European Journal of Medicinal Chemistry 46 (2011) 1919–1925

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Short communication

# Synthesis and antifungal activities of novel 5,6-dihydro-indolo[1,2-*a*]quinoxaline derivatives

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ARTICLE INFO

*Article history:*
Received 2 August 2010
Received in revised form
14 February 2011
Accepted 15 February 2011
Available online 23 February 2011

*Keywords:*
5,6-Dihydro-indolo[1,2-*a*]quinoxaline
Iron catalysis
Cyclization
Pictet–Spengler reaction
Antifungal activity

ABSTRACT

A series of new 5,6-dihydro-indolo[1,2-*a*]quinoxaline derivatives has been prepared in moderate to excellent yields from 2-(indol-1-yl)phenylamines with aromatic aldehydes by an efficient and economical iron-catalyzed Pictet–Spengler reaction. Meanwhile, as compared with hymexazol, a commercially available agricultural fungicide at the concentration of 50 μg/mL, some 5,6-dihydro-indolo[1,2-*a*]quinoxalines exhibited promising antifungal activities *in vitro* against the phytopathogenic fungi, and might be considered as novel promising lead candidates for further design and synthesis of agricultural fungicides.


## 1. Introduction

The indole moiety (**I**, Fig. 1) represents an important structural component associated with a variety of alkaloids [1,2] and wide-ranging biological activities, such as antiviral activities [3–7], antitumor activities [8–10], antimicrobial activities [11], and anti-inflammatory activities [12–14]. Meanwhile, the quinoxaline-containing polycyclic ring derivatives, such as pyrroloquinoxalines, imidazoquinoxalines and triazoloquinoxalines, exhibited the interesting activities [15]. In continuation of our program aimed at the discovery and development of bioactive molecules [16,17], we wanted to design other quinoxaline-containing polycyclic ring derivatives, 5,6-dihydro-indolo[1,2-*a*]quinoxalines (**3a-q**, Fig. 1), *via* combining the indole unit with tetrahydroquinoxaline (**II**, Fig. 1) moiety together. On the other hand, since phytopathogenic fungi are hard to control and easily infect many crops, the development of new compounds that effectively inhibit those agricultural diseases is still highly necessary. In this paper, therefore, we prepared a series of novel 5,6-dihydro-indolo[1,2-*a*]quinoxalines (**3a-q**) *via* a minor modification of the Pictet–Spengler reaction, and investigated their effect on phytopathogenic fungi. Additionally, the structure–antifungal activity relationships (SAR) of compounds **3a-q** were also preliminarily described.

## 2. Chemistry

As compared with other methods [18,19], Pictet–Spengler reaction, which has been extensively used for the construction of a variety of natural products and novel heterocycles [20–22], is still a powerful methodology for the synthesis of 5,6-dihydro-indolo[1,2-*a*]quinoxalines. Although Kundu and coauthors have reported the synthesis of indolo[1,2-*a*]quinoxalines *in situ via* the intermediates, 5,6-dihydro-indolo[1,2-*a*]quinoxalines, excess amounts (1.5 equiv.) of trifluoroacetic acid (TFA), a strong Brønsted acid, were required to prepare 5,6-dihydro-indolo[1,2-*a*]quinoxalines by the Pictet–Spengler reaction [23]. Consequently, the development of environmentally friendly and less expensive catalysts for the construction of a library of 5,6-dihydro-indolo[1,2-*a*]quinoxalines is very important.

It is well-known that iron as one of the most abundant, inexpensive and environmentally friendly metals, recently, has been widely used as a catalyst in many reactions [24–26]. To the best of our knowledge, the iron-catalyzed synthesis of 5,6-dihydro-indolo[1,2-*a*]quinoxalines from 2-(indol-1-yl)phenylamines with aromatic aldehydes has not yet been investigated. As described in

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doi:10.1016/j.ejmech.2011.02.035

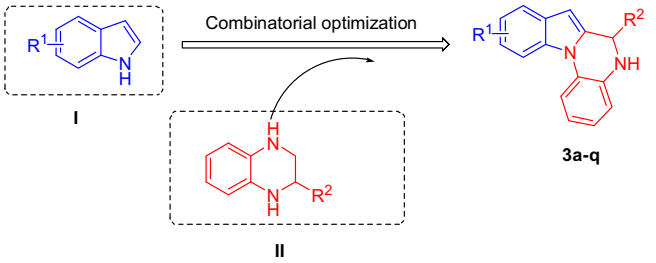
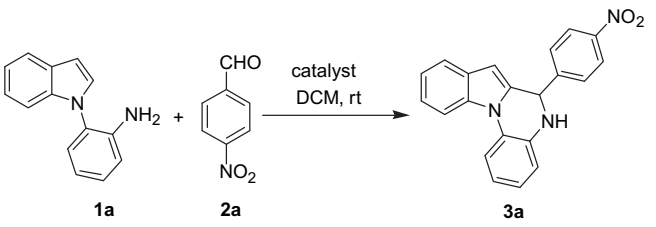



**Fig. 1.** Design strategy of the target compounds **3a**-q.

Scheme 1, therefore, the reaction of 2-(indol-1-yl)phenylamine (**1a**), prepared from 2-(indol-1-yl)nitrobenzene [27], with *p*-nitrobenzaldehyde (**2a**) in dichloromethane (DCM) at room temperature was screened as a model reaction. The results were summarized in Table 1. Firstly, we carried out the reaction without any catalyst, and 6-(*p*-nitrophenyl)-5,6-dihydro-indolo[1,2-*a*]quinoxaline (**3a**) was not obtained at all even if the reaction time was prolonged to 24 h (Table 1, entry 1). The reaction was then carried out by using $FeCl_3 \cdot 6H_2O$ (2.5 mol%) as the catalyst for 1 h, compound **3a** was obtained in a 83% yield (Table 1, entry 2). Increasing the amount of $FeCl_3 \cdot 6H_2O$ to 5 mol% resulted in the formation of **3a** in a 85% yield (Table 1, entry 3). Finally, the effect of other catalysts on this reaction was also evaluated. The catalysts such as $I_2$, TFA or *p*-TsOH gave no product or lower yields of **3a** (Table 1, entries 4–6). Although **3a** was obtained in a 89% yield by using $SnCl_2 \cdot 2H_2O$ (2.5 mol%) as the catalyst (Table 1, entry 7), it was not an environmentally friendly catalyst. Consequently, the optimum reaction conditions for the synthesis of **3a** were to use 2.5 mol% of $FeCl_3 \cdot 6H_2O$ as the catalyst in DCM at room temperature (Table 1, entry 2).

