



Universitas Scientiarum

ISSN: 0122-7483

revistascientificasjaveriana@gmail.com

Pontificia Universidad Javeriana

Colombia

Romero Bohórquez, Arnold R.; Kouznetsov, Vladimir V.; Zacchino, Susana A.
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Universitas Scientiarum, vol. 20, núm. 2, mayo-agosto, 2015, pp. 177-189
Pontificia Universidad Javeriana
Bogotá, Colombia

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Synthesis and in vitro Evaluation of Antifungal Properties of Some 4-Aryl-3-Methyl-1,2,3,4-Tetrahydroquinolines Derivatives

Arnold R. Romero Bohórquez¹✉, Vladimir V. Kouznetsov¹, Susana A. Zacchino²

Abstract

Two series of 4-aryl-3-methyl-1,2,3,4-tetrahydroquinoline derivatives were efficiently synthesized according to a two-step synthesis and evaluated as potential antifungal agents. The key step was the formation of the corresponding *N*-benzyltetrahydroquinolines 5 via a three-component cationic imino Diels-Alder cycloaddition. The second step was a catalytic debenzilation to obtain the *N*-unprotected tetrahydroquinolines 6. The products were isolated and purified by column chromatography. Substances were characterized using nuclear magnetic resonance (NMR) mass spectrometry (MS) and infrared spectroscopy (IR). All compounds were tested *in vitro* against standardized, clinically important fungi, including yeasts, hialohyphomycetes, and dermatophytes. These studies showed that between the tetrahydroquinoline series tested, compounds 6f and 6g showed antifungal activity, specifically against dermatophytes. The compound 6-methoxy-4-(4-hydroxi-3-methoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline 6g exhibited the best *in vitro* activity (MIC 32-65 µg/mL). The results indicated that the elimination of benzyl group from the *N*-benzyltetrahydroquinolines derivatives, as well as the introduction of a hydroxyl group in the 4-aryl substituent caused a significant improvement in the antifungal activity. These results were supplemented by the *in silico* prediction; most of the tetrahydroquinolines evaluated showed high bioavailability, high drugs score and low potential risk.

Keywords: antifungal activity; tetrahydroquinolines; cationic imino Diels-Alder reaction; Lipinski's rule; propenylbenzenes

Edited by Alberto Acosta ✉

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Received: 01-07-2014 **Accepted:** 11-09-2014

Published on line: 29-09-2014

Citation: Romero Bohórquez AR, Kouznetsov VV, Zacchino SA (2015) Synthesis and in vitro Evaluation of Antifungal Properties of Some 4-Aryl-3-Methyl-1,2,3,4-Tetrahydroquinolines Derivatives. *Universitas Scientiarum* 20(2): 177-189 doi: 10.11144/Javeriana.SC20-2.sica

Funding: Universidad Industrial de Santander; COLCIENCIAS.

Electronic supplementary material: N/A

Introduction

Fungal infections are a common and serious public health issue that can threaten human life, particularly in immunocompromised patients; they have a remarkable impact on morbidity and mortality worldwide especially in tropical and subtropical developing countries (Mathew & Nath 2009, Pappas 2011, Brown et al. 2012). The majority of fungal infections are caused by opportunistic pathogens, which may be endogenous or acquired from the environment. *Candida*, *Cryptococcus* and *Aspergillus* infections are the most common invasive mycotic diseases that affect humans (Pfaller et al. 2006, Senet et al. 2012). However, new fungal pathogens that pose a risk at a global scale have emerged, and their incidence continues to



increase (Seebacher et al. 2008, Galimberti et al. 2012). Some forms of dermatomycoses produced by fungal microorganisms cause high morbidity; they affect the quality of life of patients with AIDS, patients receiving anticancer chemotherapy, or those undergoing organ transplants (Hsu et al. 2011, Ramos-e-Silva et al. 2012). The prevalence of superficial mycotic infections is high; 20% of the world's population has skin mycoses, making superficial mycotic infections one of the most frequent forms of infection (Woodfolk 2005, Havlickova et al. 2008). Dermatophytic fungi of the genera *Trichophyton*, *Epidermophyton*, and *Microsporum* produce superficial mycoses. This fungi group specifically infects the keratin tissues of the body, causing superficial infections of the skin, hair, or nails, because of their ability to obtain nutrients from keratinized material (Grappel et al. 1974, Weitzman & Summerbell 1995). Significant advances have been made in the development and evaluation of new antifungal agents, especially for superficial mycoses (Kathiravan et al. 2012, Rotta et al. 2012). Although imidazole compounds such as clotrimazole and miconazole have proven to be an effective treatment for dermatomycoses (Boucher et al. 2004, Chai et al. 2011), these fungal infections are often very difficult to eradicate (Li et al. 1995, Zacchino et al. 1999). The clinical efficacy of current antifungal drugs has been limited because of drug resistance, high toxicity risks, and insufficiencies in their antifungal activity and undesirable side effects (Marr et al. 1997, Sanglard 2002). There is a need to develop new, safe and efficient chemotherapeutic agents with potent antifungal activity. As a result, developing new broad-spectrum antifungal agents with less toxicity and a better pharmacokinetic profile is crucial.

Because of their remarkable pharmacological applications, natural and synthetic quinoline compounds and their partially reduced derivatives, tetrahydroquinoline, are heterocycles of great importance in medicinal chemistry (Kouznetsov 2009, Sridharan et al. 2011). These compounds have displayed different biological activities, such as antiparasitic activity (Jaquemond-Collet et al. 2002); they are estrogen receptor modulators (Chen et al. 2007, Wallace et al. 2013) and are, therefore, considered attractive scaffolds for the development of new antifungal agents. Examples of these molecules

include a heterocyclic compound with significant antibiotic properties, called helquinoline 1 (Asolkar et al. 2004), the antifungal agent (*N*-tetrahydroquinoline) urea derivative 2, which has displayed an MIC value of 12.5 µg/mL against *A. Niger* and *T. Rubrum*, respectively (Zheng et al. 2010), the 2-(4-pyridinyl)-1,2,3,4-tetrahydroquinoline derivative 3, which is highly active against *Aspergillus* spp. (MIC = 31.2 µg/mL) and especially against dermatophytes (MIC = 8 µg/mL). More recently, Gutierrez et al. (2012) reported the 2-(furan-2-yl)-1,2,3,4-tetrahydroquinoline 4, which displayed interesting phytopathogenic fungi bioactivity against *Cladosporium cladosporioides* with MIC values of 13.75 µg/mL.

