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FULL PAPER

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4-Aminoquinolines Bearing a 1,3-Benzodioxole Moiety: Synthesis and Biological Evaluation as Potential Antifungal Agents

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In search of new environmentally friendly and effective antifungal agents, a series of 4-aminoquinolines bearing a 1,3-benzodioxole moiety were prepared and their structures were fully elucidated by spectroscopic analyses. The antifungal activities of all the target compounds against five phytopathogenic fungi were evaluated *in vitro*. The results revealed that most of the newly synthesized compounds exhibited obvious inhibitory activities at the concentration of 50 μg/mL. Among them, 6-(furan-2-yl)-*N*-(4-methylphenyl)-2*H*-[1,3]dioxolo[4,5-*g*]quinolin-8-amine hydrochloride (**7m**) displayed more promising antifungal potency with EC_{50} values of 10.3 and 14.0 μg/mL against *C. lunata* and *A. alternate*, respectively. Particularly, the EC_{50} value of **7m** against *C. lunata* was 7.3-fold as potent as the standard azoxystrobin. There were some significant morphological alterations in the mycelia of *C. lunata* when treated with **7m** at 50 μg/mL. Additionally, the preliminary structure–activity relationships (SARs) were also discussed. Thus, this study suggests that 4-aminoquinolines bearing a 1,3-benzodioxole moiety are interesting scaffolds for the development of novel antifungal agents.

Keywords: 4-aminoquinoline, 1,3-benzodioxole, antifungal activity, structure–activity relationship.

Introduction

Fungal diseases are a major threat to agricultural production worldwide, which not only result in a large reduction in grain yield, but also may pose great risks to the environment and human security.[1–3] Although many synthetic fungicides play an important role in crop protection, drug resistance and residue are becoming more and more serious with the long-term or irrational use of these agents.[4,5] In order to solve these serious problems, the discovery of novel environmentally friendly and high-efficiency antifungal agents is an imperative and challenging task.

For decades, heterocyclic compounds play an important role in the development of medicine and pesticide. Among them, quinoline derivatives have always been one of the most prominent bioactive molecules,[6,7] and have also become a class of preferred lead compounds for new agricultural chemicals.[8–10] Quinoline is a common core in many natural compounds and has diverse biological activities, such as antibacterial,[11,12] antifungal,[13,14] antiviral,[15,16] antitumor,[17,18] antimalarial,[19,20] and anti-inflammatory activities.[21] The excellent biological properties of quinolines have also been well demonstrated by a large number of practical applications, such as quinoxyfen (a commercial agricultural fungicide), tebufloquin (fungicide), 8-hydroxyquinoline copper (bactericide), hyquincarb (insecticide), fenazaquin (insecticide), quinclorac (herbicide), and ethoxyquin (feed additive). Furthermore, 1,3-benzodioxole moiety is a common natural component from dietary plants such as peppers, sesame seeds and carrots.[22] The representative bioactive molecules containing this fragment are piperine, sanguinarine, chelerythrine, podophyllotoxin, steganacin, combretastatin A-2, and so on (*Figure 1*). They possess antioxidative, antibacterial, antifungal, antitumor and other biological