Encouraged by the above-mentioned results, a variety of 2-(indol-1-yl)phenylamines (**1**, $R^1$ = H, Me, and CN) reacting with aromatic aldehydes (**2**, $R^2$ = H, OH, $NMe_2$, OMe, and $NO_2$) were investigated to explore the scope for the synthesis of 5,6-dihydro-indolo[1,2-*a*]quinoxalines. As outlined in Table 2, all reactions generally proceeded *via* a Pictet–Spengler intermolecular cyclization to give 5,6-dihydro-indolo[1,2-*a*]quinoxalines in moderate to excellent yields. The electronic effects of the 2-(indol-1-yl)phenylamines and aromatic aldehydes on this reaction were observed. In general, introduction of the electron-donating functional group on the indole rings of 2-(indol-1-yl)phenylamines (Table 2, entries 4, 6 and 13 *vs.* 15), and introduction of the electron-withdrawing functional group on the phenyl rings of aromatic aldehydes (Table 2, entries 1 *vs.* 2 and 3; 4 *vs.*5; 6 *vs.*7–12; 13 *vs.*14) would easily and rapidly result in Pictet–Spengler cyclization to give the products in excellent yields, and vice versa. For example, as compared with **1a-d**, when the electron-deficiency 2-(5-cyanoindol-1-yl)phenylamine (**1e**) reacted with **2a**, the reaction time should be prolonged to 24 h at room temperature to obtain the good yield of 6-(4-nitrophenyl)-5,6-dihydro-9-cyanoindolo[1,2-*a*]quinoxaline (**3o**) (Table 2, entries 1, 4, 6 and 13 *vs.* 15). Additionally, **1a** reacted with **2a** for 1 h at room temperature to give **3a** in a 83% yield, while **1a** reacted with 3-methoxy-4-hydroxybenzaldehyde (**2c**) to produce 6-(3-methoxy-4-hydroxyphenyl)-5,6-dihydro-indolo[1,2-*a*] quinoxaline (**3c**) only in a 23% yield, even if the reaction time was prolonged to 15 h at room temperature (Table 2, entries 1 *vs.* 3). Especially 4-(*N*,*N*-dimethylamino)benzaldehyde (**2e**) did not react with 2-(4-methylindol-1-yl) phenylamine (**1c**) at room temperature, and when the temperature was raised to reflux for 31 h, 6-(4-*N*,*N*-dimethylaminophenyl)-5,6-dihydro-8-methylindolo[1,2-*a*]quinoxaline (**3i**) was obtained in a 27% yield (Table 2, entry 9).




**Scheme 1.** Model reaction.

**Table 1**
Optimization studies[a].

| Entry | Catalyst (mol%)[b] | Time (h) | Yield (%)[c] |
|---|---|---|---|
| 1 | None | 24 | 0 |
| 2 | $FeCl_3 \cdot 6H_2O$ (2.5) | 1 | 83 |
| 3 | $FeCl_3 \cdot 6H_2O$ (5) | 1 | 85 |
| 4 | $I_2$ (2) | 24 | 0 |
| 5 | 5% TFA (110) | 5 | 23 |
| 6 | *p*-TsOH (10) | 9 | 16 |
| 7 | $SnCl_2 \cdot 2H_2O$ (2.5) | 1 | 89 |

[a] Reaction conditions: The mixture of **1a** (0.25 mmol) and **2a** (0.25 mmol) in DCM (2 mL) in the presence of catalyst was reacted at room temperature.
[b] The amount of catalyst was referred to mol% of **1a** and given in parentheses.
[c] Isolated yields.

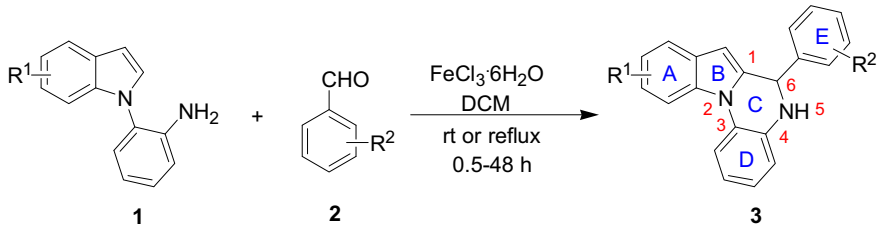
However, the steric effects of 2-(indol-1-yl)phenylamines and aromatic aldehydes on this reaction were not obvious. For example, when **2a** reacted with 2-(indol-1-yl)phenylamine (**1a**) or 2-(3-methylindol-1-yl)phenylamine (**1b**), the corresponding yields of **3a** and 6-(*p*-nitrophenyl)-5,6-dihydro-7-methylindolo[1,2-*a*]quinoxaline (**3d**) were 83% and 90%, respectively (Table 2, entries 1 and 4). Meanwhile, when **1c** reacted with 4-hydroxybenzaldehyde (**2b**) or 2-hydroxybenzaldehyde (**2g**), the corresponding 6-(*p*-hydroxyphenyl)-5,6-dihydro-8-methylindolo[1,2-*a*]quinoxaline (**3g**) and 6-(*o*-hydroxyphenyl)-5,6-dihydro-8-methylindolo[1,2-*a*]quinoxaline (**3l**) were obtained in 75% and 71% yields, respectively (Table 2, entries 7 and 12).

