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Synthesis, bioactivity and structure–activity relationships of new 2-aryl-8-OR-3,4-dihydroisoquinolin-2-iums salts as potential antifungal agents

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ABSTRACT

As our continuing research on antifungal dihydroisoquinolin-2-ium salts, forty 2-aryl-8-OR-3,4-dihydroisoquinolin-2-ium bromides were synthesized and characterized by spectroscopic analysis. By using the mycelium growth rate method, the compounds were evaluated for antifungal activity against three plant pathogenic fungi and structure–activity relationships (SAR) were derived. The vast majority of the compounds displayed the medium to high activity with inhibition rates of 50–100% at 150 μM. About half of the compounds were more active than their natural model compounds sanguinarine and chelerythrine for all the fungi, and part or most of them were more active than positive drugs thiabendazole and azoxystrobin. SAR analysis showed that both substitution patterns of the C-ring and the type of 8-OR group significantly influenced the activity. Thus, a series of new title compounds with excellent antifungal potency emerged.

Plant mycosis accounting for 70 to 80 percent of plant diseases is an important problem of agricultural production worldwide.[1] Furthermore, many of plant pathogenic fungi can also result in food safety problem due to their mycotoxins harmful to animal and human health.[2] Therefore, plant fungicides have been extensively used to control fungal plant diseases in current agriculture. However, the persistent use of some commercial fungicides has led to several defects, such as pesticide residues, drug resistance and serious environmental problems.[3,4] Therefore, the development of environmentally friendly plant fungicides is extremely urgent. In the past decades, the researchers have put attention to natural product-based antimicrobial agents with lower environmental and mammalian toxicity.[5]

2-Aryl-3,4-dihydroisoquinolin-2-ium salts (ADHIQs) (Fig. 1) is a class of quaternary imine compounds containing an iminium moiety (C=N$^+$), which can be considered as structurally simple analogues of quaternary benzo[c]phenanthridine alkaloids (QBAs),[6] such as sanguinarine and chelerythrine (Fig. 1). Our previous studies proved that like QBAs,[7–9] ADHIQs generally have excellent antifungal, anticancer and acaricidal activities.[6,10–13]

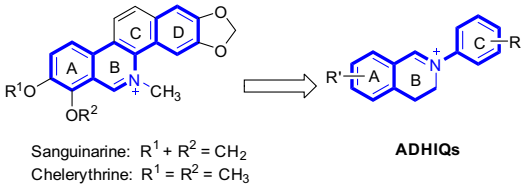

Figure 1. Structures of sanguinarine, chelerythrine and ADHIQs.

Moreover, as potential plant antifungal agents, ADHIQs also showed high safety to plant growth.[14,15] Thus, ADHIQs should be ideal alternatives to QBAs as new lead compounds to develop QBA-like antifungal agents.

Our further study suggested that antifungal activity of ADHIQs was closely related with the electron density distribution in its conjugated system and substitution patterns of the two aryl rings.[6,11,12] Therefore, in order to discover more potent antifungal ADHIQs, it is necessary to conduct more extensive modification for the two phenyl rings of ADHIQs by introduction of various substituents. Given that both sanguinarine and chelerythrine have a 7-alkoxy group adjacent to the C=N$^+$ bond (Fig. 1), in the present study, we designed a series of new 2-aryl-8-OR-3,4-dihydroisoquinolin-2-iums (R = CH_3 or H) with various substituents on the N-phenyl ring. The objective of the present study is to explore

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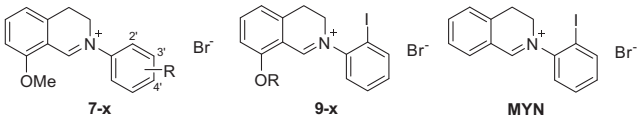
Table 1
Substitution patterns of compounds and their antifungal activity