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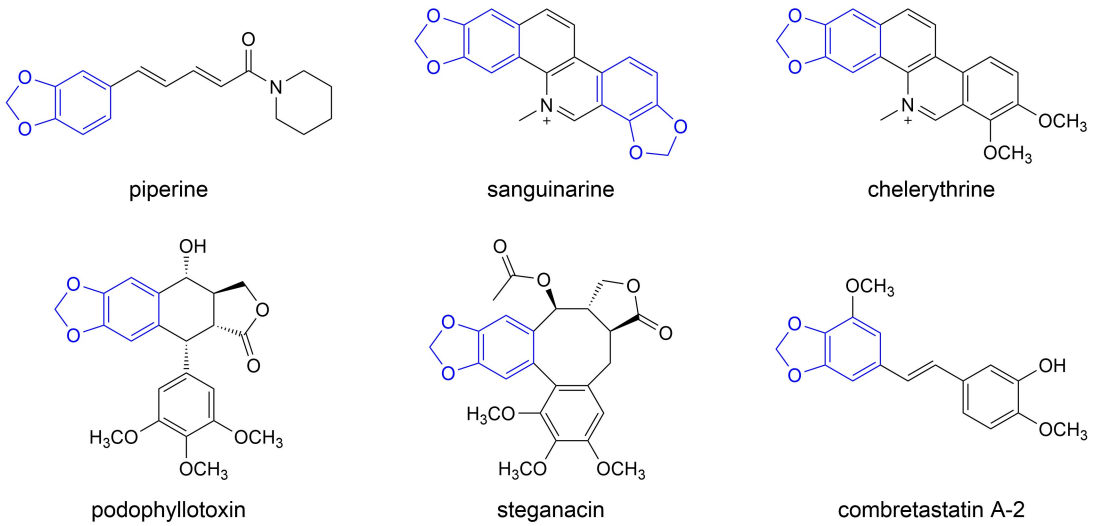


Figure 1. Some bioactive compounds containing a 1,3-benzodioxole moiety.

activities.[23–28] In particular, the good bioavailability and low mammalian toxicity is of great interest.[22,29]

Previous studies of our working group investigated some 2,4-disubstituted quinolines as potential antifungal agents.[14,30] It was found that quinoline derivatives with a phenyl substitution at position 2 and an aniline moiety at position 4 were potent antifungal candidates and the aniline moiety at position 4 played a key role in antifungal potency, which were of great value for further study. Encouraged by above mentioned, herein, a series of 4-aminoquinolines bearing a 1,3-benzodioxole moiety were prepared and evaluated for their antifungal activities against five phytopathogenic fungi *in vitro*.