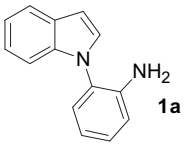
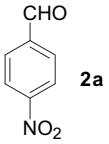
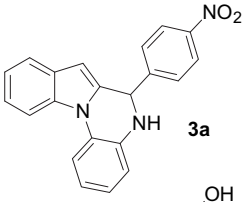
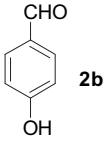
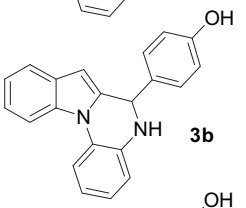
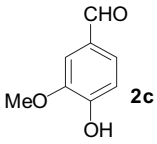
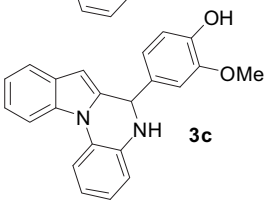
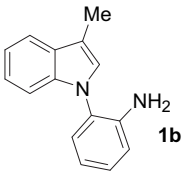
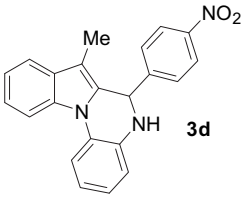
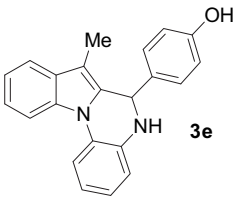
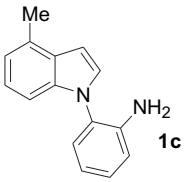
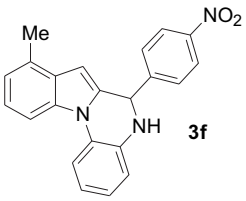
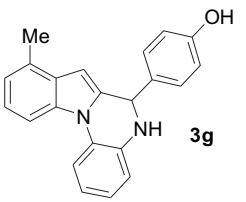
We also attempted to extend the scope to other carbonyl compounds such as acetophenon (**2h**) and 2-furaldehyde (**2i**). To our delight, the corresponding 5,6-dihydro-indolo[1,2-*a*]quinoxalines were obtained in moderate to good yields (Scheme 2). For example, when **1c** reacted with **2h** at reflux for 48 h, 6-methyl-6-phenyl-5,6-dihydro-8-methylindolo[1,2-*a*]quinoxaline (**3p**) was obtained in a 48% yield, while **1b** reacted with **2i** at room temperature only for 0.5 h to give 6-(furan-2-yl)-5,6-dihydro-7-methylindolo[1,2-*a*]quinoxaline (**3q**) in a 95% yield. The structures of all new target compounds **3a-q** were well characterized by $^1H$ NMR, $^{13}C$ NMR, HRMS, IR, and m.p.

## 3. Biological evaluation

The antifungal activities of 17 5,6-dihydro-indolo[1,2-*a*]quinoxaline derivatives (**3a-q**) against five phytopathogenic fungi (*i.e.*, *Fusarium graminearum*, *Pyricularia oryzae*, *Fusarium oxysporum* f. sp. *vasinfectum*, *Alternaria alternata*, and *Alternaria brassicae*) were investigated at the concentration of 50 μg/mL *in vitro* by poisoned food technique [28]. Hymexazol, a commercially available agricultural fungicide, was used as a positive control at 50 μg/mL. As depicted in Table 3, among all the derivatives, compounds **3b**, **3e**, **3g**, **3n**, and **3o** exhibited the good and broad spectrum of antifungal activities against the five phytopathogenic fungi. Meanwhile, some interesting results through a comparative study on the SAR of **3a-q** were found as follows: (1) Generally, when the hydroxy group was introduced at the 4-position on the E-ring, the corresponding derivatives showed the potent activities. Interestingly, if the methoxy group was simultaneously introduced at the 3-position on the E-ring of **3b** or **3g** to give **3c** or **3k**, the corresponding antifungal

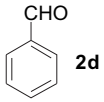
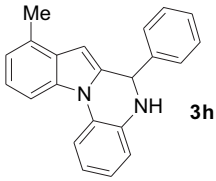
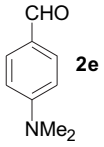
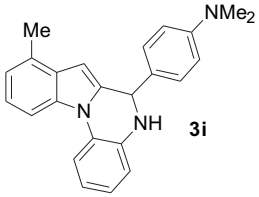
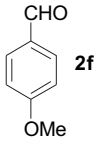
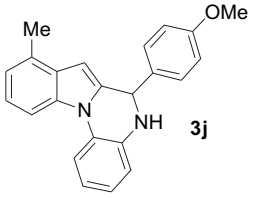
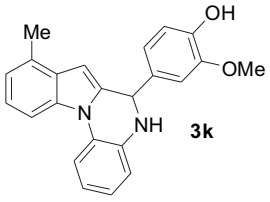
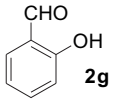
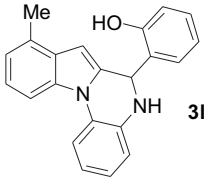
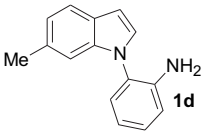
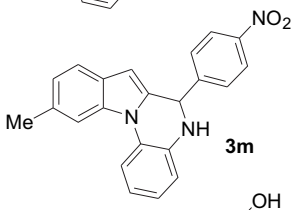
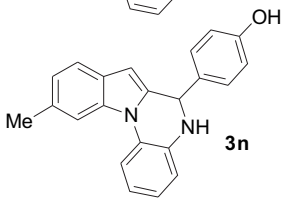
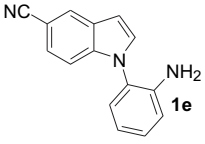
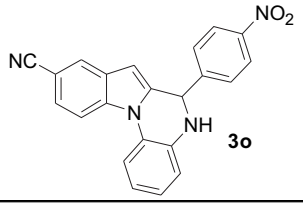
**Table 2**
Synthesis of 5,6-dihydro-indolo[1,2-*a*]quinoxalines *via* Pictet–Spengler reaction promoted by $FeCl_3 \cdot 6H_2O$.[a]




| Entry | 1 | 2 | Product (3) | Condition | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 |  **1a** |  **2a** |  **3a** | rt | 1 | 83 |
| 2 | **1a** |  **2b** |  **3b** | rt | 24 | 73 |
| 3 | **1a** |  **2c** |  **3c** | rt | 15 | 23 |
| 4 |  **1b** | **2a** |  **3d** | rt | 1 | 90 |
| 5 | **1b** | **2b** |  **3e** | rt | 48 | 79 |
| 6 |  **1c** | **2a** |  **3f** | rt | 0.5 | 98 |
| 7 | **1c** | **2b** |  **3g** | rt | 24 | 75 |

