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Note

Synthesis and biological evaluation of nicotinamide derivatives with a diarylamine-modified scaffold as succinate dehydrogenase inhibitors

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Six novel nicotinamide derivatives bearing a diarylamine-modified scaffold with flexible heterocyclic patterns were designed, synthesized, and characterized in detail *via* Hydrogen nuclear magnetic resonance (^{1}H-NMR), Carbon nuclear magnetic resonance (^{13}C-NMR), and Electrospray ionization mass spectrometry (ESI-MS). Their fungicidal activities and succinate dehydrogenase (SDH) enzymatic inhibitory abilities were evaluated. Preliminary fungicidal bioassay results showed that some of the target compounds exhibited moderate fungicidal activity. Among them, compound **4a** showed 40.54% inhibition against *Botrytis cinerea* fungi. An SDH enzymatic inhibition assay revealed that the IC_{50} of compound **4b** was 3.18 μM. This result indicated that the enzymatic inhibition level of **4b** was similar to that of boscalid. Compound **4f** exhibited superior comprehensive fungicidal and SDH enzymatic inhibitory activities. Molecular docking results suggested that **4f** could bind well to the substrate cavity and the entrance cavity of SDH (1YQ3). In particular, **4f** could react with the key catalytic site Arg 297. This phenomenon implied that **4f** could act as the lead compound for further optimization.

Keywords: nicotinamide derivatives, diarylamine-modified scaffold, fungicidal activity, SDH enzyme.

Electronic supplementary materials: The online version of this article contains supplementary materials (Supplemental Figs. S1–S18), which are available at http://www.jstage.jst.go.jp/browse/jpestics/.

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Introduction

Succinate dehydrogenase inhibitors have been developed for nearly 50 years, since carboxin was commercially launched in 1966; they are the first commercialized fungicides that contain amide groups,[1)] as shown in Fig. 1. At present, 18 fungicides belonging to a novel fungicide class have been commercialized by the Fungicidal Resistance Action Committee.[2,3)] The mode of action of these fungicides is based on disruption of the mitochondrial tricarboxylic acid cycle and respiratory chain.[4,5)]

Nicotinamide derivatives[6)] have attracted great attention since the first pyridine carboxamide boscalid was commercialized by the BASF Company because of their broad fungicidal spectrum. Wu *et al.*[7)] reported a series of nicotinamide derivatives containing a 1,3,4-oxadiazole group. Compound A shows good fungicidal activities against *Fusarium oxysporum* at 50 mg/L (Fig. 2A). Li *et al.*[8)] described compound B, which exhibits excellent fungicidal activities against *Rhizoctonia solani* and *Botrytis cinerea in vitro* (Fig. 2B). Du *et al.*[9)] studied compound C (Fig. 2C), which shows 75% inhibition against *R. solani* at 50 mg/L *in vitro*. Ye *et al.*[10)] demonstrated that compound D has good inhibitory effects against six fungi (Fig. 2D).

Diarylamine represents an important structure and group in many agrochemicals.[11)] Therefore, it may be a promising group for integration with some pharmacophores.[12–15)] Zhang *et al.*[16)] reported pyrazole amide derivatives with a diarylamine-modified scaffold and excellent fungicidal activities against three fungi *in vivo*.

Boscalid was applied as a lead compound, and a substituted diarylamine group was introduced to replace the biphenyl group through splicing to continue studying previously reported six-membered heterocyclic fungicides. Six novel nicotinamide derivatives containing a diarylamine-modified scaffold were designed, synthesized, and characterized in detail *via* ^{1}H-NMR, ^{13}C-NMR, and ESI-MS (Scheme 1). Subsequently, *in vitro* bioassays were performed to evaluate the fungicidal activity of these compounds against three phytopathogenic fungi. The SDH enzymatic inhibitory abilities of these compounds were evaluated.