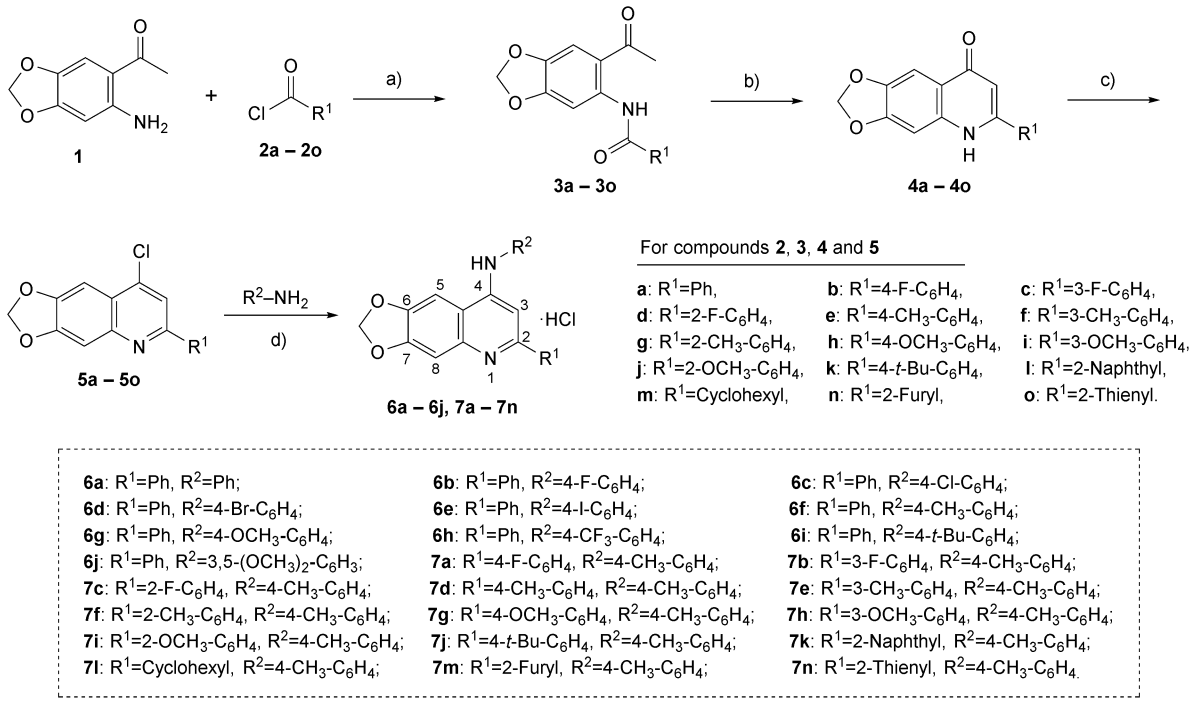
Results and Discussion

Chemistry

The preparation of target compounds has been accomplished in four steps (*Scheme 1*) according to similar procedures described previously.[30] Firstly, the amides **3a**–**3o** were obtained from ammonolysis of the corresponding acyl chlorides **2a**–**2o** with 1-(6-amino-2*H*-1,3-benzodioxol-5-yl)ethan-1-one (**1**) in the presence of triethylamine in good to excellent yields. Then, intramolecular aldol condensation of amides **3a**–**3o** afforded quinolinones **4a**–**4o** in moderate to good yields, which were then converted into the corresponding 4-chloroquinolines **5a**–**5o** in good yields by using phosphorus oxychloride in refluxing dioxane. Finally, the target compounds *N*,2-disubstituted-6,7-methylenedioxyquinolin-4-amine hydrochlorides **6a**–**6j** and **7a**–**7n** were prepared by nucleophilic substitution of the key intermediates **5a**–**5o** with suitable primary amine in moderate to good yields. The structures of all target compounds were characterized by means of IR, ^{1}H-NMR, ^{13}C-NMR and HR-MS spectra.

Antifungal Activity and Structure–Activity Relationships

As described in *Table 1*, all the target compounds (**6a**–**6j** and **7a**–**7n**), as well as the positive control azoxystrobin (a commercial agricultural fungicide), were screened *in vitro* for their antifungal activities against five phytopathogenic fungi (*P. piricola*, *A. brassicae*, *C. lunata*, *P. grisea* and *A. alternate*) at 50 μg/mL by using mycelium growth rate method.[14,30] The results revealed that most of the newly synthesized compounds exhibited moderate to excellent inhibitory activities at the concentration of 50 μg/mL, and many of them displayed comparable or more superior antifungal profiles compared with the positive control, particularly for *A. brassicae*, *C. lunata* and *A. alternate*. Among compounds **6a**–**6j**, compounds **6f** and **6i** possessed potent and broad-spectrum antifungal activities against the five tested fungi with the inhibition rates of $>$51.1%. For example, the inhibition rates of compound **6f** against *P. piricola*, *C. lunata* and *A. alternate* were 72.3%, 71.4% and 65.5%, respectively, and the inhibition rates of compound **6i** against *P. piricola*, *C. lunata* and *A. alternate* were 56.4%, 70.7%, and 62.9%, respectively. Their antifungal



Scheme 1. Synthetic route of target compounds **6a**–**6j** and **7a**–**7n**. Reagents and conditions: a) Et_3N, CH_2Cl_2, r.t., overnight. b) NaOH, 1,4-dioxane, 110 °C, 2 h. c) $POCl_3$, 1,4-dioxane, reflux 10 h. d) R^2–NH_2, 1,4-dioxane, reflux 8–36 h.