In the course of our screening for novel and selective bioactive compounds, we have reported the antiparasitic and antifungal activity of some substituted *N*-heterocycles, including some (tetrahydro)quinolines (Vargas et al. 2003, 2010, Romero et al. 2012, Kouznetsov et al. 2012, Fonseca et al. 2013). Considering our previous reports and continuing with our program in search of new antifungal agents, we decided to prepare different polyfunctionalized 1,2,3,4-tetrahydroquinolines and test their biological properties. Here, we report the synthesis and *in vitro* antifungal activity of several 4-aryl-3-methyl tetrahydroquinoline derivatives (5a-h) and (6a-h) against standardized, as well as clinically important fungi including *Cryptococcus neoformans*, several species of *Candida* and *Aspergillus* genus, and dermatophytes. These THQ compounds were prepared using a three-component cationic imino Diels-Alder cycloaddition methodology and a catalytic reduction (Romero & Kouznetsov 2010) that provided the *N*-benzyl- or *N*-H-1,2,3,4-tetrahydroquinoline derivatives with high structural diversity.

Materials & methods

In silico pharmacological properties study

The preliminary molecular design for 4-aryl-3-methyl-1,2,3,4-tetrahydroquinoline compounds series 5 and 6 was achieved based on structure-activity relationship studies and virtual screening analyses reported in the literature. Five physicochemical parameters of Lipinski's rules were calculated using the Molinspiration virtual platform (<http://www.molinspiration.com/>

services/). The profile and toxicity risk assessment was accomplished using the OSIRIS program (<http://www.organic-chemistry.org/prog/peo>). The OSIRIS and Molinspiration Property Explorers, shown in these web-pages, are an integral part of some pharmaceutical companies' *in-house* substance registration system. They allow drawing chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid.

Chemistry

The melting points (uncorrected) were determined using a Fisher-Johns melting point apparatus. We recorded IR spectra on a Lumex Infracum FT-02 spectrophotometer in KBr. ^1H and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer (400 MHz ^1H NMR and 100 MHz ^{13}C NMR), using CDCl_3 as solvent. TMS was used as an internal standard. J values are reported in Hz; chemical shifts are reported in ppm (δ) relative to the solvent peak (CHCl_3 in CDCl_3 at 7.26 ppm for protons). Signals were designated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; t, triplet; td, triplet of doublets; q, quartet; m, multiplet; br., broad. A Hewlett Packard 5890a Series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector with an HP MS ChemStation Data system was used for MS identification at 70 eV using a 60 m capillary column coated with HP-5 [5% phenylpoly(dimethylsiloxane)]. We performed elemental analyses on a Perkin-Elmer 2400 Series II analyzer, which were within ± 0.4 of theoretical values. The reaction progress was monitored using thin layer chromatography on Silufol UV 254 TLC aluminum sheets. Column chromatography was carried out using Silica gel (60-120 mesh). All reagents were purchased from Sigma and Aldrich Chemical Co. and used without further purification.

General Procedure for the synthesis of *N*-Benzyl-4-aryl-3-methyltetrahydroquinoline derivatives

The general procedure was previously described by Romero & Kouznetsov (2010) and performed as follows: A mixture of *N*-benzylaniline (1 mmol) and formaldehyde (37% in MeOH, 1.1 mmol) in MeCN (10 mL) was stirred at r.t. for 10 min. The system was cooled to 0 °C and $\text{BF}_3 \cdot \text{OEt}_2$ (1.1 mmol) was added

dropwise into the mixture. After 30 min, dienophile reagent (*trans*-anethole or *trans*-isoeugenol; 1.1 mmol) was added to the reaction mixture over 5 min. We stirred the resulting mixture at 70 °C for 8 h. After completion of the reaction as indicated by TLC, the reaction mixture was extracted with EtOAc (3×15 mL). The organic layer was separated and dried (Na_2SO_4), then, concentrated *in vacuo* and the crude product was purified by column chromatography using silica gel (60-120 mesh; petroleum ether-EtOAc) to afford pure tetrahydroquinoline 5a-h.

Selected Spectral Data

trans-*N*-Benzyl-3,6-dimethyl-4-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (5b):

This compound was isolated as a white solid with a melting point (Mp) of 88-90 °C. The molecular characterization was carried out with infrared (IR) spectroscopy; it showed the following characteristic signals: 3024, 2962, 1620, 1512, 1250 cm^{-1} . Mass spectrometry (MS) gave a molecular ion peak of $m/z = 357$ (65, M^+). Nuclear magnetic resonance on protons ^1H NMR (400 MHz, CDCl_3 , Me_4Si) showed δ (ppm) to be: 0.92 (3H, d, $J = 6.7$ Hz, 3- CH_3), 2.08 (3H, s, 6- CH_3), 2.19 (1H, m, H-3), 3.03 (1H, dd, $J = 11.4$, 7.9 Hz, H-2_{ax}), 3.27 (1H, dd, $J = 11.4$, 3.7 Hz, H-2_{eq}), 3.62 (1H, d, $J = 7.8$ Hz, H-4), 3.80 (3H, s, 4'- OCH_3), 4.49 (2H, s, N- CH_2 -Ph), 6.49 (2H, m, H-8 and H-5), 6.80 (1H, dd, $J = 8.5$, 1.5 Hz, H-7), 6.84 (2H, d, $J = 8.6$ Hz, 2'-ArH), 7.01 (2H, d, $J = 8.6$ Hz, 3'-ArH), 7.22-7.34 (5H, m, PhH); ^{13}C -NMR (100 Hz, CDCl_3 , Me_4Si), δ (ppm): 157.9, 143.2, 139.2, 137.9, 131.0, 129.9 (2C), 128.5 (2C), 127.8, 126.7 (2C), 126.6, 125.0, 124.5, 113.6 (2C), 111.0, 55.6, 55.2, 54.5, 50.7, 34.8, 20.3, 18.2. Anal. Calcd for $\text{C}_{25}\text{H}_{27}\text{NO}$ (357 g/mol): C, 83.99; H, 7.61; N, 3.92. Found: C, 83.78; H, 7.72; N, 3.88.

