound **4p** afforded compound **4r** (6-OCH_3), which showed highly similar inhibition rate (>79.8%) and broad-spectrum of antifungal activities as compound **4a** (6-Cl) against all phytopathogenic fungi at the concentration of 50 μg/mL. Unfortunately,

introducing a benzene ring, cycloalkanes or heterocycloalkanes at the C-6 position obviously decreased the antifungal effects, such as compounds **4q**, **4t**, **4u** and **4v**.

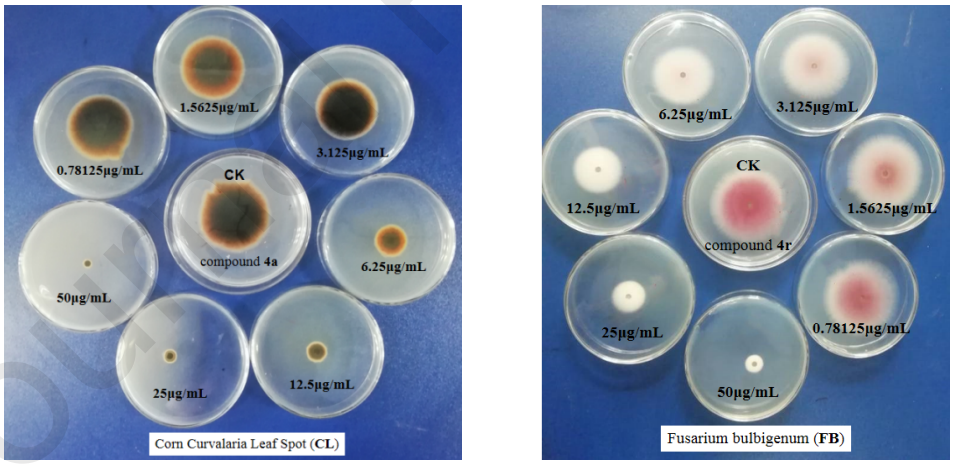
Subsequently, the median effective concentrations (EC_{50}) values of compounds **4a**, **4c**, **4d**, **4l** and **4r** against nine phytopathogenic fungi were calculated, with carbendazim and hymexazol used as positive controls. As shown in Table 2, it was clearly seen that all of the five tested compounds showed excellent activity, with EC_{50} values of 1.3-64.1 μg/mL. As for FS strain, all the compounds showed the superior activity (EC_{50}= 5.1-17.9 μg/mL) than hymexazol (EC_{50} = 27.3 mg/mL), especially compound **4l** and **4r** were found to have EC_{50} values of 5.1 μg/mL and 8.1 μg/mL against this pathogen, respectively. As for FV strain, compound **4l** (EC_{50} =8.4 μg/mL) exhibited 11.3 fold more potent activity than hymexazol (EC_{50} = 95.3 μg/mL). Regarding FB strain, all the compounds exhibited better activity than hymexazol (EC_{50} = 29.4 μg/mL) except for compound **4d** (EC_{50} = 44.3 μg/mL). Regarding **FG** and **BP** strains, compounds **4a**, **4c**, **4d**, **4l** and **4r** displayed much superior antifungal activity to hymexazol, but failed to exceed carbendazim. For CL, AA, PO and AB strains, compounds **4a**, **4c**, **4d**, **4l** and **4r** exhibited 1.9-25.5 fold more potent activities than hymexazol (EC_{50} = 16.7-33.2 μg/mL). Particularly, it was worth to note that the EC_{50} values of compounds **4c** and **4d** against CL, AA , PO and AB strains reached 2.3/1.3, 4.2/2.9, 5.7/4.9 and 4.8/6.0 μg/mL, respectively. The effects of compounds **4a** and **4r** on the growth of CL and FB at different concentrations were shown in Fig.2. It can be seen that all the tested compounds exhibited a concentration dependent antifungal activity. The morphological changing of Fusarium solani (FS) was then

viewed under the light microscope. As shown in Fig.3, the mycelium of the control group had an eel shape, smooth surface, uniform size and much-branched, while the mycelium appeared invagination, shriveling and few-branched after treated with 25 μg/mL of compound **4l**. These results indicated that compound **4l** may exert its antifungal effect by preventing fungal nutrient uptake and metabolism.

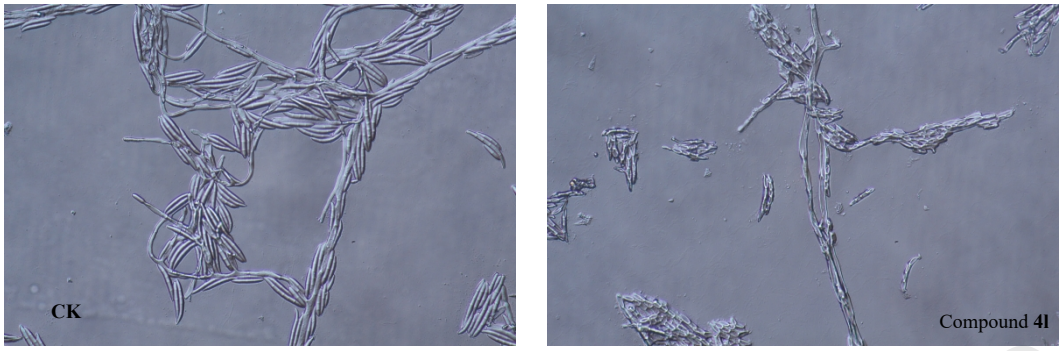
Table 2 EC_{50} values of some selected compounds against nine phytopathogenic fungi.