potencies were superior to the positive control azoxystrobin against the corresponding fungal strains in most cases. Besides, compound **6a** also displayed potent antifungal activities against *C. lunata* and *A. alternate* with the inhibition rates of 71.5 % and 63.1 %, respectively. Subsequently, in order to further investigate the influence of C-2 substituents (*Scheme 1*: R^1) on the antifungal potency, compounds **7a**–**7n** were prepared by derivatization from compound **6f**. To our delight, the majority of compounds **7a**–**7n** exhibited good to excellent antifungal activities against most of the tested fungal stains. The inhibition rates of each compound in this series against at least three strains of tested fungi were over 50 % except for compounds **7j**, **7k** and **7l**. Among them, compounds **7e** and **7m** showed more promising and broad-spectrum antifungal activities against each of the tested fungi, whose inhibition rates were almost more than 60 %. Particularly, compound **7m** displayed the highest inhibition rates of 74.2, 76.7 %, 69.9 % and 73.7 % against *P. piricola*, *C. lunata*, *P. grisea* and *A. alternate*, respectively. Compound **7b** exhibited better activities than all other analogs against *A. brassicae* with the inhibition rate of 72.3 %. In addition, compounds **7f**, **7g**, **7h** and **7i** also displayed impressive antifungal activities against *A. brassicae*, *C. lunata* and *A. alternate*, whose potencies were comparable or superior to the precursor **6f** and azoxystrobin.

Moreover, the EC_{50} values of some potent compounds with inhibition rates > 60 % at 50 μg/mL were further studied against *C. lunata* and *A. alternate*. As shown in *Table 2*, the results indicated that all of the twelve tested compounds displayed good to excellent inhibitory activities, with EC_{50} values of 10.3–43.0 μg/mL except for compound **7a** against *A. alternate*. Notably, the EC_{50} values (10.3–28.4 μg/mL) of all tested compounds against *C. lunata* were more potent than the positive control azoxystrobin (EC_{50} = 74.9 μg/mL). Particularly, compound **7m** exhibited 7.3-fold as potent as azoxystrobin against *C. lunata*. As for *A. alternate*, most of the tested compounds did not exhibit superior antifungal activities (EC_{50} = 24.3–43.0 μg/mL) over the positive control (EC_{50} = 16.0 μg/mL) except for compound **7m** (EC_{50} = 14.0 μg/mL). In addition, the effects of compound **7m** against *C. lunata* and *A. alternate* at different concentrations were displayed in *Figure 2*. It is apparent that the inhibitory activities increased in a concentration dependent manner.

From the results in *Tables 1* and *2*, some interesting SARs could be derived. Firstly, the substituent in *para* position at the aniline moiety was very important for

Table 1. Inhibition rates of target compounds against five phytopathogenic fungi at 50 μg/mL.

Compounds	Average Inhibition rate (%±SD)[a]				
	P. piricola[b]	*A. brassicae*[c]	*C. lunata*[d]	*P. grisea*[e]	*A. alternate*[f]
6a	41.3±0.69	57.8±0.21	**71.5±0.40**	43.4±1.2	**63.1±1.7**
6b	45.4±1.5	59.1±1.7	55.1±2.0	44.5±2.0	54.5±0.78
6c	34.1±1.8	24.7±1.4	30.9±1.4	21.3±1.2	34.7±1.7
6d	32.2±2.3	26.5±2.2	35.6±1.4	22.4±2.3	23.7±1.8
6e	26.9±1.8	52.2±1.6	53.0±0.63	37.1±1.8	40.9±2.2
6f	**72.3±1.9**	55.3±0.26	**71.4±0.33**	56.7±1.6	**65.5±1.2**
6g	47.5±0.42	36.9±1.3	54.6±0.67	43.0±1.2	46.5±1.5
6h	32.2±1.5	23.3±1.2	29.8±0.31	29.0±0.38	21.0±1.9
6i	56.4±1.9	58.1±0.52	**70.7±0.0**	51.1±1.1	**62.9±0.69**
6j	35.2±1.6	41.2±1.8	47.1±0.78	31.1±0.44	34.0±0.72
7a	36.1±0.62	53.4±0.89	**64.3±0.10**	45.2±1.4	53.8±0.73
7b	46.0±1.4	**72.3±0.40**	**65.0±1.4**	**63.7±1.3**	**65.8±1.9**
7c	52.5±0.61	59.3±1.7	57.0±0.30	36.3±1.4	56.4±0.49
7d	51.7±1.1	30.4±1.7	**71.8±2.0**	**66.1±1.1**	**62.4±1.7**
7e	54.8±0.0	**70.8±1.2**	**74.2±1.3**	**61.8±0.42**	**68.9±1.5**
7f	48.9±0.62	57.9±2.0	**71.1±0.30**	41.6±1.9	**65.8±1.4**
7g	49.1±1.2	**62.1±1.8**	**72.5±0.72**	49.5±1.4	**62.7±0.47**
7h	51.9±2.3	**62.4±1.1**	**68.9±0.33**	48.8±1.1	**62.0±0.83**
7i	**64.8±0.43**	**65.9±1.4**	**73.5±0.78**	49.5±0.91	**60.5±1.0**
7j	41.7±1.2	39.0±0.89	33.3±1.8	27.6±1.1	30.8±0.56
7k	47.9±0.67	49.3±1.2	42.1±0.71	44.4±2.0	24.4±1.0
7l	52.1±1.9	37.2±1.5	44.3±1.4	38.1±0.74	40.8±1.5
7m	**74.2±0.74**	**70.0±0.91**	**76.7±1.6**	**69.9±1.1**	**73.7±1.2**
7n	51.3±1.3	54.1±0.80	50.8±1.4	52.1±0.53	44.2±1.1
Azoxystrobin	**68.6±1.7**	48.8±0.42	44.9±0.0	52.9±1.0	54.7±0.47