trans-*N*-Benzyl-3,6-dimethyl-4-(4-hydroxy-3-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (5f):

This compound was isolated as a white solid with a melting point (Mp) of 127-129 °C. The molecular characterization was carried out with infrared (IR) spectroscopy showed the following characteristic signals: 3433, 3024, 2916, 1612, 1512, 1273 cm^{-1} . Mass spectrometry (MS) gave a molecular ion peak of $m/z = 373$ (77, M^+). Nuclear magnetic resonance on protons ^1H NMR (400 MHz, CDCl_3 , Me_4Si) showed δ (ppm) to be: 0.99 (3H, d, $J = 6.7$ Hz, 3- CH_3), 2.15 (3H, s, 6- CH_3),

2.27 (1H, m, H-3), 3.12 (1H, dd, $J = 11.3, 8.2$ Hz, H-2_{ax}), 3.36 (1H, dd, $J = 11.4, 3.8$ Hz, H-2_{eq}), 3.67 (1H, d, $J = 8.1$ Hz, H-4), 3.87 (3H, s, 3'-OCH₃), 4.55 (2H, br. d, $J = 7.2$ Hz, N-CH₂-Ph), 5.58 (1H, s, 4'-OH), 6.57 (1H, br. d, $J = 8.4$ Hz, H-8), 6.59 (1H, br. s, H-5), 6.69 (2H, br. d, $J = 8.3$ Hz, 2'-ArH y 6'-ArH), 6.86 (1H, dd, $J = 8.2, 1.4$ Hz, H-7), 6.88 (1H, d, $J = 8.0$ Hz, 5'-ArH), 7.26-7.40 (5H, m, PhH). ¹³C-NMR (100 Hz, CDCl₃ Me₄Si), δ (ppm): 146.5, 143.9, 143.2, 139.2, 137.6, 130.9, 128.5 (2C), 127.8, 126.7, 126.7 (2C), 125.1, 124.5, 122.2, 114.0, 111.1, 110.9, 55.9, 55.6, 54.7, 51.3, 34.7, 20.2, 18.3. Anal. Calcd for C₂₅H₂₇NO₂ (373 g/mol): C, 80.40; H, 7.29; N, 3.75. Found: C, 80.58; H, 7.10; N, 3.65.

General procedure synthesis of N-H-4-Aryl-3-methyltetrahydroquinoline derivatives

The general procedure also was previously described by Romero & Kouznetsov (2010) and performed as follows: A mixture of tetrahydroquinoline 5a-h (1 mmol), wet 10 % Pd/C (cat.) and MeOH-CH₂Cl₂ (3:1, 20 mL) was stirred under H₂ (1atm) at r.t. for 14-16 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* and extracted with CH₂Cl₂ (3 × 15 mL). The organic layer was separated and dried (Na₂SO₄), and concentrated again *in vacuo*. We purified the resulting product by flash column chromatography (silica gel; petroleum ether-EtOAc) to provide the pure tetrahydroquinoline 6a-h.

Selected Spectral Data

trans-3,6-Dimethyl-4-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (6b): This compound was isolated as a yellow solid with a melting point (Mp) of 71-73 °C. The molecular characterization was carried out using infrared (IR) spectroscopy; it showed the following characteristic signals: 3412, 2962, 1604, 1504 cm⁻¹. Mass spectrometry (MS) gave a molecular ion peak of $m/z = 267$ (65, M⁺). Nuclear magnetic resonance on protons ¹H NMR (400 MHz, CDCl₃ Me₄Si) showed δ (ppm) to be: 0.91 (3H, d, $J = 6.7$ Hz, 3-CH₃), 2.08 (4H, br. s, 6-CH₃ and H-3), 2.98 (1H, dd, $J = 11.1, 8.5$ Hz, H-2_{ax}), 3.24 (1H, dd, $J = 11.2, 3.5$ Hz, H-2_{eq}), 3.56 (1H, d, $J = 8.2$ Hz, H-4), 3.80 (3H, s, 4'-OCH₃), 6.46 (2H, br. d, $J = 8.1$ Hz, H-8 y H-5), 6.79 (1H, dd, $J = 8.1, 1.4$ Hz, H-7), 6.83 (2H, d, $J = 8.6$ Hz, 2'-ArH), 7.03 (2H, d, $J = 8.6$ Hz, 3'-ArH). ¹³C-NMR (100 Hz, CDCl₃ Me₄Si), δ (ppm): 157.9, 142.3, 138.0, 131.0, 130.0 (2C), 127.6, 126.3, 124.3, 114.1, 113.6

(2C), 55.2, 50.4, 47.2, 35.3, 20.4, 18.0. Anal. Calcd for C₁₈H₂₁NO (267 g/mol): C, 80.86; H, 7.92; N, 5.24. Found: C, 81.02; H, 7.78; N, 5.10.

trans-3,6-Dimethyl-4-(4-hydroxy-3-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (6f):