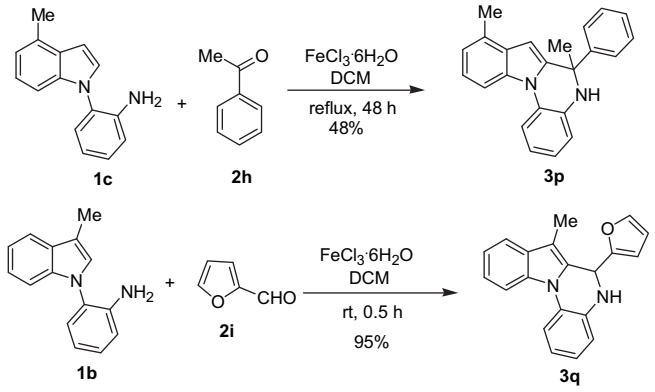
(*continued on next page*)

**Table 2** (*continued*).

| Entry | 1 | 2 | Product (3) | Condition | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 8 | **1c** |  **2d** |  **3h** | rt | 6 | 95 |
| 9 | **1c** |  **2e** |  **3i** | reflux | 31 | 27 |
| 10 | **1c** |  **2f** |  **3j** | rt | 24 | 78 |
| 11 | **1c** | **2c** |  **3k** | rt | 25 | 44 |
| 12 | **1c** |  **2g** |  **3l** | rt | 24 | 71 |
| 13 |  **1d** | **2a** |  **3m** | rt | 1 | 94 |
| 14 | **1d** | **2b** |  **3n** | rt | 24 | 89 |
| 15 |  **1e** | **2a** |  **3o** | rt | 24 | 85 |

[a] Reaction conditions: The mixture of **1** (0.25 mmol), **2** (0.25 mmol), and $FeCl_3.6H_2O$ (2.5 mol%) in DCM (2 mL) was reacted at room temperature or reflux under $N_2$, and the reaction process was checked by TLC.

[b] Isolated yields.




**Scheme 2.** Synthesis of **3p** and **3q**.

activities were decreased sharply (**3b** *vs.* **3c**; **3g** *vs.* **3k**). Moreover, introduction of hydroxyl group at the 2-position on the E-ring of **3h** gave **3l**, the antifungal activities of which were decreased as compared with **3g** bearing hydroxy group at the 4-position on the E-ring. (2) Introduction of the electron-withdrawing group (*e.g.*, cyano) on the A-ring of **3a** usually led to the more potent compound than those possessing the electron-donating group (*e.g.*, methyl) on the A-ring (**3o** *vs.* **3d**, **3f** and **3m**). (3) When the methyl group was introduced at the 6-position on the C-ring of **3h** to give **3p**, or the E-ring of **3e** was substituted by the furanyl ring to afford **3q**, the corresponding activities of **3p** and **3q** were not increased at all.

## 4. Conclusion

In summary, we have reported a convenient, economic and efficient cyclization reaction using $FeCl_3 \cdot 6H_2O$ as the catalyst for the synthesis of 5,6-dihydro-indolo[1,2-*a*]quinoxalines. The reactions proceed *via* a Pictet–Spengler intermolecular cyclization to give 5,6-dihydro-indolo[1,2-*a*]quinoxalines in moderate to excellent yields from 2-(indol-1-yl)phenylamines with aromatic aldehydes. It is noteworthy that this protocol uses inexpensive and environmentally friendly $FeCl_3 \cdot 6H_2O$ (2.5 mol%) as the catalyst. Especially compounds **3b**, **3e**, **3g**, **3n** and **3o** exhibited promising and pronounced antifungal activities *in vitro* against the phytopathogenic fungi, and might be considered as new lead structures for further design of agricultural fungicides. Generally, the SAR clearly demonstrated that the substituent $R^2$ as hydroxy group at the 4-position on the E-ring, and introduction of cyano group on the A-ring of 5,6-dihydro-indolo[1,2-*a*]quinoxalines were very vital for their antifungal activities. Further structural modification on 5,6-dihydro-indolo[1,2-*a*]quinoxalines and in-depth study on the antifungal activities are currently in progress in our research group.

## 5. Experimental protocols

### 5.1. Chemistry

#### 5.1.1. General remarks

All reagents and solvents were of reagent grade or purified according to standard methods before use. Thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were used with silica gel 60 $GF_{254}$ (Qingdao Haiyang Chemical Co., Ltd., China). Melting points were determined on a digital melting-point apparatus and were uncorrected. Infrared spectra (IR) were recorded on a Bruker TENSOR 27 spectrometer. Proton nuclear magnetic resonance spectra ($^1$H NMR) and carbon-13 nuclear magnetic resonance spectra ($^{13}$C NMR) were recorded on Bruker Avance DMX 300, 400 or 500 MHz and 125 MHz instruments, respectively, using TMS as the internal standard and $CDCl_3$ as the solvent. High-resolution mass spectra (HR-MS) were carried out with APEX II Bruker 4.7T AS instrument.

#### 5.1.2. General procedures for the synthesis of 5,6-dihydro-indolo [1,2-a]quinoxalines (*3a-q*)

A mixture of **1** (0.25 mmol) and **2** (0.25 mmol) in DCM (2 mL) in the presence of $FeCl_3 \cdot 6H_2O$ (2.5 mol%) was reacted at room temperature or reflux under $N_2$, and the reaction process was checked by TLC analysis. When the reaction was complete, the organic solvent was removed, and the residue was directly purified by preparative thin-layer chromatography (PTLC) to give the desired products **3a-q**, which were characterized by $^1$H NMR, $^{13}$C NMR, HRMS, IR and m.p.