7-x 9-x MYN

Compounds		Average inhibition rate ± SD[a] (%) (n = 3)			EC_{50} [μmol/L (μg/mL)]		
No.	R	*F. solani*	*F. graminearum*	*V. mali*	*F. solani*	*F. graminearum*	*V. mali*
7-1	H	74.3 ± 1.1	72.9 ± 2.6	70.4 ± 0.4	65.5 (20.8)	108.1 (34.4)	145.0 (47.7)
7-2	2′-F	83.2 ± 1.1	98.7 ± 1.1	81.5 ± 1.8	12.5 (4.20)	11.4 (3.82)	53.2 (17.9)
7-3	3′-F	75.4 ± 3.8	100.0 ± 0.0	80.8 ± 5.4	13.5 (4.55)	26.0 (8.73)	36.6 (12.3)
7-4	4′-F	62.4 ± 0.5	39.4 ± 2.5	66.4 ± 0.5	—	—	—
7-5	2′-Cl	93.0 ± 0.7	97.0 ± 1.0	88.1 ± 1.6	8.01 (2.83)	27.2 (9.59)	15.0 (5.30)
7-6	3′-Cl	90.0 ± 1.6	100.0 ± 0.0	83.2 ± 1.2	1.81 (0.64)	7.88 (2.78)	18.1 (6.37)
7-7	4′-Cl	61.6 ± 2.4	37.6 ± 1.0	74.2 ± 0.1	—	—	—
7-8	2′-Br	95.0 ± 2.4	95.4 ± 1.1	88.9 ± 0.9	8.84 (3.51)	27.5 (10.9)	20.1 (8.00)
7-9	3′-Br	75.3 ± 3.4	100.0 ± 0.0	82.1 ± 1.9	—	13.1 (5.21)	16.6 (6.60)
7-10	4′-Br	68.0 ± 1.6	77.0 ± 2.8	80.3 ± 1.2	—	—	—
7-11	2′-I	98.9 ± 1.9	96.7 ± 0.5	100.0 ± 0.0	3.25 (1.44)	17.4 (7.73)	13.2 (5.88)
7-12	3′-I	86.9 ± 1.1	80.0 ± 0.9	86.6 ± 2.7	6.19 (2.75)	15.0 (6.68)	16.5 (7.31)
7-13	4′-I	72.0 ± 1.9	74.4 ± 2.8	82.0 ± 0.7	—	—	—
7-14	2′-CF_3	88.0 ± 2.0	95.1 ± 0.9	83.8 ± 1.5	11.3 (4.36)	36.0 (13.9)	26.4 (10.2)
7-15	3′-CF_3	82.4 ± 1.7	87.4 ± 3.8	81.8 ± 0.4	9.49 (3.67)	17.6 (6.81)	24.3 (9.37)
7-16	4′-CF_3	86.9 ± 3.8	66.4 ± 1.5	73.1 ± 1.9	41.2 (15.9)	—	—
7-17	2′-CN	93.4 ± 1.8	80.3 ± 0.5	85.8 ± 0.3	29.4 (10.1)	26.5 (9.10)	44.1 (15.1)
7-18	3′-CN	93.4 ± 1.0	74.2 ± 3.0	69.2 ± 1.5	15.1 (5.19)	—	—
7-19	4′-CN	97.0 ± 1.5	99.6 ± 0.7	84.8 ± 0.8	62.9 (21.6)	20.7 (7.10)	43.9 (15.1)
7-20	2′-NO_2	13.3 ± 7.1	<5	<5	—	—	—
7-21	3-NO_2	86.1 ± 2.6	100.0 ± 0.0	70.6 ± 0.8	13.9 (5.04)	11.0 (3.99)	—
7-22	2′-CH_3	67.2 ± 1.3	30.4 ± 2.3	22.3 ± 1.8	—	—	—
7-23	3′-CH_3	71.2 ± 2.7	26.0 ± 3.3	46.9 ± 4.3	—	—	—
7-24	4′-CH_3	62.1 ± 1.3	20.6 ± 1.8	34.6 ± 1.4	—	—	—
7-25	2′-OMe	43.4 ± 2.0	7.1 ± 8.7	6.7 ± 3.8	—	—	—
7-26	3′-OMe	43.2 ± 2.9	7.8 ± 8.8	26.4 ± 3.4	—	—	—
7-27	4′-OMe	<5	<5	<5	—	—	—
7-28	2′-OH	6.4 ± 5.5	<5	1.6 ± 5.9	—	—	—
7-29	3′-OH	16.1 ± 11.5	11.4 ± 7.9	16.5 ± 2.0	—	—	—
7-30	4′-OH	<5	<5	<5	—	—	—
7-31	2′,6′-diF	65.7 ± 2.4	98.6 ± 1.5	35.0 ± 1.4	—	—	—
7-32	2′,4′-diCl	94.4 ± 1.9	97.9 ± 0.0	91.9 ± 1.3	4.26 (1.65)	9.66 (3.74)	10.0 (3.89)
7-33	3′,5′-diCl	83.8 ± 0.4	81.5 ± 3.3	74.0 ± 1.4	13.4 (5.19)	21.3 (8.23)	—
7-34	2′,4′-diBr	94.5 ± 2.9	77.0 ± 2.7	90.5 ± 0.5	6.73 (3.21)	15.4 (7.32)	8.71 (4.15)
7-35	2′-F-4′-Br	93.4 ± 1.0	78.7 ± 2.1	90.5 ± 1.4	17.0 (7.06)	—	15.2 (6.29)
7-36	2′-F-4′-I	90.1 ± 1.6	100.0 ± 0.0	86.6 ± 0.4	23.6 (10.9)	25.0 (11.5)	15.9 (7.33)
9-1	H	55.4 ± 3.6	45.2 ± 3.5	23.4 ± 1.4	—	—	—
9-2	Ac	41.9 ± 3.6	43.9 ± 2.3	25.1 ± 1.1	—	—	—
9-3	Et	97.0 ± 0.0	92.9 ± 1.9	88.6 ± 0.2	9.31 (4.27)	49.7 (22.8)	14.2 (6.53)
9-4	Bn	83.3 ± 0.3	98.7 ± 1.2	84.8 ± 1.1	9.27 (4.82)	9.61 (5.00)	13.2 (6.85)
MYN		95.1 ± 2.1	100.0 ± 0.0	92.5 ± 0.7	8.33 (3.45)	7.24 (3.00)	21.0 (8.68)
Sanguinarine		89.0 ± 0.1	76.3 ± 2.4	91.5 ± 0.1	90.8 (41.7)	27.0 (12.41)	55.7 (25.6)
Chelerythrine		90.3 ± 2.0	74.7 ± 1.7	93.0 ± 0.1	55.8 (26.5)	39.8 (18.9)	83.5 (39.7)
Thiabendazole		85.2 ± 3.2	95.0 ± 3.5	98.3 ± 1.4	12.5 (2.5)	3.0 (0.6)	11.7 (2.3)
Azoxystrobin		64.0 ± 0.2	63.4 ± 3.1	52.4 ± 0.4	—	—	—