This compound was isolated as a white solid with a melting point (Mp) of 139-141 °C. The molecular characterization carried out with infrared spectroscopy (IR) showed the following characteristic signals: 3548, 3425, 2924, 1612, 1512 cm⁻¹. Mass spectrometry (MS) gave a molecular ion peak of $m/z = 283$ (59, M⁺); Nuclear magnetic resonance on protons ¹H NMR (400 MHz, CDCl₃ Me₄Si) showed δ (ppm) to be: 0.93 (3H, d, $J = 6.6$ Hz, 3-CH₃), 2.12 (4H, br. s, H-3 and 6-CH₃), 3.02 (1H, dd, $J = 10.7, 9.2$ Hz, H-2_{ax}), 3.29 (1H, dd, $J = 11.1, 3.1$ Hz, H-2_{eq}), 3.56 (1H, d, $J = 8.5$ Hz, H-4), 3.82 (3H, s, 3'-OCH₃), 4.64 (1H, br. s, 4'-OH), 6.49 (2H, br. d, $J = 8.0$ Hz, H-5 y H-8), 6.63 (1H, br. s, 2'-ArH), 6.66 (1H, dd, $J = 8.8$ Hz, 6'-ArH), 6.82 (1H, dd, $J = 7.7$ Hz, H-7), 6.86 (1H, d, $J = 7.9$ Hz, 5'-ArH). ¹³C-NMR (100 Hz, CDCl₃ Me₄Si), δ (ppm), presents the following data: 146.5, 144.0, 142.2, 137.6, 130.9, 127.5, 126.4, 124.4, 122.3, 114.2, 113.9, 111.1, 55.9, 51.1, 47.5, 35.3, 20.4, 18.0. Anal. Calcd for C₁₈H₂₁NO₂ (283 g/mol): C, 76.29; H, 7.47; N, 4.94. Found: C, 75.98; H, 7.68; N, 4.81.

Biology

Microorganisms and media

For the first screening in the antifungal evaluation, we used standardized strains of *Candida albicans* ATCC 10231, *Candida tropicalis* CCC 131, *Saccharomyces cerevisiae* ATCC 9763, *Cryptococcus neoformans* ATCC 32264, *A. fumigatus* ATCC 26934, *A. niger* ATCC 9029, *Trichophyton rubrum* CCC 110, *T. mentagrophytes* ATCC 9972 and *M. gypseum* CCC 115 from the American Type Culture Collection (ATCC), Rockville, MD, USA, and CEREMIC (CCC), and the Centro de Referencia en Micología, Facultad de Ciencias Bioquímicas y Farmacéuticas, Suipacha 531-(2000)-Rosario, Argentina. The strains were grown on Sabouraud-chloramphenicol agar slants for 48 h at 30°C, and maintained on slopes of Sabouraud-Dextrose agar (SDA, Oxoid); they were sub-cultured every 15 days to prevent pleomorphic transformations. Inocula of cell or spore suspensions were obtained according to reported procedures and adjusted to 1-5x10⁻³ cells/spores with colony forming units (CFU)/mL (CLSI 2008 a,b).

Antifungal susceptibility testing

The minimum inhibitory concentration (MIC) of each compound was determined by using broth microdilution techniques according to the guidelines of the National Committee for Clinical Laboratory Standards for yeasts (M27-A3)(CLSI 2008 a) and filamentous fungi (M 38-A2)(CLSI 2008 b). MIC values were determined in RPMI-1640 (Sigma, St. Louis, Mo, USA) buffered to pH 7.0 with MOPS. Microtiter trays were incubated at 30 °C for yeasts and species of *Aspergillus* and 28-30 °C for dermatophytes in a moist, dark chamber. MICs were visually recorded at 48 h for yeasts, and at intervals according to control fungus growth for the rest of fungi.

For the assay, stock solutions of pure compounds were twofold diluted with RPMI from 250-0.98 µg/mL (final volume = 100 µL) and a final DMSO concentration ≤ 1%. A volume of 100 µL of an inoculum suspension was added to each well with the exception of the sterility control (sterile water was

added instead). We used ketoconazole (Sigma Chem. Co.) and terbinafine (Novartis, Bs. As.) as positive controls. Endpoints recorded in **Table 4** were defined as the lowest concentration of drug resulting in total inhibition (MIC₁₀₀) of visual growth compared to the growth in the control wells containing no antifungal. We conducted all tests in duplicate and considered compounds with MICs >250 µg/mL as inactive.

Results

In silico chemoinformatics tools




The pre-screening for hit identification from synthetic compounds libraries was based on the oral bioavailability using Lipinski's rules concepts (Lipinski et al. 1997) through the analysis of the rule of five, employing Molinspiration free software (**Table 1**).









































































We calculated the principal molecular properties, including the number of hydrogen donors (nHND), number of hydrogen acceptors (nHA), number of rotatable bonds (nRB) and molecular weight

Table 1. Calculated Lipinski's rule of five parameters for the 4-aryl-3-methyl-1,2,3,4- tetrahydroquinolines (5, 6) assayed. ^a Confirmed by elemental analysis with ± 0.5 % of calculated values. ^b Number of hydrogen bond acceptors. ^c Number of hydrogen bond donors. ^d Number of rotatable bonds. Reference drug: Ketoconazole (Ket) and terbinafine (Terb).