Materials and Methods

1. General information

All reagents and solvents were commercially available and used directly without further purification. ^{1}H-NMR and ^{13}C-NMR spectra were obtained with $CDCl_3$ as a solvent and tetramethylsilane as an internal standard by using a 400 MHz Bruker NMR spectrometer (Bruker Co., Switzerland). MS data were obtained on a Mainer System Saimofei LCQ fleet mass spectrometer. Thin-layer chromatography was performed on silica gel 60 F_{254} (Qingdao Marine Chemical Ltd., P. R. China). Column chromatography purification was conducted on silica gel (200–300

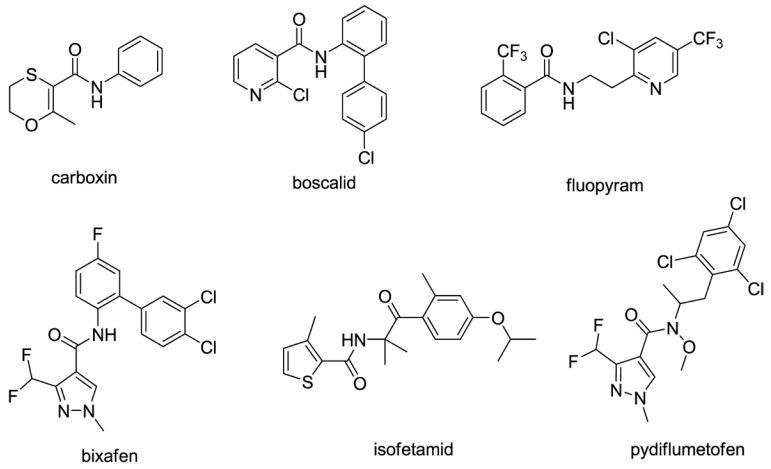


Fig. 1. Structures of some commericalized Succinate Dehydrogenase Inhibitors

mesh, Qingdao Marine Chemical Ltd., P. R. China).

2. Synthesis

*2.1. Synthesis of intermediate **1***

Anhydrous K_2CO_3 (20 mmol) was added to a mixture of 1-chloro-2-nitrobenzene (20 mmol) and aniline (30 mmol) in PEG1000 (2 mmol), and the resulting mixture was heated at 180°C for 13 hr. The reaction mixture was cooled and quenched with water at room temperature and then extracted with ethyl acetate (3×30 mL). The organic phase was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude product was subjected to flash column chromatography to produce intermediate **1**.

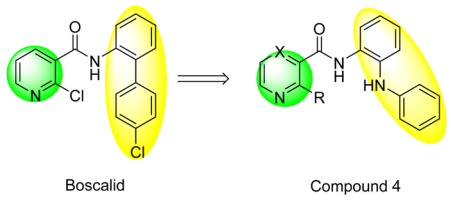
*2.2. Synthesis of intermediate **2***

Intermediate **1** (15 mmol), reductive iron powder (15 mmol), NH_4Cl (45 mmol), and aqueous ethanol solution (75%, 60.84 mL) were added to a flask. The reaction was refluxed at 90°C for 5 hr. When the reaction was finished, the mixture was cooled at room temperature, filtered, and extracted with ethyl acetate (3×20 mL). The organic phase was evaporated *in vacuo* to obtain intermediate **2**.

*2.3. General synthesis of compounds **4a–4f***

Intermediate **3** (1.1 mmol) was dissolved in 3 mL of CH_2Cl_2 solvent, and the mixture was cooled to 0°C. EDCI (1.2 mmol) and HOBt (1.2 mmol) were initially added to the mixture.While stirring the mixture, intermediate **2** (1.0 mmol) was added slowly. Then the mixture was reacted for 2–5 hr. When the reaction was completed, the mixture was quenched with water, and the water phase was extracted with CH_2Cl_2 (2×2 mL). Then the CH_2Cl_2 phase was combined, washed with brine (2×2 mL), dried with Na_2SO_4, and filtered. The solvent was removed *in vacuo*, and the crude product was purified through column chromatography(eluent ratio of mixed solvent of petroleum ether(PE) and ethyl acetate (EA) was from 10:1 to 4:1) to obtain compounds **4a**–**4f**.