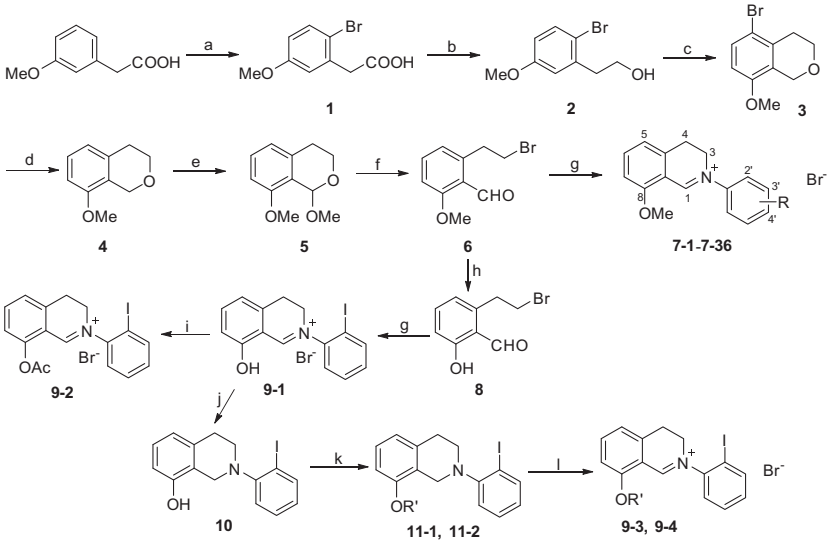
[a] The test concentration of the compound was 150 μmol/L.

the activity of the target compounds against phyto-pathogenic fungi and discover more potent antifungal ADHIQs, and meanwhile understand their preliminary SAR.

The synthetic route of compounds **7-x** and **9-x** is outlined in Scheme 1, and their substitution patterns were shown in Table 1. Commercially available 2-(3-methoxyphenyl)acetic acid reacted with dry Br_2 in DCM to obtain **1** in 92% yield.[16] Compound **1** was reduced with $NaBH_4$ at presence of equimolar iodine to get **2** in quantitative yield.[17,25] Treatment of **2** with paraformaldehyde in trifluoroacetic acid provided **3** in 62% yield.[11] Compound **3** was debrominated with *n*-butyllithium, followed by treatment of water to give **4** in 95% yield.[18] Oxidization of **4** with DDQ in DCM containing MeOH afforded **5** in 51% yield.[19] Compound **5** in toluene was treated with Bu_4NBr and TMSBr to yield a key intermediate **6** in 77% yield.[20] Demethylation of **6** with tribromoborane gave an intermediate **8** in 86% yield.[21] The intermediate **6** reacted with various primary aromatic amines to yield a series of target compounds **7-x**.[11,13] The similar reaction was used for **8** and 2-iodoaniline to yield the target compound **9-1**.

