Antifungal Activity of Tetrahydroquinolines against Some Phytopathogenic Fungi

Margarita Gutiérrez[a,*], Unai Carmona[a], Gabriel Vallejos[b], and Luis Astudillo[a]

[a] Laboratory of Organic Synthesis, Institute of Chemistry of Natural Resources, University of Talca, Casilla 747, Talca, Chile. E-mail: mgutierrez@utalca.cl
[b] Bioorganic Laboratory, Institute of Chemistry, Science Faculty, Austral University of Chile, Valdivia, Casilla 567, Isla Teja S/N, Valdivia, Chile

* Author for correspondence and reprint requests

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Seven synthetic tetrahydroquinolines with different substitution patterns were obtained by an imino Diels-Alder condensation reaction and were evaluated against phytopathogenic fungi. Compounds with a methoxy group showed interesting activity against *Cladosporium cladosporoides* with a MIC value of 13.75 μg/mL

Key words: Substituted Tetrahydroquinolines, Antifungal, Imino Diels-Alder Reaction

Introduction

Tetrahydroquinolines (THQs) are important heterocycles that possess diverse biological activities and multiple applications. They are widely used as antimalarial (Bendale *et al*., 2007), antibacterial (Jervest *et al*., 2004), antiviral (Bedoya *et al*., 2010), and antitumour agents (Alqasoumi *et al*., 2010), as inhibitors of thromboxane A_2 synthase (Hartmann and Frotscher, 1999) and in other applications (Dodiya *et al*., 2001).

For these reasons, the synthesis of new THQs is still of great interest. An efficient route for the preparation of THQs is the acid-catalyzed Povarov reaction, which is classified as an imino Diels-Alder cycloaddition (Katrizky *et al*., 1995). Moreover, this methodology, that permits the condensation of anilines, aldehydes, and electron-rich alkenes using acidic catalysts under mild conditions to afford new THQs, can overcome synthetic limitations for the construction of functionalized quinolines substituted at the C-2 position and unsubstituted at the C-3 and C-4 positions. This is a useful tool for the generation of quinoline derivatives with several structural diversities. The appropriate choice of aldehydes and alkenes in this cycloaddition reaction provides a facile entry to a heterocyclic system, which is an essential moiety in many active pharmaceuticals (Kouznetsov *et al*., 2010).

A series of synthesized THQs have been reported as antifungal agents against dermatophytes (Vargas *et al*., 2010). Diverse polyfunctionalized quinolines prepared using the Lewis acid-catalyzed imino Diels-Alder reaction were tested for their antifungal properties against standard fungi as well as isolates of clinically important fungi. The 4-pyridyl derivatives displayed the best activities, mainly against dermatophytic fungi. The activity appeared to be related neither to the lipophilicity nor to the basicity of the compounds (Melendez *et al*., 2008).

In another study, a series of homoallylamines, including THQs, were evaluated against dermatophytic fungi (Vargas *et al*., 2003). The active compounds were able to reduce the activities of the enzymes (1,3)-β-D-glucan and chitin synthetase, respectively. These enzymes catalyze the synthesis of the major fungal cell wall polymers.

Pathogenic fungi are the main infectious agents in plants, causing alterations during developmental stages including post-harvest. In fruit and vegetables, there is a wide variety of fungal genera causing quality problems related to several aspects such as nutritional value, organoleptic characteristics, and limited shelf life (Diaz *et al*., 2011). Phytopathogenic fungi that easily infect many crops are hard to control, and there is the risk of the development of resistance to the widely used commercial fungicides; therefore, there is a continuous need for new classes of antifungal agents. Nevertheless, microorganisms are constantly generating resistance against traditional therapeutic agents. The necessity to discover novel biologically active molecules to

replace those with reduced effectiveness is in high demand. In this sense, a series of hydroxyquinolines were synthesized and tested as inhibitors of phytopathogenic fungi. The most active compound found so is 5-acetyl-8-quinolinol (Khalil *et al.*, 1988).

In the present work, we report the synthesis of seven THQs, easily prepared by Lewis acid-catalyzed imino Diels-Alder reactions, and their evaluation as germination inhibitors of spores of phytopathogenic fungi.