Comp.	Mol. formula ^a	MW,g/mol	Parameters					
			Log P	TPSA, Å	nNO ^b	nOHNH ^c	RBN ^d	Violations
5a	C ₂₄ H ₂₅ NO	347.47	5.619	12.472	2	0	4	1
5b	C ₂₅ H ₂₇ NO	357.50	6.044	12.472	2	0	4	1
5c	C ₂₅ H ₂₇ NO ₂	373.50	5.652	21.706	3	0	5	1
5d	C ₂₄ H ₂₄ ClNO	377.92	6.273	12.472	2	0	4	1
5e	C ₂₄ H ₂₅ NO ₂	359.47	4.902	32.700	3	1	4	0
5f	C ₂₅ H ₂₇ NO ₂	373.50	5.326	32.700	3	1	4	1
5g	C ₂₄ H ₂₇ NO ₃	389.50	4.934	41.934	4	1	5	0
5h	C ₂₄ H ₂₄ ClNO ₂	393.91	5.556	32.700	3	1	4	1
6a	C ₁₇ H ₁₉ NO	253.34	3.976	21.261	2	1	2	0
6b	C ₁₈ H ₂₁ NO	267.37	4.400	21.261	2	1	2	0
6c	C ₁₈ H ₂₁ NO ₂	283.37	4.009	30.495	3	1	3	0
6d	C ₁₇ H ₁₈ ClNO	287.79	4.630	21.261	2	1	2	0
6e	C ₁₇ H ₁₉ NO ₂	269.34	3.258	41.489	3	2	2	0
6f	C ₁₈ H ₂₁ NO ₂	283.37	3.683	41.489	3	2	2	0
6g	C ₁₈ H ₂₁ NO ₃	299.34	3.291	50.723	4	2	3	0
6h	C ₁₇ H ₁₈ ClNO ₂	303.79	3.912	41.489	3	2	2	0
Ket	C ₂₆ H ₂₈ Cl ₂ N ₄ O ₄	531.44	3.772	69.075	8	0	7	1
Terb	C ₂₁ H ₂₅ N	291.43	5.719	3.238	1	0	4	1

(MW), as well as, another recognized parameter for membrane permeation, prerequisite for bioavailability, the topological polar surface area (TPSA) (Table 1). Other molecular properties tested for the potential risk assessment and associated to some fragments of the synthesized tetrahydroquinoline compounds were evaluated employing Osiris software (Table 2).

Table 2. Toxicity risk, drug-likeness and drug-score parameters obtained for the 4-aryl-3-methyl-1,2,3,4-tetrahydroquinolines (5,6) assayed. ^a Colors code for potential risk:  drug-conform,  middle risk,  undesired effects. ^b (Mut.) possible mutagenic, (Tum.) tumorigenic, (Irr.) irritant and (Rep. Eff.) reproductive effective.

Comp.	Potential Risk ^{a,b}				Drug-likeness	Drug-Score
	Mut.	Tum.	Irr.	Rep. Eff.		
5a					4.78	0.57
5b					3.31	0.50
5c					4.54	0.57
5d					4.79	0.45
5e					4.87	0.62
5f					3.35	0.55
5g					4.58	0.61
5h					4.83	0.48
6a					2.87	0.79
6b					1.33	0.68
6c					2.60	0.62
6d					2.88	0.68
6e					2.98	0.82
6f					1.38	0.72
6g					2.65	0.65
6h					2.93	0.72
Terb					-3.84	0.17
Ket					0.17	0.63

The data from this topological analysis allowed us to obtain information on fragments with possible mutagenic (Mut.), tumorigenic (Tum.), irritant (Irr.) and effective reproductive (Eff. Rep.) effects. Prediction results were valued, and color-coded. Properties with medium risks of undesired effects like a mutagenicity or poor intestinal absorption are shown in light orange while green indicates that the substance evaluated has a drug-like behavior. Final molecular properties calculated in this work were the drug-score and the drug-likeness (Table 2). The molecular fragments with frequent occurrence in trade drugs yield positive drug-likeness values.

Chemistry

Two series of 4-aryl-3-methyl-1,2,3,4-tetrahydroquinolines derivatives were easily and efficiently synthesized according to a two-step synthesis. The first and key step was the formation of the corresponding *N*-benzyltetrahydroquinolines 5 via a “one pot” three-component cationic imino Diels-Alder cycloaddition from readily available *N*-benzylanilines, inexpensive formalin (37% formaldehyde in methanol), and a commercially available *trans*-anethole (and isoeugenol) in the presence of BF₃ · OEt₂ at 70 °C in acetonitrile, according to the literature procedure (Romero & Kouznetsov 2010). The second step was their catalytic debenzylation using hydrogen gas and Pd/C as catalyst to obtain the respective *N*-unprotected tetrahydroquinolines 6 (Figure 1).

Both series of compounds were obtained in good yields after column chromatography purification on silica gel (Table 3). The stereochemistry of all these tetrahydroquinoline compounds synthesized (5,6) were determined by IR and MS and confirmed by ¹H and ¹³C NMR spectroscopy and supported by inverse-detected 2D NMR experiments (COSY, HSQC and HMBC spectra).

Antifungal assays

The *in vitro* antifungal activity of the 4-aryl-3-methyl-1,2,3,4-tetrahydroquinolines series 5a-h and 6a-h was evaluated against standardized clinically important fungi, including yeasts, hialohyphomycetes, and dermatophytes (Table 4). To carry out the antifungal evaluation, concentrations of compounds up to

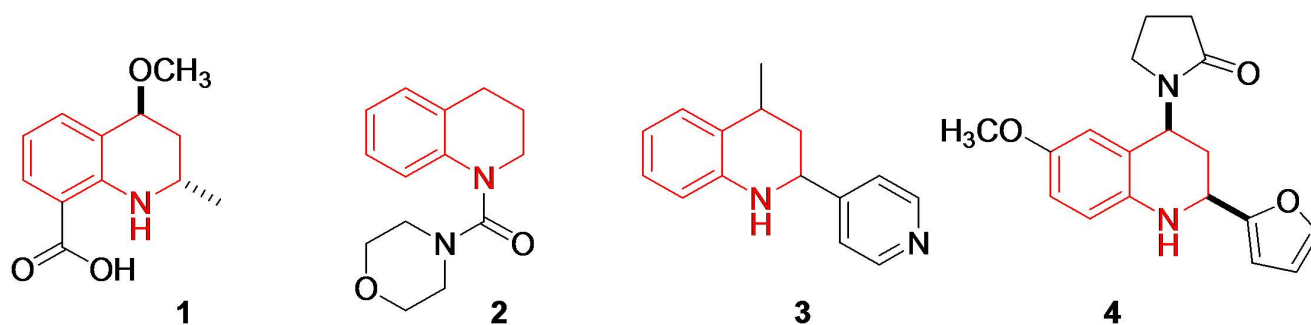


Fig. 1. Tetrahydroquinolines derivatives with remarkable antifungal activity.