Compound **4a**, white powder, yield 72%, ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.14 (d, J=14.0 Hz, 1H, pyridine), 8.55–8.59 (m, 1H, pyridine), 8.30 (d, J_1=4.6 Hz, 1H, pyridine), 8.16 (dd, J_1=8.0 Hz, J_2=2.0 Hz, 1H, phenyl), 7.29–7.36 (m, 2H, phenyl), 7.14–7.21 (m, 4H, phenyl), 6.85 (t, J=7.4 Hz, 1H, phenyl), 6.80 (d, J=8.5 Hz, 2H, phenyl), 5.50 (s, 1H, NH). ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 160.92, 159.98, 158.45, 150.72, 150.55, 144.79, 143.51, 133.94, 132.10, 129.38, 126.08, 125.16, 124.33, 122.65, 122.56,



Scheme 1. Design route of target compound **4**

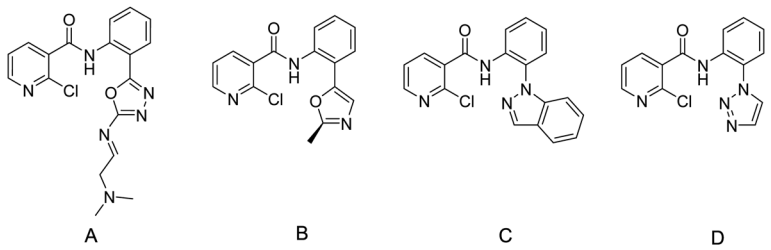
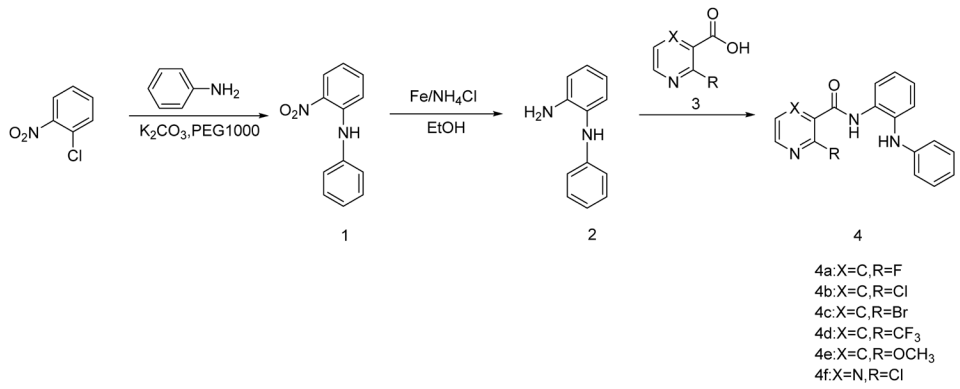


Fig. 2. Structures of some pyridine carboxamide derivatives



Scheme 2. Synthesis route of the target compound of **4a**–**4f**

122.52, 120.52, 116.33. ESI-MS: *m*/*z* 308.20 $[M+H]^+$.

Compound **4b**, pink powder, yield 82%, ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 8.75 (s, 1H, CONH), 8.43 (d, *J*=2.8 Hz, 1H, pyridine), 8.17 (dd, J_1=7.2 Hz, J_2=1.2 Hz, 1H, pyridine), 7.99 (dd, J_1=7.2 Hz, J_2=1.2 Hz, 1H, pyridine), 7.28–7.31 (m, 2H, phenyl), 7.17–7.25 (m, 4H, phenyl), 6.88 (t, *J*=7.2 Hz, 1H, phenyl), 6.78 (d, *J*=8.0 Hz, 2H, phenyl), 5.48 (s, 1H, NH). ^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 163.00, 151.17, 147.16, 144.87, 139.75, 133.71, 132.02, 131.24, 129.55, 129.44, 126.21, 125.32, 124.58, 124.49, 122.78, 122.54, 120.55, 116.22. ESI-MS: *m*/*z* 324.22 $[M+H]^+$.

Compound **4c**, pink powder, yield 65%, ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 8.37–8.43 (m, 2H, CONH, pyridine), 8.10–8.13 (m, 1H, pyridine), 7.75 (dd, $J_{1=}$8.0 Hz, $J_{2=}$6.0 Hz, 1H, pyridine), 7.29 (dd, J_1=8.4 Hz, J_2=4.0 Hz, 2H, phenyl), 7.17–7.23 (m, 4H, phenyl), 6.88 (t, $J_{1=}$7.2 Hz, 1H, phenyl), 6.78 (d, *J*=8.0 Hz, 2H, phenyl), 5.64 (s, 1H, NH). ^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 163.89, 151.11, 144.62, 138.28, 138.23, 134.45, 133.86, 133.78, 131.42, 129.26, 126.33, 126.15, 124.96, 124.08, 122.68, 122.52, 120.40, 116.07. ESI-MS: *m*/*z* 368.15 $[M+H]^+$.