[a] Values are means±standard deviation of three replicates. [b] *P. piricola*: *Physalospora piricola*; [c] *A. brassicae*: *Alternaria brassicae*; [d] *C. lunata*: *Curvularia lunata*; [e] *P. grisea*: *Pyricularia grisea*; [f] *A. alternate*: *Alternaria alternate*.

Table 2. EC_{50} values of some potent compounds against *C. lunata* and *A. alternate*.

Compound	*C. lunata*			*A. alternate*		
	EC_{50} (μg/mL)	Toxic regression equation	r^2	EC_{50} (μg/mL)	Toxic regression equation	r^2
6a	28.4±1.6	$y=1.9150x-3.5281$	0.9970	43.0±0.42	$y=2.7196x-7.6087$	0.9912
6f	22.5±0.18	$y=1.7907x-2.7938$	0.9996	28.2±0.0	$y=1.6501x-2.3405$	0.9955
6i	22.7±0.58	$y=1.5367x-1.7033$	0.9942	27.9±0.37	$y=1.5319x-1.8137$	0.9938
7a	23.8±0.67	$y=1.1927x-0.2183$	0.9951	–[a]	–	–
7b	26.9±0.38	$y=1.4674x-1.4999$	0.9995	28.7±0.41	$y=1.5031x-1.7062$	0.9927
7d	21.1±0.23	$y=1.5071x-1.5116$	0.9984	28.3±0.43	$y=1.6278x-2.2479$	0.9949
7e	22.1±0.38	$y=1.5860x-1.8856$	0.9903	24.3±0.061	$y=1.4628x-1.4070$	0.9972
7f	22.6±0.86	$y=1.4610x-1.3590$	0.9908	30.5±0.42	$y=1.6285x-2.2871$	0.9906
7g	23.0±0.040	$y=1.6617x-2.2424$	0.9938	33.4±0.71	$y=1.8728x-3.4857$	0.9950
7h	21.7±0.45	$y=1.1822x-0.1208$	0.9906	29.2±0.83	$y=1.3214x-0.9085$	0.9938
7i	26.8±0.055	$y=1.7648x-2.8246$	0.9910	36.2±0.50	$y=1.6035x-2.3130$	0.9934
7m	10.3±0.53	$y=0.7952x+1.8094$	0.9995	14.0±0.35	$y=1.0851x+0.5004$	0.9987
Azoxystrobin	74.9±0.91	$y=0.7624x+1.2819$	0.9982	16.0±0.82	$y=0.2271x+4.0451$	0.9972

[a] –: not detected.