Compounds	EC_{50}±SD values (μg/mL)[a]								
	FS	*FV*	*FB*	*FG*	CL	*BP*	*AA*	*PO*	*AB*
4a	13.5 ± 0.3	25.6 ± 1.9	18.6 ± 1.6	13.2 ± 0.9	5.6 ± 0.7	13.8 ± 1.0	6.7 ± 1.5	13.5 ± 0.7	10.0 ± 1.1
4c	10.7 ± 0.4	28.6 ± 0.8	16.0 ± 0.3	14.8 ± 0.5	2.3 ± 0.8	5.9 ± 0.1	4.2 ± 1.1	5.7 ± 1.2	4.8 ± 1.5
4d	17.9 ± 1.3	64.1 ± 0.9	44.3 ± 0.6	16.6 ± 0.4	1.3 ± 0.8	7.1 ± 0.3	2.9 ± 2.5	4.9 ± 0.9	6.0 ± 1.4
4l	5.1 ± 0.3	8.4 ± 1.8	7.5 ± 0.2	14.3 ± 0.7	6.8 ± 0.5	9.1 ± 2.2	8.9 ± 1.6	11.8 ± 1.4	13.2 ± 3.1
4r	8.1 ± 0.1	18.5 ± 2.2	13.0 ± 1.4	10.6 ± 1.5	6.4 ±0.2	11.8 ± 3.8	7.8 ± 1.5	12.0 ± 1.9	11.3 ± 0.9
Hymexazol	27.3 ± 0.5	95.3 ± 1.6	29.4 ± 2.0	62.3 ± 4.7	33.2 ± 3.5	65.5 ± 0.5	16.7 ± 3.5	25.5 ± 2.7	33.9 ± 0.2
Carbendazim	0.7 ± 0.2	1.2 ± 0.3	0.8 ± 0.6	0.5 ± 0.1	>100	0.2 ± 0.1	>100	>100	>100

[a] 50% Effective concentration: concentration of compound that inhibits the fungi growth



Figs.2 Effects of compounds **4a** and **4r** on the growth of CL and FB at different concentrations (**CK**: blank control group)



Figs.3 The effects of compound **4l** on the growth of Fusarium solani (FS) at 25 μg/mL (**CK**: blank control group)

In summary, we have synthesized a series of 3,6-disubstitued imidazo[1,2-b]pyridazine derivatives and evaluated their antifungal activities against nine phytopathogenic fungi. Among them, compounds **4a**, **4c**, **4d**, **4l** and **4r** exhibited excellent and broad-spectrum of antifungal activities compared with the two positive control hymexazol and carbendazim; especially against CL, AA, PO and AB strains, some derivatives exhibited 1.9-25.5 fold more potent activities than hymexazol. Structure-activity relationship analysis showed that substituents on the benzene ring and pyridazine ring could have significant effects on the activity. Furthermore, to the best of our knowledge, this is the first report on the antifungal activity against plant pathogens of the imidazo[1,2-b]pyridazine skeleton, which will pave the way for further preparation and application of imidazo[1,2-b]pyridazine derivatives as antifungal agents.

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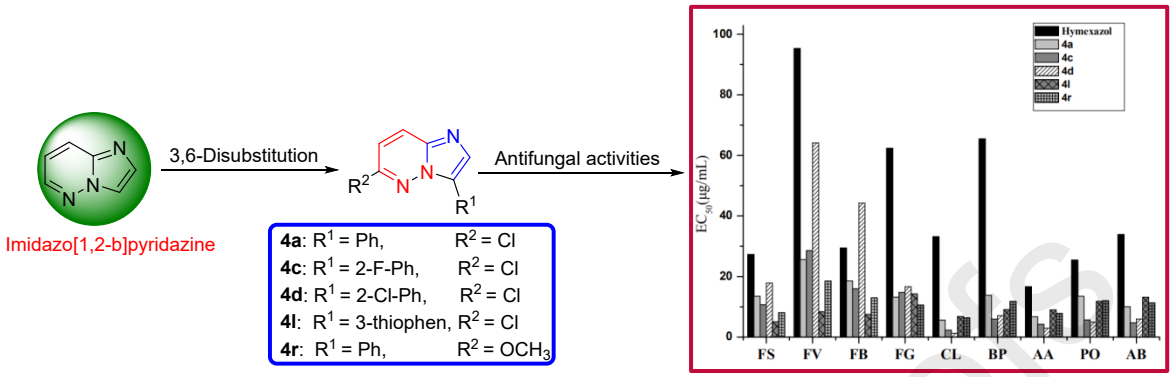
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

none

Graphical Abstract



Highlights:

- Some novel 3,6-disubstituted imidazo[1,2-b]pyridazine derivatives were prepared.
- This is the first report on the antifungal activity against plant pathogens of imidazo[1,2-b]pyridazine skeleton.
- Compounds **4a, 4c, 4d, 4l and 4r** exhibited more potent antifungal activities compared with the two positive controls hymexazol and carbendazim.

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