Table 3. Physico-chemical data of the 4-aryl-3-methyl-1,2,3,4-tetrahydroquinolines (5,6). ^a Isolated yield after column chromatography; ^b Melting point Uncorrected.

Comp.	R ₁	R ₂	R ₃	m.p., °C ^a	Yield, % ^b
5a	H	CH ₃	H	89-91	59
5b	CH ₃	CH ₃	H	88-90	61
5c	OCH ₃	CH ₃	H	113-115	67
5d	Cl	CH ₃	H	125-127	76
5e	H	H	OCH ₃	167-169	49
5f	CH ₃	H	OCH ₃	127-129	76
5g	OCH ₃	H	OCH ₃	121-123	60
5h	Cl	H	OCH ₃	136-138	77
6a	H	CH ₃	H	73-75	94
6b	CH ₃	CH ₃	H	71-73	92
6c	OCH ₃	CH ₃	H	Sticky oil	95
6d	Cl	CH ₃	H	116-118	93
6e	H	H	OCH ₃	118-120	96
6f	CH ₃	H	OCH ₃	139-141	96
6g	OCH ₃	H	OCH ₃	118-120	98
6h	Cl	H	OCH ₃	112-114	97

250 µg/mL were incorporated to growth media according to CLSI standardized procedures (CLSI 2008 a,b). Terbinafine (Terb) and ketoconazole (Ket) were used as positive controls under the same assay conditions. Table 4 summarizes the minimum concentration of compounds that completely inhibited the growth (MIC₁₀₀) obtained by nine opportunistic pathogenic fungi including yeasts (*Candida albicans*, *C. neoformans*, *Saccharomyces cerevisiae*), hialohyphomycetes (*Aspergillus* spp.) as well as dermatophytes (*Microsporum* and *Trichophyton* spp.). Table 4 shows the structure of each tetrahydroquinoline derivative to facilitate the analysis of the results.

Discussion

The recognizable need to combat diseases caused by pathogenic fungi has brought about significant advancement in the development and implementation of strategies to obtain new and more potent antifungal agents. In this regard, the pursuit of effective and safer drug against pathogens fungi is an urgent priority. With the preceding in mind and considering that the tetrahydroquinoline ring is a key structural scaffold in many bioactive heterocyclic compounds, including some antifungal agents; here, we report the synthesis, characterization and results of the antifungal assays of the two series of 3-methyl-4-aryl-1,2,3,4-tetrahydroquinolines 5a-h and 6a-h.

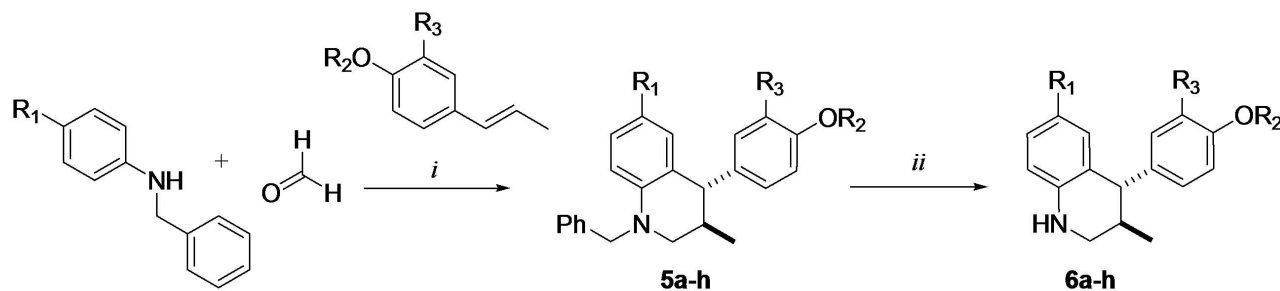


Fig. 2. Preparation of substituted 3-methyl-4-aryl-1,2,3,4-tetrahydroquinolines (5,6): Reagents and conditions: (i) BF₃·OEt₂ (1 mmol), dry acetonitrile, reflux (70 °C), 6-8 h.; (ii) wet 10 % Pd/C (cat.), MeOH/CH₂Cl₂ (3:1), H₂ (1 atm.), r.t., 14-16 h.

Chemistry

Figure 2 illustrates the overall synthesis route of the *N*-benzyl-3-methyl-4-aryl-1,2,3,4-tetrahydroquinoline derivatives 5 and its debenzylated analogous THQs 6; this includes the cycloaddition reaction used as a key-step based on the BF₃·OEt₂-catalyzed multicomponent cationic imino Diels-Alder reaction among substituted *N*-benzylanilines, formalin (37 % formaldehyde in methanol), and propenylbenzenes (*trans*-anethole and isoeugenol) at 70 °C in CH₃CN for 6-8 hours. The catalytic debenzylation (10mol% Pd/C) using hydrogen gas (H₂) at room temperature over night yielded the corresponding 3-methyl-4-aryl-1,2,3,4-tetrahydroquinoline derivatives 6. Both series of tetrahydroquinolines were largely obtained as stable solid substances with defined melting points and 49-77 % (5a-h) and 93-98 % (6a-h) yields after their chromatography purification (Table 3). All the studied tetrahydroquinolines were isolated and purified by column chromatography (on silica gel) using petroleum ether/ethyl acetate mixtures with gradients of polarity. We confirmed the stereochemistry of all THQ compounds using 1D and 2D NMR experiments. ¹H NMR analysis indicated that the structure of the distinctive diastereoisomers obtained for 5 and 6 were *trans*-configured with respect to the 3-CH₃/4-Ar substituents (Figure 2).