the antifungal activity. Generally, the 4-methyl and 4-*tert*-butyl substituted compounds **6f** and **6i** achieved higher potencies than the others in this series. The trend could also be supported by the fact that the set of products **7a**–**7n**, derived from **6f** (4-CH_3), possessed good to excellent antifungal activities with few exceptions. Secondly, the substituent at position 2 of the quinoline scaffold was an important modulator of

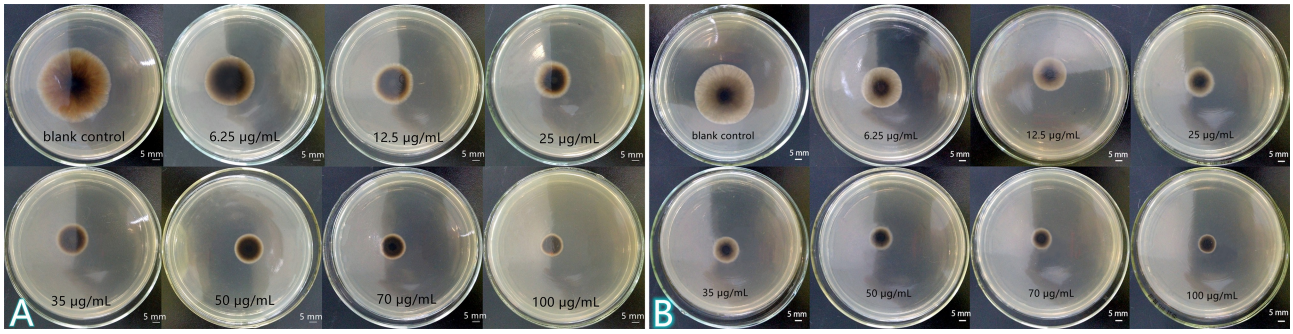


Figure 2. The growth inhibition of *C. lunata* (A) and *A. alternate* (B) by compound **7m** at different concentrations.

the antifungal activity as well. When a small residue 2-furyl was introduced at position 2, compound **7m** displayed about 2-fold as active as the precursor **6f** as shown in *Table 2*. Whereas, by the exchange of 2-furyl with a similar small residue 2-thienyl (**7n**), a significant reduction could be observed. Meanwhile, it is found that the introduction of a bulky substituent or cyclohexyl at position 2 resulted in drastically reduced potencies, such as compounds **7j** (4-*t*-Bu–Ph), **7k** (2-naphthyl) and **7l** (cyclohexyl). Furthermore, only minor differences in the inhibitory activities were observed for the introduction of fluorophenyl (**7a**–**7c**), tolyl (**7d**–**7f**) and methoxyphenyl (**7g**–**7i**).

In addition, as shown in *Figure 3*, the mycelial morphology alterations of *C. lunata* treated with compound **7m** at 50 μg/mL for 24 h at 28 °C were observed by microscopy. It is obvious that the mycelia exposed to compound **7m** showed significant morphological alterations, compared with the untreated control. The surfaces of mycelia in the untreated group (*Figure 3*, A) were relatively smooth and the chromatin was regular and equipped with a uniform color, whereas there was conspicuous shrinkage, coarseness and nonuniform color when treated with compound **7m** (*Figure 3*, B).

Conclusions

In summary, a series of 4-aminoquinolines bearing a 1,3-benzodioxole moiety were prepared and evaluated for their antifungal activities against five phytopathogenic fungi *in vitro*. Most of the target compounds showed moderate to excellent inhibitory activities at the concentration of 50 μg/mL, and some of them displayed comparable or more superior antifungal potencies compared with the commercial fungicide azoxystrobin. Among them, compound **7m** exhibited more promising and broad-spectrum antifungal activities against all tested fungi, and the EC_{50} values of it