Compound **9-1** was acetylated with acetic anhydride to obtain **9-2** in 30% yield, and reduced with $NaBH_4$ to yield **10** in 100% yield.[7] Compound **10** was treated with NaH in DMF, followed by reaction with bromoethane or benzyl chloride to afford **11-1** and **11-2**, respectively.[22] Compounds **11-1** or **11-2** were oxidized with iodine to afford **9-3** and **9-4**, respectively.[23]

The structures of the compounds were confirmed by ^1H NMR, ^{13}C NMR and MS. Due to the structural similarity of the compounds, only eighteen and two representative compounds were analyzed for HRMS and bromine anion, respectively. All the compounds presented similar spectral characteristics because of



Scheme 1. Synthetic route of compounds **7-x** and **9-x.** Reagents and conditions: (a) Br_2, dry CH_2Cl_2; (b) $NaBH_4$, I_2, dry THF, 40 °C; (c) $(HCHO)_n$, TFA, 0 °C to rt; (d) *n*-BuLi, dry THF, −78 °C; (e) DDQ, dry MeOH, dry CH_2Cl_2; (f) TMSBr, Bu_4NBr, dry toluene, 80 °C; (g) Ar-NH_2, dioxane; (h) BBr_3, dry CH_2Cl_2, −78 °C, rt overnight; (i) acetic anhydride; (j) $NaBH_4$, MeOH; (k) NaH, alkyl halide, dry DMF; (l) I_2, ethanol, reflux.

their similar structures. In the NMR spectra, **7-x** and **9-x** showed one singlet signal in the range of δ_H 9.19–9.65 and δ_C 161.5–168.1 ppm due to the iminium moiety (C=N^+), and signals of one CH_2CH_2 moiety at δ_H ca. 3.4 (2H, t, *J* = ca. 7.8 Hz) and ca. 4.4 (2H, t, *J* = ca. 7.8 Hz). Additionally, **7-x** also showed signals of one methoxyl group at δ_H ca. 4.05 (3H, s) and δ_C ca. 57.5. Compared with **7-11**, **9-x** showed less signals of one methoxyl group in the ^1H and ^{13}C NMR spectra, while **9-2**, **9-3** and **9-4** showed additional signals of one acetyl, one ethoxy and one benzyloxy group, respectively. All the compounds showed a characteristic ion peak at *m/z* $[M-Br]^+$ in positive ESI-MS or HRMS spectra. The presence of bromide anion was confirmed by ion peaks at *m/z* $[^{79}Br]^-$ and $[^{81}Br]^-$ in negative ESI-MS spectra.

According to the mycelia growth rate method,[11] compounds **7-x** and **9-x** were screened for antifungal activities in vitro at 150 μM (ca. 50 μg/mL) against three plant pathogenic fungi. Thiabendazole (TBZ), and azoxystrobin (ASB), two commercial fungicides, were used as positive controls. Sanguinarine (SA), chelerythrine (CH) and MYN were used as reference controls. The results were listed in Table 1.

The data in Table 1 clearly showed that most of the test compounds presented the inhibition activity in varying degrees against each of the tested fungi. For each of the fungi, the vast majority of the compounds displayed the medium to high activity with inhibition rates of 50–100%, superior to ASB. Some of the compounds were more active than TBZ, SA and CH against part or all of the fungi. Generally, the order of susceptibility of the three strains of fungi to the target compounds is *Fusarium solani* > *V. mali* > *Fusarium graminearum*.

In order to explore the antifungal potential in more detail and the structure–activity relationship, the compounds with the inhibition rates of >80% in Table 1 were subjected to median effective concentrations (EC_{50}) assay. TBZ was used as a positive control, and SA, CH and 2-(2-iodophenyl)-3,4-dihydroisoquinolin-2-ium bromide (MYN) were used as reference controls. The results were shown in Table 1.