*5.1.2.1. 6-(p-Nitrophenyl)-5,6-dihydro-indolo[1,2-a]quinoxaline (**3a**).* Yellow solid, m.p. 168–170 °C; IR $cm^{-1}$: 735, 745, 1350, 1455, 1510, 1598, 3329; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 4.22 (1H, s, NH), 5.63 (1H, s), 5.85 (1H, s), 6.90–6.91 (1H, m), 7.04–7.06 (2H, m), 7.15 (1H, t, $J$ = 7.6 Hz), 7.27 (1H, t, $J$ = 7.2 Hz), 7.52 (1H, d, $J$ = 7.6 Hz), 7.65–7.67 (2H, m), 7.93–8.02 (2H, m), 8.23 (2H, d, $J$ = 8.4 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$:

**Table 3**
Antifungal activities of compounds **3a-q** at 50 μg/mL.

| Compd | Antifungal activities (inhibition %) | | | | |
|---|---|---|---|---|---|
| | *F. graminearum* | *P. oryzae* | *F. oxysporium* f. sp. *vasinfectum* | *A. alternata* | *A. brassicae* |
| **3a** | 17.2 (±0.7) | 5.8 (±0.7) | 9.2 (±1.1) | 19.4 (±0.6) | 11.2 (±0.6) |
| **3b** | 52.1 (±0.7) | 50.8 (±1.2) | 39.2 (±1.0) | 58.3 (±0) | 31.4 (±0) |
| **3c** | 15.7 (±0.6) | 4.4 (±1.2) | 11.0 (±1.5) | 9.2 (±0.6) | 15.7 (±0.5) |
| **3d** | 26.6 (±0.7) | 11.8 (±0.7) | 11.4 (±0.5) | 18.2 (±1.2) | 13.3 (±0.6) |
| **3e** | 48.0 (±0.7) | 46.5 (±07) | 44.0 (±1.2) | 55.6 (±1.2) | 53.0 (±0.5) |
| **3f** | 24.6 (±0) | 10.1 (±1.2) | 5.3 (±0.5) | 17.7 (±1.0) | 10.4 (±0.6) |
| **3g** | 51.3 (±0.8) | 50.8 (±1.2) | 41.2 (±0.6) | 72.9 (±0) | 55.9 (±1.0) |
| **3h** | 32.0 (±0.7) | 22.1 (±1.2) | 8.8 (±1.0) | 29.2 (±1.0) | 30.4 (±1.0) |
| **3i** | 17.6 (±0.4) | 7.7 (±1.2) | 6.9 (±1.0) | 19.8 (±1.0) | 10.4 (±1.1) |
| **3j** | 12.2 (±0.7) | 15.1 (±1.3) | 9.7 (±1.2) | 14.9 (±0.6) | 7.2 (±1.6) |
| **3k** | 12.3 (±1.0) | 16.0 (±1.3) | 20.2 (±1.2) | 17.9 (±0.6) | 21.0 (±1.2) |
| **3l** | 8.8 (±1.2) | 7.8 (±0.7) | 11.7 (±1.2) | 12.0 (±0.6) | 55.8 (±0.5) |
| **3m** | 12.2 (±0.7) | 1.6 (±1.2) | 11.7 (±1.2) | 7.8 (±1.5) | 13.0 (±0.5) |
| **3n** | 41.2 (±0.4) | 43.7 (±0) | 37.3 (±0.6) | 56.3 (±0.6) | 49.0 (±1.5) |
| **3o** | 56.3 (±0.7) | 62.8 (±1.2) | 60.8 (±0.6) | 64.6 (±0.4) | 52.4 (±0.6) |
| **3p** | 43.0 (±0.4) | 34.6 (±1.3) | 23.6 (±0.6) | 32.7 (±0.6) | 29.9 (±0.5) |
| **3q** | 31.5 (±1.0) | 33.4 (±0.7) | 17.8 (±1.2) | 37.3 (±0) | 30.1 (±0.5) |
| Hym | 57.0 (±0.4) | 53.5 (±0.7) | 62.7 (±1.0) | 68.8 (±0) | 47.1 (±0.5) |

56.7, 100.8, 112.0, 116.5, 117.3, 121.0, 121.4, 121.5, 123.3, 124.3, 124.6, 127.5, 129.4, 129.7, 134.4, 136.9, 137.5, 147.6, 148.3; HRMS-ESI: Calcd. for $C_{21}H_{15}N_3O_2$ $[M + H]^+$: 342.1237. Found: 342.1239.

*5.1.2.2. 6-(p-Hydroxyphenyl)-5,6-dihydro-indolo[1,2-a]quinoxaline (**3b**).* Pale yellow solid, m.p. 146–148 °C; IR $cm^{-1}$: 738, 747, 1229, 1452, 1508, 1598, 3307; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 4.11 (1H, s, NH), 4.92 (1H, s, OH), 5.42 (1H, s), 5.87 (1H, s), 6.80–6.88 (3H, m), 6.99–7.04 (2H, m), 7.11 (1H, t, $J = 7.5$ Hz), 7.22–7.28 (1H, m), 7.35 (2H, d, $J = 8.7$ Hz), 7.51 (1H, d, $J = 7.5$ Hz), 7.90–7.93 (1H, m), 7.98 (1H, d, $J = 8.1$ Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 56.6, 100.1, 111.6, 115.5, 116.0, 116.9, 120.1, 120.8, 121.0, 122.5, 124.0, 127.3, 129.6, 129.8, 132.3, 134.2, 137.7, 139.6, 155.77; HRMS-ESI: Calcd. for $C_{21}H_{16}N_2O$ $[M + H]^+$: 313.1335. Found: 313.1339.

*5.1.2.3. 6-(3-Methoxy-4-hydroxyphenyl)-5,6-dihydro-indolo[1,2-a]quinoxaline (**3c**).* Pale yellow solid, m.p. 212–214 °C; IR $cm^{-1}$: 745, 779, 1031, 1150, 1227, 1266, 1454, 1505, 1595, 3317, 3485; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 3.84 (3H, s, $OCH_3$), 4.14 (1H, s, NH), 5.43 (1H, s), 5.70 (1H, s), 5.90 (1H, s), 6.87–6.89 (1H, m), 6.94–6.96 (1H, m), 7.00–7.08 (4H, m), 7.13 (1H, t, $J = 7.6$ Hz), 7.25–7.29 (1H, m), 7.53 (1H, d, $J = 7.6$ Hz), 7.93–7.95 (1H, m), 8.00 (1H, d, $J = 8.4$ Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 56.0, 57.1, 100.1, 110.4, 111.6, 114.0, 116.0, 116.9, 120.1, 120.8, 121.0, 121.6, 122.4, 124.0, 127.3, 129.6, 131.8, 134.1, 137.7, 139.7, 145.9, 146.9; HRMS-ESI: Calcd. for $C_{22}H_{18}N_2O_2$ $[M + H]^+$: 343.1441. Found: 343.1448.