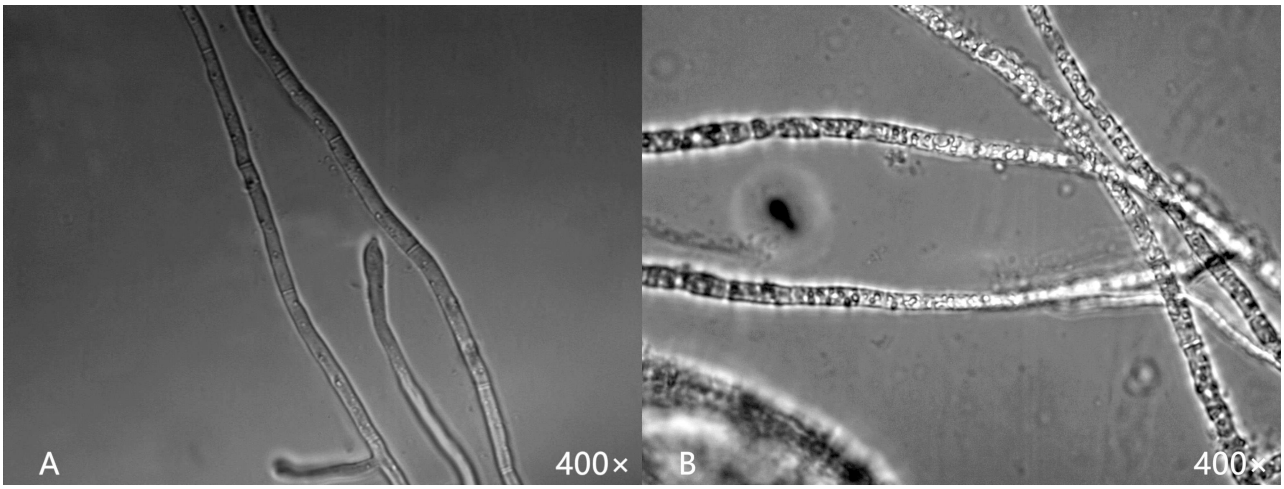


Figure 3. Mycelial morphology of *C. lunata*: (A) is untreated, (B) is treated with compound **7m** at 50 μg/mL for 24 h at 28 °C.

against *C. lunata* and *A. alternate* were 10.3 and 14.0 μg/mL, respectively. SARs analysis revealed that the substituent in *para* position at the aniline moiety and the substituent at position 2 of the quinoline scaffold played key roles in the antifungal activities together.

Experimental Section

Reagents and Instruments

All chemicals and reagents were of analytical grade and obtained from commercial resources. Anhydrous solvents were dried according to standard methods before use. Thin-layer chromatography (TLC) was used to monitor the progression of the reactions on silica gel plates (GF_{254}, Qingdao Haiyang Chemical Co., Ltd., China). Melting points were detected on a X-4 melting point apparatus (Shanghai instrument physical optics instrument Co., Ltd., China) and were uncorrected. IR spectra were performed on a Agilent Cary 630 FT-IR spectrometer with KBr disks. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Advance 400 or 600 instrument using $CDCl_3$, CD_3OD or (D_6)DMSO as deuterated solvent. HR-MS-ESI spectra were carried out with a SCIEX X500R QTOF mass spectrometer.

Synthesis of Intermediates **3a**–**3o**

To a mixture of 1-(6-amino-2*H*-1,3-benzodioxol-5-yl) ethan-1-one (**1**; 0.1 mol), triethylamine (0.1 mol) and anhydrous CH_2Cl_2 (100 mL), a solution of acyl chloride **2a**–**2o** (0.1 mol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise in an ice bath. The solution was stirred overnight at room temperature and then extracted with CH_2Cl_2 (3×80 mL). The combined organic layers were washed with water (3×100 mL), then, dried with Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was recrystallized from petroleum ether/ethyl acetate (10:1, *v/v*) to afford **3a**–**3o** in 64–98% yields, respectively.

Synthesis of Intermediates **4a**–**4o**

A mixture of NaOH (0.27 mol) and the respective amide **3a**–**3o** (0.09 mol) in 1,4-dioxane (200 mL) was refluxed for 2 h until the reaction was complete. Then, the solvent was removed under vacuum and the residue was dissolved in water, adjusted to pH = 5–6 by addition of diluted HCl. With acidification of the solution, copious precipitate appeared. The precipitate was collected and washed with water and a cold mixture of CH_2Cl_2 and AcOEt (1:1, *v/v*) to give the pure products **4a**–**4o** in 52–93% yields, respectively.