Experimental

General procedure for the three-component reaction of N-vinylpyrrolidin-2-one with aldehydes and anilines

The Lewis acid $InCl_3$ (20 mol-%) was added to a solution of furfural (2-furfurylaldehyde, 3.4 mmol) and aniline (1.0 mmol) in dry MeCN (15 mL), and the mixture was stirred at room temperature. A solution of *N*-vinylpyrrolidin-2-one (1.0 mmol) in dry MeCN (15 mL) was then added, and the resulting suspension was stirred at room temperature (unless otherwise specified) under N_2 atmosphere for 18–24 h (Scheme 1). A saturated aqueous $NaHCO_3$ solution was added, and the resulting mixture was extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, *n*-hexane/EtOAc) to give the desired compounds **1**–**7**.

The reaction progress was monitored by means of thin-layer chromatography (TLC) using Merck (Darmstadt, Germany) silica gel 60. All reagents were purchased from commercial suppliers and used without further purification. Final purification of all products for analysis was carried out by recrystallization. Acetonitrile was distilled from calcium hydride and dried over 4-Å molecular sieves.

Chemistry

^{1}H and ^{13}C NMR spectra were recorded on a Bruker (Rheinstetten, Germany) AM-400 spectrometer (400 MHz), using $CDCl_3$ as solvent. Tetramethylsilane (TMS) was used as an internal standard. Chemical shifts (δ) and J values are reported in ppm and Hz, respectively, relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.27 ppm for protons and 77.00 ppm for carbon atoms). Signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; br.s, broad singlet. On DEPT-135 spectra, the signals of CH_3, CH_2, and CH carbon atoms are shown as positive (+), negative (–), and positive (+), respectively. Quaternary carbon atoms are not shown.

ESI-MS(/MS) data were collected using a high-resolution mass spectrometer (Waters Q-TOF Micromass; Milford, MA, USA) with a constant nebulizer temperature of 100 °C. The ESI source and the mass spectrometer were operated in the positive ion mode, and the cone and extractor potentials were set to 40 and 5 V, respectively, with a scan range of m/z 80–1000. Samples were infused into the ESI source at flow rates of ca. 5 μL/min via a microsyringe pump. ESI-MS/MS experiments were carried out by selection of a specific ion in Q1 and by performing its collision-induced dissociation (CID) with argon in the collision chamber. The given values are average masses and correspond to the $[M+H]^+$ ion. The collision energy ranged from 10 to 25 eV, depending on the stability of the precursor ion undergoing collision-induced dissociation.

Antifungal activity (in vitro)

The antifungal activity against *Botrytis cinerea*, *Cladosporium cladosporoides*, *Penicillium* sp., and *Dothiorella* sp. was determined in triplicate experiments by the microdilution method (Gutiérrez *et al.*, 2005), and results are presented as the minimum inhibitory concentration (MIC). The spores were cultured on Sabouraud medium at 25 °C for 7 d. The compounds were assessed in the dilution interval of 250–15 μg/mL, while the standard antifungal compounds were assessed in the range of 250–3.9 μg/mL. Spores were obtained from well-grown and sporulating fungal cultures maintained on potato-glucose-agar medium by suspension in sterile distilled water, filtration through glass wool, and centrifugation. The spores were counted in a Neubauer chamber and diluted with sterile distilled water to a final concentration of 10^4–10^5 spores/mL. The assay was carried out in 96-well microtiter plates. One hundred μL of the spore suspension were incubated with 100 μL of the sample compound suspended in Sabouraud medium. A spore germination control and a Sabouraud medium control were included in all experiments as well as the reference

fungicides iprodione and myclobutanil. The MIC is defined as the lowest concentration of the compound preventing visible spore germination after the incubation time (7 d).