In silico chemoinformatics tools

The most significant theoretical pharmacokinetic parameters for all tetrahydroquinoline derivatives

synthesized (5a-h and 6a-h) in this work were obtained using chemoinformatics platforms. Molinspiration software was used to obtain five properties associated with the Lipinski's rules (Lipinski et al. 1997) that indicate whether a chemical can be orally active in humans (drug-likeness). TPSA parameters (Chohan et al. 2010) proved to be a very good descriptor to characterize drug absorption, including intestinal absorption and bioavailability and blood-brain barrier penetration. We found that tetrahydroquinoline derivatives 5a-h violate no more than one of Lipinski's rules while the debenzylated derivatives 6a-h meets the five criteria. All the analyzed tetrahydroquinoline compounds showed high bioavailability properties, similar and comparable with the structures of reference drugs (ketoconazole and terbinafine), largely fulfilling all the parameters set by this rule (molecular weight = 253.34-393.91, log P = 3.26-6.27, nON = 2-4 and nOHNH = 0-2). Prediction results by TPSA parameters for the compounds 5a-h and 6a-h (Table 1) showed TPSA values between 12.5 and 50.7 Å², confirming that this pharmacokinetic parameter is a relevant property in drug design. It should be noted that TPSA values less than 60 Å² are defined for compounds with good membrane permeability, as well as penetration of the blood-brain barrier.

In order to assess the possible pharmacological properties and predict the compounds drug-score of the tetrahydroquinolines 5a-h and 6a-h, a toxicity profile evaluation was performed employing the OSIRIS software. Exploring virtually the potential risk associated to different fragments of the synthesized tetrahydroquinoline compounds, it can be noted that

Table 4. Minimum inhibitory concentrations (MIC in g/mL) of *N*-benzyl-4-aryl-3-methyl-1,2,3,4-tetrahydroquinoline (5) and *N*-H-4-aryl-3-methyl-1,2,3,4-tetrahydroquinoline derivatives (6). *Ca*: *Candida albicans* ATCC 10231, *Ct*: *Candida tropicalis* CCC 131, *Sc*: *Saccharomyces cerevisiae* ATCC 9763, *Cn*: *Cryptococcus neoformans* ATCC 32264, *Afu*: *Aspergillus fumigatus* ATCC 26934, *Ani*: *Aspergillus niger* ATCC 9029, *Mg*: *Microsporium gypseum* CCC 115, *Tr*: *Trichophyton rubrum* CCC 113, *Tm*: *Trichophyton mentagrophytes* ATCC 9972. CCC = CEREMIC (Centro de Referencia en Micología). ATCC: American Type Culture Collection. MIC \geq 250 g/mL is indicative that the compound is inactive, Reference drug: ketoconazole (Ket) and terbinafine (Terb).

Compd.	Structure	<i>Ca</i>	<i>Ct</i>	<i>Sc</i>	<i>Cn</i>	<i>Afu</i>	<i>Ani</i>	<i>Mg</i>	<i>Tr</i>	<i>Tm</i>
5a		>250	>250	>250	>250	>250	>250	>250	>250	>250
5b		>250	>250	>250	>250	>250	>250	250	250	250
5c		>250	>250	>250	>250	>250	>250	250	250	250
5d		>250	>250	>250	>250	>250	>250	>250	>250	>250
5e		>250	>250	>250	>250	>250	>250	>250	>250	>250
5f		>250	>250	>250	>250	>250	>250	250	250	250
5g		>250	>250	>250	>250	>250	>250	250	250	250
5h		>250	>250	>250	>250	>250	>250	>250	>250	>250
6a		>250	>250	>250	>250	>250	>250	>250	>250	>250
6b		>250	>250	>250	>250	>250	>250	>250	>250	>250
6c		>250	>250	>250	>250	>250	>250	125	125	125
6d		>250	>250	>250	>250	>250	>250	>250	>250	>250
6e		>250	>250	>250	>250	>250	>250	>250	>250	>250
6f		>250	>250	>250	>250	>250	>250	31,25	62,5	62,5

all obtained and evaluated products presented low biological risks and have few negative effect. The methoxy group in the 6c and 6g compounds on the C-6 position of the tetrahydroquinoline scaffolds showed a moderate mutagenic risk. Nevertheless, the fragments and topology of the reference compound present higher potential risk than all the tetrahydroquinoline molecules evaluated. Performing calculations on drug-likeness and drug-score parameters, we could note that both series afforded favorable numbers, especially for the molecular structures 6a-h. Compared with the antifungal activity of the most active molecules (6f and 6g), the drug-likeness calculation showed good correlation and confirmed the importance of removing the benzyl group, and the introduction of a hydroxyl group in the 4-aryl substituent of the tetrahydroquinoline structure (Table 3). Furthermore, the drug-score obtained for each analyzed molecule showed an important relationship with the *in vitro* antifungal evaluation for tetrahydroquinolines 6f and 6g, whose values were above the average of all calculated compounds.

Antifungal assays

All compounds were tested *in vitro* against standardized clinically important fungi, including yeasts, hialohyphomycetes, and dermatophytes. Table 3 presents the results for antifungal activities of all the title compounds; ketoconazole and terbinafine were used as the controls. The table also shows the structure of each tetrahydroquinoline derivative to facilitate the analysis of the results. Between the two tetrahydroquinoline series tested, the results showed that N-H-tetrahydroquinoline derivatives 6a-h have moderate inhibition activities while the N-benzyl-tetrahydroquinoline series 5a-h showed no antifungal activity (their MIC exceeded 250 µg/mL).

Compounds 6c, 6f and 6g showed particular antifungal activity against the dermatophyte strains assayed. The 6-methoxy-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline 6g exhibit the best *in vitro* antifungal activity, especially against dermatophytes, including *Microsporum gypseum* (MIC 31.25 µg/mL), *Trichophyton rubrum* (MIC 62.5 µg/mL) and *Trichophyton mentagrophytes* (MIC 62.5 µg/mL).