Synthesis of Intermediates **5a**–**5o**

A mixture of $POCl_3$ (50 mL) and the respective quinolinone **4a**–**4o** (0.05 mol) in 1,4-dioxane (30 mL) was refluxed for 10 h. After cooling, the most solvent was removed by evaporation and the residue was carefully poured into cold water. Then, the mixture was slowly neutralized with a cold solution of NaOH and extracted with CH_2Cl_2 (3×80 mL). The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was recrystallized from petroleum ether/ethyl acetate (20:1, *v/v*) to yield **5a**–**5o** in 55–93% yields, respectively.

General Procedure for the Synthesis of Target Compounds **6a**–**6j** *and* **7a**–**7n**

To a solution of 4-chloroquinoline **5a**–**5o** (3 mmol) in 1,4-dioxane (8 mL), the respective primary amine (5 mmol) was added, and the mixture was refluxed for several hours until the reaction was complete according to TLC analysis (8–36 h). The solid formed was filtered and washed with petroleum ether/ethyl acetate (5:1, *v/v*) to obtain the target compounds **6a**–**6j** and **7a**–**7n** in 41–96% yields, respectively.

Spectroscopic data of all the target compounds and intermediates **3**, **4** and **5** can be found in the *Supporting Information*.

Antifungal Activity

All title compounds were evaluated for their antifungal activities against five phytopathogenic fungi (*Physalospora piricola*, *Alternaria brassicae*, *Curvularia lunata*, *Pyricularia grisea* and *Alternaria alternate*) by using mycelium growth rate method as reported previously.[14,30] Azoxystrobin, a commercial agricultural fungicide, was used as the positive control. Each of the tested compounds was dissolved in 20 mL of sterile water containing 1 mL of dimethyl sulfoxide (DMSO), and the solution as described above was mixed with 180 mL of sterilized potato dextrose agar (PDA) medium to fix the final concentration of the title compound at 50 μg/mL. Meanwhile, 0.5% DMSO in PDA medium (180 mL PDA + 20 mL sterile water containing 5% DMSO) was served as the blank control. The prepared medium was then poured into sterilized

Petri dishes. Subsequently, a 5-mm-diameter mycelium disk was inoculated to the center of the medium to incubate at 28 °C for 72 h. Each treatment was repeated three times. After 72 h of incubation, the colony diameter of each fungus was measured, and the growth inhibition rate of mycelia was calculated according to the following formula.

Inhibition rate (%) = (C − T)/(C − 5) × 100 %, where C represents the colony diameter in the blank control group, and T represents the colony diameter in the compound-treated group.

Determination of EC_{50}: A series of concentration gradients of some potent compounds were prepared by serial dilution method, containing 100, 70, 50, 35, 25, 12.5 and 6.25 μg/mL. Antifungal toxicity regression equations were established by the linear least-square fitting method for lg[concentration (ng/mL)] values *vs.* the probit values of the corresponding inhibition rate. And the EC_{50} values were analyzed by the GraphPad Prism 7.0 software (GraphPad Software, San Diego, CA, USA).

Morphological observation: The *C. lunata* strain was inoculated in potato dextrose broth (PDB) medium and shaking cultured at 28 °C for 24 h. Then compound **7m** was added to one of the above PDB medium to fix the final concentration at 50 μg/mL. And they were shaking cultured for another 24 h at 28 °C. Subsequently, an optical microscope was used to observe the mycelial morphology of *C. lunata* with and without **7m** treatment.

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Author Contribution Statement

Rui Yang conceived the experiments and prepared the manuscript. Zhuolin Li, Jialing Xie, and Haoyun Ye performed the experiments. Jianchuan Liu and Tianhong Qin carried out the antifungal assays. Junda Liu and Haiying Du analyzed the data and revised the manuscript.

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