The results in Table 1 showed that the vast majority of the tested compounds presented EC_{50} values of <20 μM for all the fungi, much lower than SA and CH. Part of the compounds with EC_{50} values of <10 μM were more active than TBZ against *F. solani* and *V. mali*. For *F. solani*, ten out of the compounds showed EC_{50} values of ⩽10 μM. A similar case was observed for three compounds (**7-6**, **7-32**, **9-4**) for *F. graminearum* and two compounds (**7-32**, **7-34**) for *V. mali*. Among the compounds, **7-6** gave the highest activities against *F. solani* and *F. graminearum* [EC_{50} = 1.81 μM (0.64 μg/mL), 7.88 μM (2.78 μg/mL)], whereas **7-34** had the highest activity against *V. mali*, with an EC_{50} value of 8.71 μM (4.15 μg/mL).

Based on the EC_{50} values in Table 1, it was concluded that both substitution patterns of the C-ring and the type of 8-OR on the A-ring significantly influenced the activity of the compounds (Fig. 2). By comparison with **7-1** (R = H), it was found that the introduction of electron-donating groups like $-CH_3$, $-OCH_3$ or –OH (**7-22–7-30**) to the C ring always leads to a decrease of the activity in all cases (Table 1). On the contrary, in most cases, the presence of electron-withdrawing groups like halogen atoms, $-CF_3$, $-NO_2$ or –CN on the C-ring is able to increase the activity. It was worth noting that the effect of halogen atoms or $-NO_2$ is obviously related with its type and position. Unlike the cases of 2′- or 3′-substituted isomers, 4′-F and 4′-Cl isomers (**7-4, 7-7**) gave the decreased activities in most cases relative to **7-1** (Table 1). In contrast, for Br- or I-substituted compounds (**7-8–7-13**), almost all the position isomers showed the increased activity in all cases. The presence of 4′-NO2 (**7-21**) is able to significantly increase the activity, whereas the presence of 2′-NO2 (**7-20**) leads to the dramatic decrease of the activity.

Comparison of the activities of compounds **7-32–7-36** and **7-1** showed that the presence of two halogen atoms also increases the activity against in all cases. However, when compared with the corresponding mono-halogenated compounds, the effect of the second halogen atom on the activity varies with its type and substitution position. For example, 2′,4′-dichlorinated compound had the higher activity than the corresponding 2′- or 4′-chlorinated compounds (**7-32** vs **7-5**, **7-7**). A similar case was also observed for 2′,4′-dibrominated compound (**7-34** vs. **7-8**, **7-10**). But the opposite case was observed for 3′,5′-diCl combination (**7-33** vs. **7-6**). Both 2′-F-4′-Br and 2′-F-4′-I combinations reduce the activity, relative to 2′-F substitution, but increase the activity, relative to 4′-Br or 4′-I substitution.

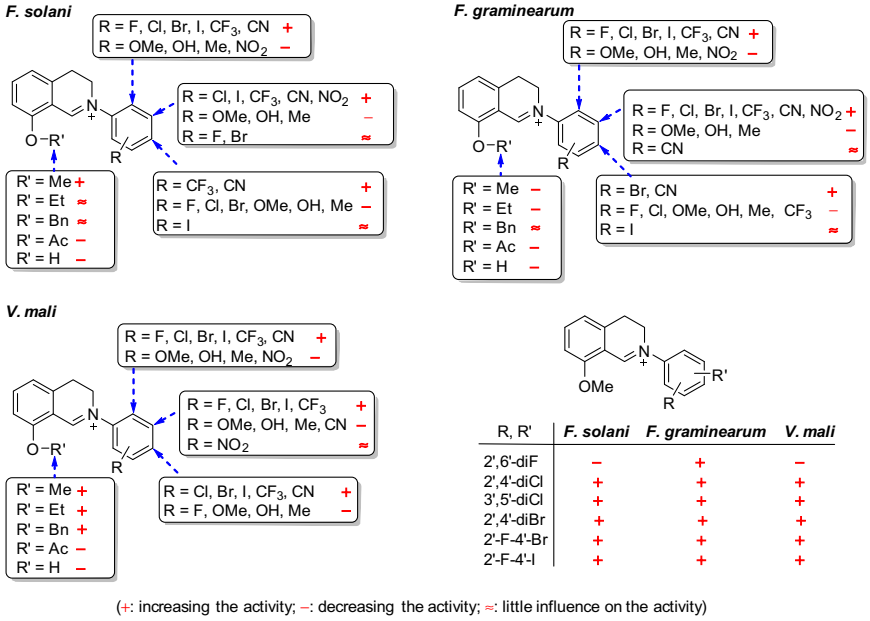


Figure 2. Structure–activity relationship of compounds **7-x** and **9-x**.