1-[2-(Furan-2-yl)-6-methyl-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (**1**): Orange powder. – M.p. 190–193 °C. – Yield 85.0%. – ^{1}H NMR ($CDCl_3$): δ = 7.40 (1H, d, J = 1.52 Hz), 6.87 (1H, d, J = 8.08 Hz), 6.68 (1H, s), 6.53 (1H, d, J = 8.08 Hz), 6.36 (1H, dd, J = 3.20 and 1.77 Hz), 6.26 (1H, d, J = 3.28 Hz), 5.68 (1H, dd, J = 11.12 and 6.82 Hz), 4.62 (1H, dd, J = 10.61 and 3.03 Hz), 4.00 (1H, br.s, NH), 3.29–3.15 (2H, m), 2.60–2.45 (2H, m), 2.30–2.18 (2H, m), 2.22 (3H, s, -CH_3), 2.07–1.99 (2H, m). – ^{13}C NMR ($CDCl_3$): δ = 175.78(+), 155.19(+), 142.76(+), 141.92(+), 128.91(+), 127.89(+), 127.10(+), 119.01(+), 115.44(+), 110.18(+), 105.38(+), 49.75(–), 47.72(–), 42.27(+), 31.37(+), 31.30(+), 20.56(–), 18.18(–). – MS (EI): m/z = 296.36 [M^+]. – $C_{18}H_{20}N_2O_2$: calcd. C 72.95, H 6.80, N 9.45, O 10.80; found C 72.88, H 6.74, N 9.44.

1-[2-(Furan-2-yl)-5,7-dimethyl-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (**2**): Rose powder. – M.p. 163–165 °C. – Yield 87.0%. – ^{1}H NMR ($CDCl_3$): δ = 7.37 (1H, s), 6.42 (1H, s), 6.33 (2H, s), 6.21 (1H, d, J = 2.93 Hz), 5.49 (1H, t, J = 7.78 Hz), 4.44 (1H, dd, J = 9.24 and 2.47 Hz), 4.14 (1H, br.s, NH), 3.01–2.72 (2H, m), 2.44–2.37 (2H, m), 2.38–2.28 (2H, m), 2.20 (3H, s), 2.04 (3H, s), 1.86–1.78 (2H, m). – ^{13}C NMR ($CDCl_3$): δ = 174.40(+), 155.59(+), 146.20(+), 141.76(+), 137.93(+), 122.07(+), 114.56(+), 113.91(+), 110.15(+), 105.19(+), 48.70(–), 45.61(–), 42.82(+), 32.00(+), 31.09(+), 20.85(–), 19.04(–), 17.89(+). – MS (EI): m/z = 310.39 [M^+]. – $C_{19}H_{22}N_2O_2$: calcd. C 73.52, H 7.14, N 9.03, O 10.31; found C 73.50, H 7.08, N 9.02.

1-[2-(Furan-2-yl)-6,8-dimethyl-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (**3**): Yellow powder. – M.p. 170–173 °C. – Yield 90.0%. – ^{1}H NMR ($CDCl_3$): δ = 7.41 (1H, s), 6.79 (1H, s), 6.58 (1H, s), 6.38 (1H, br.s), 6.29 (1H, d, J = 3.11 Hz), 5.70 (1H, dd, J = 10.79 and 6.95 Hz), 4.64 (1H, dd, J = 10.43 and 3.11 Hz), 3.92 (1H, br.s, NH), 3.40–3.13 (2H, m), 2.60–2.45 (2H, m), 2.30–2.18 (2H, m), 2.20 (3H, s), 2.10 (3H, s), 2.05–1.98 (2H, m). – ^{13}C NMR ($CDCl_3$): δ = 175.73(+), 155.43(+), 143.34(+), 141.94(+), 135.99(+), 124.83(+), 124.32(+), 116.79(+), 112.07(+), 110.17(+), 105.38(+), 49.80(–), 48.04(–), 42.38(+), 31.46(+), 31.28(+), 20.57(–), 18.24(+), 17.26(–). – MS (EI): m/z = 310.39 [M^+]. – $C_{19}H_{22}N_2O_2$: calcd. C 73.52, H 7.14, N 9.03, O 10.31; found C 73.50, H 7.08, N 9.02.