Compound **4d**, pink powder, yield 73%, ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 8.67 (d, *J*=4.0 Hz, 1H, pyridine), 8.10 (s, 1H, pyridine), 7.99 (dd, J_1=6.8 Hz, J_2=4.0 Hz, 1H, pyridine), 7.57 (d, *J*=7.2 Hz, 1H, phenyl), 7.40 (dd, J_1=7.2 Hz, $J_{2=}$4.8 Hz, 1H, phenyl), 7.16–7.25 (m, 5H, phenyl), 6.88 (t, *J*=7.2 Hz, 1H, phenyl), 6.74 (d, *J*=7.6 Hz, 2H, phenyl), 5.42 (s, 1H, NH). ^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 163.96, 150.00, 144.40, 144.12, 143.78, 136.59, 133.81, 131.44, 131.19, 129.27, 126.22, 126.15, 124.85, 123.96, 122.78, 122.46, 120.42, 119.79, 116.15. ESI-MS: *m*/*z* 358.24 $[M+H]^+$.

Compound **4e**, pink powder, yield 91%, ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 10.34 (s, 1H, CONH), 8.55 (dd, J_1=7.6 Hz, J_2=2.0 Hz, 1H, pyridine), 8.31 (dd, J_1=8.0 Hz, J_2=1.6 Hz, 1H, pyridine), 8.23 (dd, J_1=4.8 Hz, J_2=2.0 Hz, 1H, pyridine), 7.27 (d, *J*=1.5 Hz, 1H, phenyl), 7.16–7.22 (m, 3H, phenyl), 7.10 (td, J_1=7.6 Hz, J_2=1.5 Hz, 1H, phenyl), 7.01–7.05 (m, 1H, phenyl), 6.79–6.85 (m, 3H, phenyl), 5.74 (s, 1H, NH), 3.79 (s, 3H, OCH_3). ^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 162.50, 160.67, 150.34, 145.96, 142.09, 134.15, 134.11, 133.66, 129.83, 125.83, 125.66, 125.10, 122.68, 122.64, 120.31, 118.27, 116.60, 116.02, 54.39. ESI-MS: *m*/*z* 320.14 $[M+H]^+$.

Compound **4f**, yellow powder, yield 68%, ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 9.87 (s, 1H, CONH), 8.39 (d, *J*=2.0 Hz, 1H, pyrazine), 8.29 (d, *J*=2.0 Hz, 1H, pyrazine), 8.11 (dd, J_1=8.0 Hz, J_2=2.0 Hz, 1H, phenyl), 7.03–7.22 (m, 5H, phenyl), 6.74–6.79 (m, 3H, phenyl), 5.39 (s, 1H, NH). ^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 160.04, 148.70, 146.16, 145.05, 142.72, 140.73, 134.26, 134.18, 131.80, 129.54, 126.05, 125.20, 125.12, 124.21, 122.23, 120.58, 116.60. ESI-MS: *m*/*z* 325.17 $[M+H]^+$.

3. Procedure for fungicidal activity assay in vitro

The fungicidal activities of the target compounds **4a**–**4f** against the three phytopathogenic fungi *B. cinerea*, *V. mali*, and *S. sclerotiorum* (%) were tested *in vitro* using the mycelium growth rate method. The commercially available fungicide boscalid was used as the positive control, and acetone was set as the negative control. The compounds were dissolved in acetone to prepare a 100 mg/L stock solution for the following antifungal test. The diameter of each strain was measured after the mycelia were incubated at 25°C for a certain duration. The percentage of inhibition was calculated as follows:

$$I = (B - A)/B \times 100\%$$

where I is the inhibition percentage, *A* is the average mycelial diameter(mm) in petri dishes with the compounds, and *B* is the diameter(mm) with the negative group. The inhibition percentage of the compounds was determined at 50 mg/L.