*5.1.2.4. 6-(p-Nitrophenyl)-5,6-dihydro-7-methylindolo[1,2-a]quinoxaline (**3d**).* Yellow solid, m.p. 160–162 °C; IR $cm^{-1}$: 704, 737, 1342, 1454, 1507, 1596, 3367; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 2.12 (3H, s, $CH_3$), 4.39 (1H, s, NH), 5.78 (1H, s), 6.76 (1H, d, $J = 6.8$ Hz), 6.94–7.01 (2H, m), 7.21–7.25 (1H, m), 7.30–7.36 (3H, m), 7.59 (1H, d, $J = 8.0$ Hz), 7.89 (1H, d, $J = 6.8$ Hz), 8.01 (1H, d, $J = 8.0$ Hz), 8.07–8.09 (2H, m); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 8.4, 53.9, 107.9, 111.9, 116.50, 116.58, 119.2, 120.5, 120.7, 123.0, 124.0, 124.1, 127.3, 127.8, 130.4, 131.0, 133.5, 134.4, 147.4, 148.8; HRMS-ESI: Calcd. for $C_{22}H_{17}N_3O_2$ $[M + H]^+$: 356.1394. Found: 356.1399.

*5.1.2.5. 6-(p-Hydroxyphenyl)-5,6-dihydro-7-methylindolo[1,2-a]quinoxaline (**3e**).* Pale yellow solid, m.p. 204–206 °C; IR $cm^{-1}$: 740, 754, 1174, 1222, 1454, 1509, 1597, 3300; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 1.99 (3H, s, $CH_3$), 5.59 (1H, s), 6.65 (2H, d, $J = 8.0$ Hz), 6.73–6.75 (1H, m), 6.93–6.95 (2H, m), 7.06 (2H, $J = 8.4$ Hz), 7.16–7.29 (2H, m), 7.54 (1H, d, $J = 7.6$ Hz), 7.86–7.89 (1H, m), 7.98 (1H, d, $J = 8.8$ Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 8.3, 54.6, 107.2, 111.7, 115.5, 116.2, 116.4, 118.9, 119.8, 120.3, 122.5, 123.6, 127.4, 128.7, 130.7, 132.9, 133.3, 134.1, 135.7, 155.2; HRMS-ESI: Calcd. for $C_{22}H_{18}N_2O$ $[M + H]^+$: 327.1492. Found: 327.1499.

*5.1.2.6. 6-(p-Nitrophenyl)-5,6-dihydro-8-methylindolo[1,2-a]quinoxaline (**3f**).* Yellow solid, m.p. 218–220 °C; IR $cm^{-1}$: 730, 758, 1277, 1342, 1504, 1515, 1561, 1595, 3362; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 2.44 (3H, s, $CH_3$), 4.23 (1H, s, NH), 5.67 (1H, s), 5.86 (1H, s), 6.90–6.92 (1H, m), 6.97 (1H, d, $J = 7.6$ Hz), 7.04–7.08 (2H, m), 7.19 (1H, t, $J = 7.6$ Hz), 7.70 (2H, d, $J = 8.4$ Hz), 7.85 (1H, d, $J = 8.8$ Hz), 7.94–7.96 (1H, m), 8.27 (2H, d, $J = 8.4$ Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 18.7, 56.5, 98.9, 109.4, 116.2, 117.0, 120.7, 121.5, 123.1, 124.0, 124.2, 127.3, 129.1, 129.2, 130.6, 133.8, 136.6, 136.7, 147.4, 148.1; HRMS-ESI: Calcd. for $C_{22}H_{17}N_3O_2$ $[M + H]^+$: 356.1394. Found: 356.1387.

*5.1.2.7. 6-(p-Hydroxyphenyl)-5,6-dihydro-8-methylindolo[1,2-a]quinoxaline (**3g**).* Pale yellow solid, m.p. 178–180 °C; IR $cm^{-1}$: 735, 766, 1220, 1275, 1427, 1508, 1567, 1596, 1611, 3309; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 2.44 (3H, s, $CH_3$), 4.10 (1H, s, NH), 4.98 (1H, s, OH), 5.43 (1H, s), 5.88 (1H, s), 6.84 (3H, d, $J = 8.8$ Hz), 6.94–7.02 (3H, m), 7.15 (1H, t, $J = 8.0$ Hz), 7.37 (2H, d, $J = 8.4$ Hz), 7.83 (1H, d, $J = 8.4$ Hz), 7.90–7.93 (1H, m); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 18.7, 56.7, 98.4, 109.3, 115.5, 115.9, 116.9, 120.1, 121.1, 122.5, 123.9, 127.4, 129.3, 129.8, 130.4, 132.4, 133.8, 137.7, 139.0, 155.7; HRMS-ESI: Calcd. for $C_{22}H_{18}N_2O$ $[M + H]^+$: 327.1492. Found: 327.1488.

*5.1.2.8. 6-Phenyl-5,6-dihydro-8-methylindolo[1,2-a]quinoxaline (**3h**).* Pale yellow solid, m.p. 158–160 °C; IR $cm^{-1}$: 628, 699, 739, 769, 1281, 1433, 1505, 1556, 1598, 3336; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 2.43 (3H, s, $CH_3$), 4.16 (1H, s, NH), 5.51 (1H, s), 5.88 (1H, s), 6.84–6.86 (1H, m), 6.94 (1H, d, $J = 7.2$ Hz), 7.00–7.02 (2H, m), 7.15 (1H, t, $J = 8.0$ Hz), 7.41–7.45 (3H, m), 7.52–7.53 (2H, m), 7.84 (1H, d, $J = 8.4$ Hz), 7.92–7.94 (1H, m); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 18.7, 57.3, 98.5, 109.3, 116.0, 116.9, 120.1, 121.2, 122.6, 123.9, 127.4, 128.4, 128.6, 128.8, 129.3, 130.4, 133.8, 137.6, 138.6, 140.1; HRMS-ESI: Calcd. for $C_{22}H_{18}N_2$ $[M + H]^+$: 311.1543. Found: 311.1549.