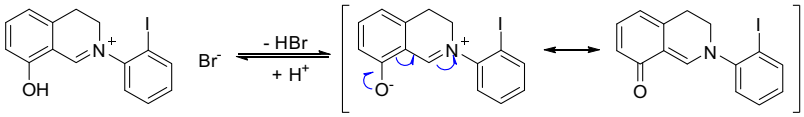


Figure 3. Existing forms of **9-1** in an aqueous solution.

Furthermore, by comparison with the activities of **9-1**–**9-4** and MYN without substituents at 8 position, it was found that the characteristics of 8-OR also has significant effects on the activity. The introduction of 8-OMe leads to increase of the activity for both *F. solani* and *V. mali*, but decrease for *F. graminearum* (**7-11** vs MYN). Some similarly, the presence of 8-OEt or 8-OBn increases the activity against *V. mali*, but reduces the activities against both *F. solani* and *F. graminearum* (**9-3**, **9-4** vs MYN). By contrast, both 8-OH and 8-OAc cause a dramatic decrease of the activity (**9-1**, **9-2** vs MYN) in all the cases.

The low activity of **9-1** may be related with its being able to partly form non-ionic compounds in an aqueous solution. Theoretically, the C=N$^+$ moiety in **9-1** is a strong electron-withdrawing group, and can make 8-OH possess higher acidity than common phenolic hydroxyl groups. Therefore, **9-1** is theoretically able to co-exist in ionic and non-ionic forms in an aqueous solution (Fig. 3). A similar case was observed in 7-hydroxybenzo[*c*]phenanthridinium salts.[24] However, the non-ionic form (**9-1A**) is inactive because of the absence of the C=N$^+$ moiety, a determinant for the activity.[10,11] Similarly, the low activity of **9-2** may be related with its being able to transform into **9-1** in physiological environments by bio-enzyme or acidic catalysis.

In our previous works, some analogues of **7-x** and **9-x**, such as ADHIQs (As), 6,7-methylenedioxy-type ADHIQs (Bs) and 6-chloro-type ADHIQs (Cs), had been studied for antifungal SAR.[6,11,12] Comparison with three class of the compounds mentioned above showed that the present compounds displayed some obvious difference in SAR. For example, for compounds Cs, the introduction of electron-donating groups like –CH_3 to the C-ring led to significant increase of the activity, but an opposite case was observed for the present compounds. A similar case was also observed for compounds As. Besides, in aspect of position effect of some substituents such as halogen atoms on the activity, the present compounds also show obvious difference from compounds As, Bs or Cs, where 4′-halogenated compounds were generally more active than its 3′-substituted isomer. The results above again suggested that the activity of ADHIQs depends on the combined electron effect of substituents on both the A-ring and C-ring, or the electron density distribution in the conjugated system.[11] Therefore, it is necessary to further study QSAR of ADHIQs. At present, this work has been included in our plans.

In summary, a series of new title compounds were synthesized and evaluated for antifungal activity in vitro against three plant pathogenic fungi. Most of the compounds displayed inhibition rates of 50–100% at 150 μM, superior to ASB. Some of them were more active than TBZ, SA and CH against part or all of the fungi. Generally, compounds **7-5**, **7-11**, **7-32**, **7-34** and **9-4** were of great potential to be developed as new antifungal agents for plant protection. SAR analysis showed that both substitution patterns of the C-ring and the type of 8-OR significantly influence the activity. In most cases, the presence of electron-withdrawing groups like halogen atoms, like –CF_3, –NO_2 or –CN on the C-ring is able to increase the activity, whereas electron-donating groups like –CH_3, –OCH_3 or –OH always decrease the activity against each of the fungi. The effect of 8-OR on the activity varies with the type of R and species of the fungi. 8-Alkoxy groups are able to improve the activity against some of the fungi while 8-OH or 8-OAc cause a dramatic decrease of the activity in all cases. Thus, the present results are of importance for the design, synthesis and development of novel isoquinoline antifungal agents. It is necessary to

further conduct more extensive structural modification, determination of an antifungal spectrum and the in vivo activity of these compounds.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedure, ^{1}H and ^{13}C NMR, MS spectra and antifungal toxicity regression equations of the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.04.001.

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