Table 1. Antifungal activities of compounds **4a**–**4f** *in vitro* (inhibition%, 50 mg/L)

Compound	*B. cinerea* (%)	*V. mali* (%)	*S. sclerotiorum* (%)
4a	40.54	6.82	30.59
4b	32.41	3.41	0
4c	35.17	4.55	8.2
4d	33.79	12.5	47.1
4e	36.55	3.41	0
4f	36.56	13.62	32.9
Boscalid	100	100	100

Table 2. SDH enzymatic inhibition of compounds **4a–4f**

Compound	Inhibition (%)			
	8 μM	2 μM	1 μM	0.5 μM
4a	10.68	6.02	6.41	5.05
4b	54.95	50.10	39.42	21.75
4c	38.06	25.63	25.44	12.62
4d	45.44	33.59	25.05	16.70
4e	53.59	40.00	33.01	22.33
4f	48.93	21.94	14.37	8.16
Boscalid	80.97	53.59	43.30	21.55

Table 3. SDH enzymatic inhibition of compounds **4a–4f** (IC_{50})

Compound	IC_{50} (μM)
4a	>100
4b	3.18
4c	30.03
4d	10.47
4e	4.95
4f	11.18
Boscalid	1.67

4. SDH enzymatic inhibition assay

The concentration of SDH in swine was determined using the double-antibody sandwich method. A purified porcine SDH antibody was coated with a microplate to make a solid-phase antibody, and a monoclonal antibody was subsequently added to the plate. Then the SDH antibody which Horseradish Peroxidase (HRP)-labeled was also added into the mixture to form antibody–antigen-enzyme-labeled antibody complex. After the specimen was thoroughly washed, a substrate was added to color TMB. TMB is converted to blue and yellow by the Horseradish Peroxidase (HRP) enzyme and acid, respectively. Color intensity was positively correlated with SDH in the sample. Absorbance (OD value) was measured with a microplate analyzer at 450 nm, and the activity concentration of porcine SDH in the sample was calculated on the basis of a standard curve.

The standard curve was drawn on a sheet of coordinate paper. The concentration of the standard substance was taken as the horizontal coordinate, and the OD value was set as the vertical coordinate. The corresponding concentration could be determined in accordance with the sample OD value by referring to the standard curve. The OD value of the sample was calculated by multiplying the sample concentration by the dilution times. Therefore, the accurate sample concentration was provided.

5. Molecular docking

Discovery Studio 2016 was used for molecular docking studies. First, a small molecule module was used for small molecule preparation. Then a macromolecule module was used for protein processing (PDB: 1YQ3). Finally, a CDOCKER module was used for flexible docking. Other parameters were set by default.

Results and Discussion

1. Chemistry

Scheme 2 provides the details of the synthesis route of compound **4**. Diarylamine intermediate **2** was obtained through the reduction of intermediate **1**, which can be easily prepared with high yields. The title compounds were prepared by reacting pyridine carboxylic acid with intermediate **2** *via* a classic synthetic approach called condensation reaction. EDCI was used as condensation and HOBt was used as the catalyst. The structure of **4** was confirmed through ^{1}H-NMR, ^{13}C-NMR, and ESI-MS. The spectral data of compounds **4a–4f** are given in the supplemental material.

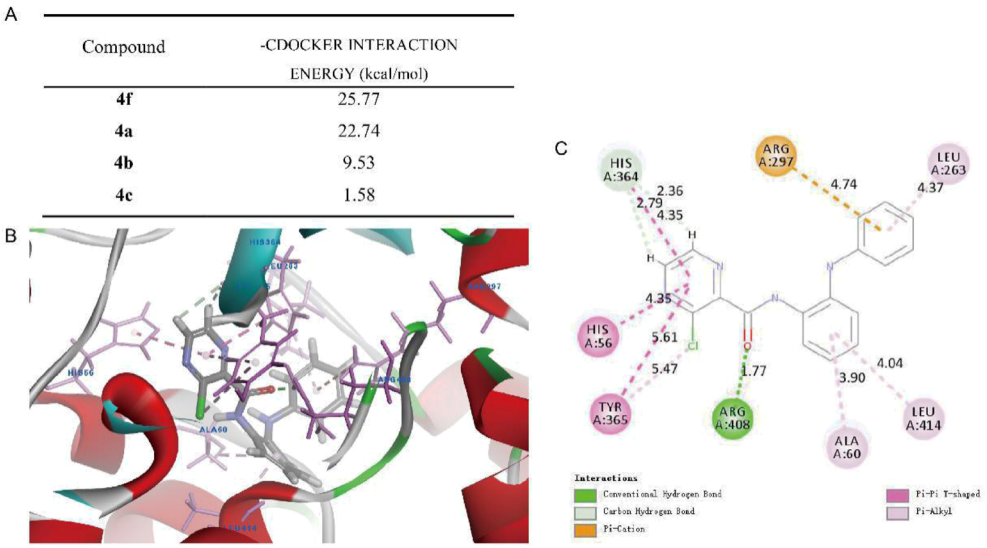


Fig. 3. Molecular docking results. A. Molecular docking scores of compounds **4a–4f** and 1YQ3. B. 3D results of molecular docking between **4f** and 1YQ3. C. 2D results of molecular docking between **4f** and 1YQ3.