*5.1.2.9. 6-(4-N,N-Dimethylaminophenyl)-5,6-dihydro-8-methylindolo[1,2-a]quinoxaline (**3i**).* Pale yellow solid, m.p. 186–188 °C; IR $cm^{-1}$: 613, 668, 731, 807, 1276, 1348, 1506, 1560, 1609, 3366; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$: 2.44 (3H, s, $CH_3$), 3.00 (6H, s, $N(CH_3)_2$), 4.09 (1H, s, NH), 5.41 (1H, s), 5.93 (1H, s), 6.76 (2H, d, $J = 9.0$ Hz), 6.83–6.85 (1H, m), 6.94 (1H, d, $J = 7.0$ Hz), 6.99–7.01 (2H, m), 7.14 (1H, t, $J = 7.5$ Hz), 7.38 (2H, d, $J = 8.5$ Hz), 7.83 (1H, d, $J = 8.5$ Hz), 7.91–7.93 (1H, m); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 18.7, 40.5, 56.8, 98.3, 109.3, 112.4, 115.9, 116.9, 119.8, 121.0, 122.3, 123.8, 127.4, 127.5, 129.3, 129.4, 130.3, 133.9, 138.1, 139.5, 150.7; HRMS-ESI: Calcd. for $C_{24}H_{23}N_3$ $[M + H]^+$: 354.1965. Found: 354.1963.

*5.1.2.10. 6-(p-Methoxyphenyl)-5,6-dihydro-8-methylindolo[1,2-a]quinoxaline (**3j**).* Orange solid, m.p. 194–196 °C; IR $cm^{-1}$: 742, 763, 825, 1027, 1234, 1262, 1561, 1597, 3318, 3343; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 2.44 (3H, s, $CH_3$), 3.85 (3H, s, $OCH_3$), 4.12 (1H, s, NH), 5.45 (1H, s), 5.87 (1H, s), 6.84–6.86 (1H, m), 6.94 (3H, d, $J = 8.8$ Hz), 7.00–7.02 (2H, m), 7.15 (1H, t, $J = 8.0$ Hz), 7.44 (2H, d, $J = 8.4$ Hz), 7.83 (1H, d, $J = 8.0$ Hz), 7.91–7.94 (1H, m); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 18.7, 55.3, 56.7, 98.4, 109.3, 114.0, 115.9, 116.9, 120.0, 121.1, 122.5, 123.9, 127.4, 129.3, 129.6, 130.4, 132.2, 133.9, 137.8, 139.0, 159.8; HRMS-ESI: Calcd. for $C_{23}H_{20}N_2O$ $[M + H]^+$: 341.1648. Found: 341.1651.

*5.1.2.11. 6-(3-Methoxy-4-hydroxyphenyl)-5,6-dihydro-8-methylindolo[1,2-a]quinoxaline (**3k**).* White solid, m.p. 192–194 °C; IR $cm^{-1}$: 621, 750, 1029, 1230, 1263, 1321, 1430, 1508, 1560, 1598, 1610, 3350, 3506; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 2.44 (3H, s, $CH_3$), 3.84 (3H, s, $OCH_3$), 4.12 (1H, s, NH), 5.42 (1H, s), 5.72 (1H, s), 5.89 (1H, s), 6.85–6. 88 (1H, m), 6.95–6.97 (2H, m), 7.01–7.03 (3H, m), 7.08 (1H, s), 7.16 (1H, t, $J = 8.0$ Hz), 7.84 (1H, d, $J = 8.4$ Hz), 7.91–7.94 (1H, m); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 18.7, 56.0, 57.2, 98.5, 109.3, 110.4, 114.0, 115.9, 116.9, 120.1, 121.1, 121.7, 122.5, 123.9, 127.4, 129.3, 130.4, 132.0, 133.8, 137.7, 139.1, 145.9, 146.9; HRMS: Calcd. for $C_{23}H_{20}N_2O_2$ $[M + H]^+$: 357.1598. Found: 357.1603.

*5.1.2.12. 6-(o-Hydroxyphenyl)-5,6-dihydro-8-methylindolo[1,2-a]quinoxaline (**3l**).* White solid, m.p. 192–194 °C; IR $cm^{-1}$: 730, 758, 824, 1243, 1278, 1491, 1509, 1560, 1590, 3299; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$: 2.42 (3H, s, $CH_3$), 5.58 (1H, s), 5.93 (1H, s), 6.95–6.99 (4H, m), 7.05 (1H, t, $J = 7.6$ Hz), 7.13–7.21 (2H, m), 7.23–7.25 (1H, m), 7.34–7.38 (1H, m), 7.81 (1H, d, $J = 8.4$ Hz), 7.94 (1H, d, $J = 8.0$ Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$: 18.7, 57.5, 99.3, 109.2, 117.1, 117.4, 117.8, 119.8, 121.5, 122.1, 122.4, 123.0, 123.9, 128.4, 129.3, 129.9, 130.4, 130.8, 134.2, 135.7, 136.0, 156.7; HRMS-ESI: Calcd. for $C_{22}H_{18}N_2O$ $[M + H]^+$: 327.1492. Found: 327.1490.

*5.1.2.13. 6-(p-Methoxyphenyl)-5,6-dihydro-10-methylindolo[1,2-a]quinoxaline (**3m**).* Yellow solid, m.p. 216–218 °C; IR $cm^{-1}$: 712, 742,

796, 807, 830, 851, 1343, 1434, 1491, 1515, 1598, 3318; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 2.52 (3H, s, $CH_3$), 4.20 (1H, s, NH), 5.63 (1H, s), 5.80 (1H, s), 6.88–6.91 (1H, m), 6.99–7.07 (3H, m), 7.39 (1H, d, $J$ = 7.8 Hz), 7.65 (2H, d, $J$ = 9.0 Hz), 7.81 (1H, s), 7.92–7.95 (1H, m), 8.23 (2H, d, $J$ = 8.7 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 22.1, 56.4, 100.3, 111.8, 116.2, 117.0, 120.70, 120.77, 122.8, 123.9, 124.1, 127.1, 127.3, 129.1, 132.9, 134.5, 136.6, 136.7, 147.4, 148.0; HRMS-ESI: Calcd. for $C_{22}H_{17}N_3O_2$ $[M + H]^+$: 356.1394. Found: 356. 1401.