1-[2-(Furan-2-yl)-6-methoxy-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (**4**): Coffee powder. – M.p. 165–167 °C. – Yield 87.0%. – ^{1}H NMR ($CDCl_3$): δ = 7.58 (1H, d, J = 9.09 Hz), 7.44 (1H, s), 6.74 (1H, d, J = 4.02 Hz), 6.73 (1H, dd, J = 8.08 and 2.78 Hz), 6.64 (1H, br.s), 6.54 (1H, d, J = 2.02 Hz), 6.38 (1H, dd, J = 3.02 and 1.77 Hz), 5.66 (1H, dd, J = 11.37 and 6.57 Hz), 4.64 (1H, dd, J = 11.87 and 1.77 Hz), 3.97 (1H, br.s, NH), 3.74 (3H, s, -OCH_3), 3.38–3.12 (2H, m), 2.75 – 2.37 (2H, m), 2.55–2.43 (2H, m), 2.07–1.95 (2H, m). – ^{13}C NMR ($CDCl_3$): δ = 175.84(+), 166.00(+), 147.62(+), 142.59(+), 128.75(+), 123.95(+), 117.86(+), 114.63(+), 112.41(+), 110.51(+), 105.75(+), 55.74(–), 47.63(–), 42.20(+), 31.21(+), 29.84(+), 20.77(–), 18.21(–). – MS (EI): m/z = 312.36 [M^+]. – $C_{18}H_{20}N_2O_3$: calcd. C 69.21, H 6.45, N 8.97, O 15.37; found C 69.15, H 6.40, N 8.96.

1-[6-Chloro-2-(furan-2-yl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (**5**): Orange powder. – M.p. 175–177 °C. – Yield 85.5%. – ^{1}H NMR ($CDCl_3$): δ = 7.40 (1H, d, J = 1.26 Hz), 7.01 (1H, dd, J = 8.59 and 2.27 Hz), 6.83 (1H, d, J = 1.52 Hz), 6.52 (2H, d, J = 8.59 Hz), 6.37 (1H, dd, J = 3.16 and 1.89 Hz), 6.28 (1H, d, J = 3.28 Hz), 5.65 (1H, t, J = 9.35 Hz), 4.67 (1H, dd, J = 8.97 and 4.93 Hz), 4.13 (1H, br.s, NH), 3.30–3.16 (2H, m), 2.61–2.44 (2H, m), 2.26–2.18 (2H, m), 2.10–2.03 (2H, m). – ^{13}C NMR ($CDCl_3$): δ = 175.84(+), 154.55(+), 143.59(+), 142.14(+), 128.28(+), 126.35(+), 123.18(+), 120.56(+), 116.37(+), 110.28(+), 105.75(+), 49.56(–), 47.55(–), 42.23(+), 31.20(+), 30.72(–), 18.18(–). – MS (EI): m/z = 316.78 [M^+]. – $C_{17}H_{17}ClN_2O_2$: calcd. C 64.46, H 5.41, N 8.84, O 10.10, Cl 11.19; found C 64.39, H 5.37, N 8.83, Cl 11.20.

1-[2-(Furan-2-yl)-6-iodo-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (**6**): Coffee powder. – M.p. 190–192 °C. – Yield 90.0%. – ^{1}H NMR ($CDCl_3$): δ = 7.40 (1H, s), 7.31 (1H, dd, J = 8.59 and 1.26 Hz), 7.12 (1H, s), 6.37 (1H, d, J = 8.80 Hz), 6.36 (1H, dd, J = 3.20 and 1.77 Hz), 6.27 (1H, d, J = 3.28 Hz), 5.63 (1H, t, J = 8.97 Hz), 4.67 (1H, t, J = 7.07 Hz), 4.15 (1H, br.s, NH), 3.28–3.16 (2H, m), 2.63–2.44 (2H, m), 2.24–2.20 (2H, m), 2.08–2.02 (2H, m). – ^{13}C NMR ($CDCl_3$): δ = 175.84(+), 154.47(+), 144.66(+), 142.16(+),

136.91(+), 135.07(+), 121.48(+), 121.48(+), 117.21(+), 110.29(+), 105.78(+), 49.40(–), 47.33(–), 42.24(+), 31.23(+), 30.64(–), 18.25(–). – MS (EI): *m/z* = 408.23 [M^+]. – $C_{17}H_{17}IN_2O_2$: calcd. C 50.02, H 4.20, N 6.86, O 7.84, I 31.06; found C 49.97, H 4.16, N 6.85, I 31.10.