2. Fungicidal bioassay in vitro

The preliminary *in vitro* screening results of the fungicidal activities of compounds **4a–4f** against three fungi are listed in Table 1. The bioassay results indicated that most of the synthesized compounds exhibited potential fungicidal activities. In general, fungicidal activities against *B. cinerea* followed the order of **4a**>**4f**>**4e**>**4c**>**4b**>**4d**, whereas fungicidal activities against *V. mali* followed the order of **4f**>**4d**>**4a**>**4c**>**4e**=**4b**. The fungicidal activities against *S. sclerotiorum* followed the order of **4d**>**4f**>**4a**>**4c**. The fungicidal tendencies of **4a–4f** against *V. mali* were similar to those against *S. sclerotiorum*. In particular, **4f** exhibited superior comprehensive fungicidal activity against the three fungi.

3. SDH enzymatic inhibition

The fungal SDH inhibition assay was performed to investigate whether SDH is a potential target enzyme of the title compounds. As illustrated in Table 2, **4a–4f** inhibited the SDH enzyme in a dose-dependent manner, and relationship which was from strong to weak followed the order of **4b**>**4e**>**4f**>**4d**>**4c**>**4a** (82 μM). The relationship of IC_{50} followed the order of **4b**>**4e**>**4d**>**4f**>**4c**>**4a** (Table 3). Therefore, the pyridine carboxamides designed in this work displayed certain inhibitory effects against SDH. These results implied that SDH is an important action target of novel pyridine carboxamides.

4. Docking analysis

Related reports have shown that SDH inhibitors are mainly composed of four parts: a core, an amide bond, a phenyl group, and a hydrophobic group. The core is mainly composed of five- or six-membered ring systems. The amide bond is an essential common feature. The remaining part of an SDH inhibitor is mainly a hydrophobic group.[17] The characteristics of the compounds designed in this study were consistent with those of SDH inhibitors. To further understand the mechanism of action of the compounds, we studied their bonding with succinic ubiquinone oxidoreductase by molecular docking. As shown in Fig. 3A, compounds **4a**, **4b**, **4c**, and **4f** could dock with 1YQ3, whereas **4d** and **4e** could not be docked because the spatial structure of $-CF_3$ and $-OCH_3$ was larger than that of other substituents. The CDOCKER interaction energy scores of the compounds followed the order of **4f**>**4a**>**4b**>**4c**. This result suggested that **4f** had the best inhibitory activity against avian respiratory complex II. Further analysis revealed that **4f** could connect well with the substrate cavity and the entrance cavity of 1YQ3 (Fig. 3B) and could form bonds with key amino acid residues within the crystal; for example, His 364 and Arg 408 are two key hydrogen bond–forming sites (Fig. 3C). Similar to the results of crystal structure analysis, **4f** could react with the key catalytic site Arg 297, but it formed different bonds at different positions.[18] In addition, the core owned numerous chemical bonds, and the critical key here was between Arg 297 and the target (Fig. 3C).

Conclusions

Six novel nicotinamide derivatives bearing a diarylamine-modified scaffold with flexible heterocyclic patterns were designed, synthesized, and characterized in detail *via* ^{1}H-NMR, ^{13}C-NMR, and ESI-MS. The preliminary results of fungicidal bioassays revealed that some of the target compounds exhibited moderate fungicidal activity against the three studied fungi. Among them, compound **4a** showed 40.54% inhibition against *B. cinerea*. The results of the SDH enzymatic inhibition test showed that the IC_{50} of **4b** was 3.18 μM, which was similar to that of boscalid, but **4f** exhibited superior comprehensive fungicidal and SDH enzymatic inhibitory activities. Molecular docking implied that **4f** could bind to the substrate cavity and the entrance cavity of 1YQ3. These results suggested that **4f** would be the lead compound for further investigation.

Acknowledgements

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Declaration of Competing Interest

All authors declared no conflict of interest.

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