*5.1.2.14. 6-(p-Hydroxyphenyl)-5,6-dihydro-10-methylindolo[1,2-a]quinoxaline (**3n**).* White solid, m.p. 154–156 °C; IR cm$^{-1}$: 740, 751, 811, 833, 877, 941, 1235, 1251, 1346, 1432, 1508, 1602, 3294; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 2.51 (3H, s, $CH_3$), 4.09 (1H, s, NH), 4.91 (1H, s, OH), 5.39 (1H, s), 5.81 (1H, s), 6.80–6.85 (3H, m), 6.96–7.04 (3H, m), 7.33–7.41 (3H, m), 7.80 (1H, s), 7.90–7.93 (1H, m); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 22.1, 56.6, 99.9, 111.7, 115.4, 115.9, 116.9, 120.0, 120.6, 122.4, 123.8, 127.41, 127.48, 129.8, 132.2, 132.4, 134.6, 137.7, 139.0, 155.7; HRMS-ESI: Calcd. for $C_{22}H_{18}N_2O$ $[M + H]^+$: 327.1492. Found: 327.1493.

*5.1.2.15. 6-(4-Nitrophenyl)-5,6-dihydro-9-cyanoindolo[1,2-a]quinoxaline (**3o**).* Yellow solid, m.p. 180–181 °C; IR cm$^{-1}$: 684, 718, 753, 850, 888, 1332, 1349, 1513, 1589, 2213, 3118; $^1$H NMR (400 MHz, $CDCl_3$ ) $\delta$: 6.72 (1H, d, $J$ = 2.8 Hz), 7.30–7.34 (2H, m), 7.38–7.42 (2H, m), 7.47–7.49 (1H, m), 7.53–7.57 (2H, m), 7.74 (2H, d, $J$ = 8.8 Hz), 8.02 (1H, s), 8.20 (2H, d, $J$ = 8.8 Hz), 8.50 (1H, s); HRMS-ESI: Calcd. for $C_{22}H_{14}N_4O_2$ $[M + H]^+$: 367.1190. Found: 367.1193.

*5.1.2.16. 6-Methyl-6-phenyl-5,6-dihydro-8-methylindolo[1,2-a]quinoxaline (**3p**).* White solid, m.p. 174–176 °C; IR cm$^{-1}$: 699, 737, 765, 1423, 1506, 1597, 2923, 3351; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 1.98 (3H, s, $CH_3$), 2.57 (3H, s, $CH_3$), 6.45 (1H, s), 6.87–7.01 (4H, m), 7.16–7.22 (4H, m), 7.33 (2H, d, $J$ = 7.6 Hz), 7.80–7.85 (2H, m); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 18.8, 29.0, 57.7, 97.3, 109.4, 116.4, 116.8, 119.8, 121.2, 122.5, 124.0, 126.0, 127.1, 127.4, 128.2, 129.2, 130.4, 133.8, 136.2, 140.9, 145.0; HRMS-ESI: Calcd. for $C_{23}H_{20}N_2$ $[M + H]^+$: 325.1699. Found: 325.1691.

*5.1.2.17. 6-(Furan-2-yl)-5,6-dihydro-7-methylindolo[1,2-a]quinoxaline (**3q**).* Pale yellow solid, m.p. 44–46 °C; IR cm$^{-1}$: 743, 751, 801, 1012, 1090, 1456, 1507, 1598, 2916, 3364; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 2.25 (3H, s, $CH_3$), 4.52(1H, s, NH), 5.79–5.82 (2H, m), 6.15 (1H, s), 6.81–6.97 (3H, m), 7.21–7.30 (3H, m), 7.60 (1H, d, $J$ = 7.5 Hz), 7.83–7.86 (1H, m), 7.97 (1H, d, $J$ = 8.1 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 8.0, 48.2, 107.2, 107.6, 110.3, 111.7, 116.4, 119.1, 120.2, 120.4, 122.6, 123.6, 127.3, 130.1, 130.3, 133.5, 135.2, 142.2, 153.8; HRMS-ESI: Calcd. for $C_{20}H_{16}N_2O$ $[M + H]^+$: 301.1335. Found: 301.1337.

### 5.2. Biological assay

Seventeen 3-acylindole derivatives (**3a-q**) were screened *in vitro* for their antifungal activities against five phytopathogenic fungi (*i.e.*, *F. graminearum*, *A. alternata*, *P. oryzae*, *F. oxysporum* f. sp. *vasinfectum*, and *A. brassicae*). Potato dextrose agar (PDA) medium was prepared in the flasks and sterilized. Compounds **3a-q** were dissolved in acetone before mixing with PDA, and the concentration of test compounds in the medium was fixed at 50 μg/mL. The medium was then poured into sterilized Petri dishes. All types of fungi were incubated in PDA at 28 ± 1 °C for 5 d to get new mycelium for the antifungal assays, and a mycelia disk of approximately 5 mm diameter cut from culture medium was picked up with a sterilized inoculation needle and inoculated in the center of the PDA Petri dishes. The inoculated Petri dishes were incubated at 28 ± 1 °C for 4 d. Acetone without any compounds mixed with PDA was served as the control, while hymexazol, a commercially available agricultural fungicide at 50 μg/mL, was used as a positive control. For each treatment, three replicates were conducted. The radial growths of the fungal colonies were measured and the data were statistically analyzed. The inhibitory effects of the test compounds on these fungi *in vitro* were calculated by the formula:

$$\text{Inhibition rate } (\%) = (C - T) \times 100/C$$

where $C$ represents the diameter of fungi growth on untreated PDA, and $T$ represents the diameter of fungi on treated PDA.

## Acknowledgments

This work was financially in part supported by the Program for New Century Excellent University Talents, State Education Ministry of China (NCET-06-0868), the National Natural Science Foundation of China (no. 31071737), the Fok Ying Tong Education Foundation for Young Talents (no. 121032), the Special Funds of Central Colleges Basic Scientific Research Operating Expenses (QN2009045), and the State Key Laboratory of Applied Organic Chemistry, Lanzhou University. We also would like to thank the editor and the referees for very constructive suggestions and comments.

## Appendix. Supplementary data

Supplementary data related to this article can be found online version at doi:10.1016/j.ejmech.2011.02.035.

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