1-[6-Fluoro-2-(furan-2-yl)-1,2,3,4-tetrahydroquinolin-4-yl]pyrrolidin-2-one (**7**): Beige powder. – M.p. 160–162 °C. – Yield 90%. – ^{1}H NMR ($CDCl_3$): δ = 7.40 (1H, d, J = 1.01 Hz), 6.79 (1H, m), 6.61 (1H, dd, J = 9.22 and 2.15 Hz), 6.55 (1H, dd, J = 8.84 and 4.80 Hz), 6.37 (1H, dd, J = 3.16 and 1.89 Hz), 6.27 (1H, d, J = 3.28 Hz), 5.66 (1H, dd, J = 11.12 and 7.07 Hz), 4.65 (1H, dd, J = 10.36 and 3.28 Hz), 4.04 (1H, br.s, NH), 3.31 – 3.15 (2H, m), 2.57–2.44 (2H, m), 2.27–2.17 (2H, m), 2.09–2.02 (2H, m). – ^{13}C NMR ($CDCl_3$): δ = 175.81(+), 157.54(+), 154.79(+), 142.06(+), 141.28(+), 120.54(+), 116.27(+), 115.04(+), 112.85(+), 110.24(+), 105.61(+), 49.77(–), 47.75(–), 42.24(+), 31.20(+), 30.82(–), 18.13(–). – MS (EI): *m/z* = 300.32 [M^+]. – $C_{17}H_{17}FN_2O_2$: calcd. C 67.99, H 5.71, N 9.33, O 10.65, F 6.33; found C 67.92, H 5.66, N 9.32, F 6.32.

Results and Discussion

Synthesis and characterization

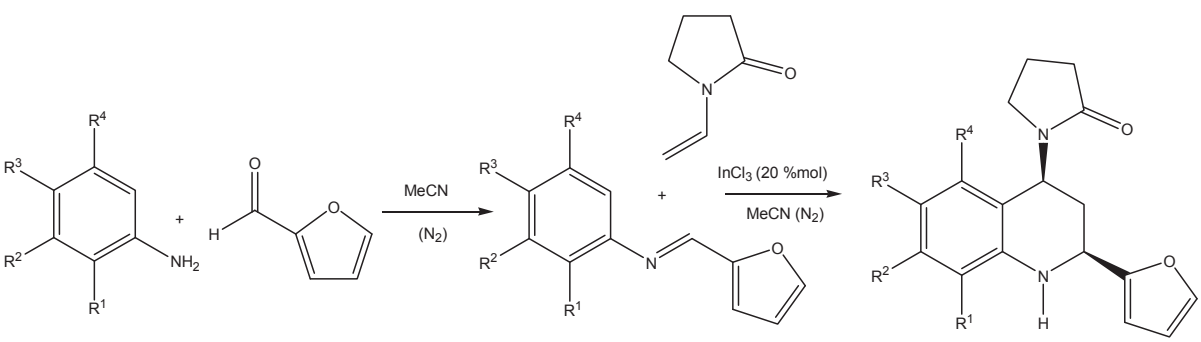
The synthesis of the THQs **1**–**7** was accomplished by multi-component imino Diels-Alder reactions between various anilines, furfural, and *N*-vinylpyrrolidin-2-one (Scheme 1). Seven THQs were obtained with different substitution patterns (Table I). The chosen catalyst indium trichloride ($InCl_3$) has emerged as a mild and water-tolerant Lewis acid imparting high regio- and chemoselectivity in various organic transformations. The catalyst can be conveniently used in aqueous and non-aqueous media and can also be recovered from the aqueous layer and recycled for use in subsequent reactions. The catalyst $InCl_3$ has been reported as highly efficient in activating nitrogen-containing compounds such as imines and hydrazones, especially in acetonitrile as solvent (Manian *et al.*, 2006). In general the overall yields ranged from 85% to 96%.

The principal starting materials in this investigation, *N*-arylaldimines, were prepared from the commercially available aromatic aldehyde furfural and substituted anilines according to procedures previously reported (Kouznetsov *et al.*, 2006). The THQ derivatives were obtained from the reaction of *N*-arylaldimines with the electron-rich alkene *N*-vinylpyrrolidin-2-one in the presence of $InCl_3$. The amines used were selected on the basis of their ability to donate electrons and thus facilitate the formation of the imines (Table I).

The coupling reactions were performed under mild conditions (room temperature, 24 h) in the presence of $InCl_3$ (20 mol-%) in acetonitrile. The THQs were obtained in good yield with almost no by-products. They were purified by SiO_2 column chromatography and obtained as solids and

Table I. Substituents of THQs **1**–**7**. See Scheme 1 for THQ structure and numbering.

Compound	R^1	R^2	R^3	R^4
1	H	H	CH_3	H
2	H	CH_3	H	CH_3
3	CH_3	H	CH_3	H
4	H	H	OCH_3	H
5	H	H	Cl	H
6	H	H	I	H
7	H	H	F	H



Scheme 1. Reagents and conditions for the synthesis of THQs.

exclusively as the *cis*-diastereoisomers. The *cis*-configuration of the substituents was determined by measurement of the relevant H-H coupling constants in their ^{1}H NMR spectra.

The THQs **1**–**7** were identified by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. The ^{1}H NMR spectra of all THQs synthesized were very similar, and characterized by the presence of three groups of signals (aromatic protons, protons near heteroatoms, and aliphatic protons), which resonated in different zones.

The mass spectra showed similar fragmentation patterns among the compounds, always showing the molecular ion $[M+H]^+$ and the characteristic loss of a fragment of 85 units corresponding to the *N*-vinylpyrrolidin-2-one moiety.

Products **4** and **5** have been reported previously and the aromatized derivatives obtained by simple fusion with elemental sulfur (S_8) at 200 °C were less active against clinically important fungi (Melendez *et al.*, 2008). Product **7** has also been reported previously and was not active against clinically important bacteria and fungi, including yeasts (Kouznetsov *et al.*, 2004).

Antifungal activity

The inhibitory effect of the THQ derivatives on phytopathogenic fungi was studied. The four fungi used in the fungicidal bioassay were: *Botrytis cinerea*, *Cladosporium cladosporoides*, *Penicillium* sp., and *Dothiorella* sp. The fungi were collected in the field and isolated from commercial crops.

The synthesized compounds were evaluated in bioassays, and their efficiency compared to that of commercial agricultural fungicides, *viz.* two fungicides currently used in the field in Chile, namely iprodione and myclobutanil. As can be seen in Table II, all tested compounds showed moderate to high antifungal activities against all fungi tested. Compound **2** was selective against *Dothiorella* sp. On the other hand, compound **4** was the only one exhibiting moderate activity against *Penicillium* sp. and higher activity against *Cladosporium cladosporoides* similar to that of the reference compounds.

The analysis of the biological activities indicated that the position of the substituent plays an important role in the inhibitory activity on the germination of spores, especially in the case of *Cladosporium cladosporoides*, against which the compounds substituted at the *para*-position (R^3) were more active than the unsubstituted compounds. The most active compound against *Cladosporium cladosporoides* was **4**, substituted at R^3 with the electron-donating methoxy group. In the case of *Dothiorella* sp., compound **4** was the less active, whereas **6** with an iodine substituent was the most active one. No relevant activity was found against the other two fungi tested. These results agree with the results of a computer-based study on the activity of THQs reported by Suvire and co-workers (2006), according to which the following structural features are required for activity:

- Presence of two aromatic rings (rings A and B).
- Presence of a heteroatom (with lone electron pairs) or CH_3O groups on ring B.
- A particular length of the connecting chain.
- Presence of a halogen atom in R^3 on ring A.

Table II. Antifungal activity of the THQs **1**–**7**. MIC values are expressed in μg/mL.

Compound	*Botrytis cinerea*	*Penicillium* sp.	*Cladosporium cladosporoides*	*Dothiorella* sp.
1	135	>200	55	35
2	>200	>200	>200	125
3	100	>200	35	100
4	115	120	13.75	>200
5	105	>200	100	67.5
6	150	>200	37.5	28.75
7	>200	>200	33.75	75
Iprodione	31.3	35.8	12.7	6.5
Myclobutanil	15.6	54.2	37.2	18.4

Conclusion

Seven tetrahydroquinoline derivatives were easily synthesized using Lewis acid-catalyzed imino Diels-Alder reactions and were evaluated as inhibitors of the germination of spores of phytopathogenic fungi. The structures were verified by spectroscopic data. In the antifungal bioassay, compound **2** only showed antifungal activity against *Dothiorella* sp., while spore germination of *Penicillium* sp. was inhibited by compound **4**. The same compound showed the highest activity against *Cladosporium cladosporoides*. Compound **4**, with the electron-donating methoxy group, can be evaluated in other assays to study a possible mechanism of action. Structure-activity relationship indicated the rel-

evance of the position of the substituents; the compounds substituted at *para*-position were more active than the unsubstituted compounds. These results can be used for the development of new compounds for the treatment of fungal diseases in agriculture.

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