Seeking structural parameters that might enhance antifungal activity, we introduced chlorine,

methoxy, and methyl substituents onto the 2,4-diaryl 1,2,3,4-tetrahydroquinoline ring; we also used two different dienophiles for the cycloaddition reaction (anethole and isoeugenol) and performed N-debenzylation of the tetrahydroquinoline derivatives 5a-h. Antifungal results indicated that the presence of the methoxy group in compounds 6 showed noteworthy performance; this compound presented bioactivity in comparison to all the other tetrahydroquinoline derivatives tested. Furthermore, inhibition activity results indicated that the elimination of a benzyl group and introduction of a hydroxyl group on 4-aryl substituent of the N-benzyltetrahydroquinolines derivatives 5a-h generated a significant improvement of the antifungal activity of this series (Table 3).

Conclusion

An easy and efficient synthetic route was employed to prepare two series of 4-aryl-3-methyl-1,2,3,4-tetrahydroquinoline derivatives. The key step involved a three-component cationic imino Diels-Alder reaction. This study showed that between the tetrahydroquinolines (THQ) series tested, compounds 6f and 6g showed antifungal activity, specifically against dermatophytes (MIC ≤ 62.5 µg/mL). The compound 6-methoxy-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline 6g exhibited the best *in vitro* activity (MIC 32-65 µg/mL). Results indicated that the elimination of a benzyl group from the N-benzyltetrahydroquinolines derivatives and the introduction of a hydroxyl group in the 4-aryl substituent produced a significant improvement in antifungal activity. These results were complemented by an *in silico* prediction, which revealed the high bioavailability, high drugs score and low potential risk of most of the tetrahydroquinolines evaluated. We are currently pursuing more complete structure-activity relationship studies to increase *in vitro* antifungal activity.

Acknowledgments

The authors appreciate the financial support provided by the Universidad Industrial de Santander (VIE-UIS, project 5714). ARRB thanks COLCIENCIAS for the PhD studies scholarship (2005-2010).

Conflict of Interest

The authors declare that no conflicts of interest exist in relation to this work.

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Síntesis y evaluación in vitro de las propiedades antifúngicas de algunos derivados de 4-aril-3-metil-1,2,3,4-tetrahidroquinolinas

Resumen. Dos series de 4-aril-3-metil-1,2,3,4-tetrahidroquinolinas fueron sintetizadas de acuerdo con una metodología sintética de dos pasos y evaluadas como potenciales agentes antifúngicos. El paso clave involucró la formación de las correspondientes N-bencil tetrahidroquinolinas 5 vía una cicloadición imino Diels-Alder catiónica. El segundo paso consistió en obtener las tetrahidroquinolinas N-desprotegidas 6 vía una desbencilación catalítica. Los productos fueron aislados y purificados usando cromatografía en columna (CC). Las sustancias fueron identificadas usando resonancia magnética nuclear (RMN), espectrometría de masas (EM) y espectroscopia infrarroja (IR). Los compuestos fueron evaluados in vitro frente a cepas estandarizadas de hongos clínicamente relevantes, incluyendo levaduras, hialohifomicetes y dermatofitos. Estos estudios mostraron que, de las tetrahidroquinolinas ensayadas, los compuestos 6f y 6g mostraron actividad antifúngica, específicamente frente a dermatofitos. El compuesto 6-metoxi-4-(4-hidroxi-3-metoxifenil)-3-metil-1,2,3,4-tetrahidroquinolina 6g exhibió la mejor actividad (MIC 32-65 µg/mL). Los resultados indican que remover el grupo bencilo e introducir un grupo hidroxilo en el sustituyente arilo de las N-bencil tetrahidroquinolinas produce un mejoramiento de la actividad antifúngica. Predicciones in silico complementaron los resultados: la mayoría de las tetrahidroquinolinas ensayadas mostraron alta biodisponibilidad, altos “drug scores” y bajo riesgo potencial.

Palabras clave: actividad antifúngica; tetrahidroquinolinas; reacción imino Diels-Alder catiónica, regla de Lipinski, propenilbencenos

Síntese e avaliação in vitro das propriedades antifúngicas de alguns derivados de 4-Aryl-3-Methyl-1,2,3,4-Tetrahydroquinolines

Resumo. Duas séries de 4-aril-3-metil-1,2,3,4-tetrahidroquinolina foram sintetizadas de acordo com um método de síntese em duas etapas e avaliadas como potenciais agentes antifúngicos. O passo chave envolveu a formação dos correspondentes N-bencil tetrahidroquinolinas 5 via uma cicloadição de imino Diels-Alder catiónica. O segundo passo foi obter as N-tetrahidroquinolinas 6 através de uma desbenzilação catalítica. Os produtos foram purificados utilizando cromatografia em coluna. As substâncias foram identificadas por ressonância magnética nuclear (RMN), espectrometria de massa (EM) e espectroscopia de infravermelho (IR). Todos os compostos foram testados in vitro contra as estirpes padrão e os fungos clinicamente importantes, incluindo as leveduras, hialohifomicetes e dermatófitos. Estes estudos mostraram que entre a série de tetrahidroquinolinas (THQ) os compostos 6f e 6g mostraram atividade antifúngica, particularmente contra dermatófitos. O composto 6-metoxi-4-(4-hidroxi-3-metoxifenil)-3-metil-1,2,3,4-tetrahidroquinila 6g mostrou melhor atividade (MIC 32-65 µg/mL). Os resultados indicam que a remoção do grupo benzilo e a introdução de um grupo hidroxilo no substituinte arilo do N-benzil-tetrahidroquinolina, resultou num aumento significativo da atividade antifúngica. Os resultados foram suplementados por previsões in silico, que mostraram alta biodisponibilidade e pouco risco potencial da maioria dos tetrahidroquinolinas avaliados.

Palavras-chave: atividade antifúngica; tetrahidroquinolinas; reação imino Diels-Alder catiónica, regra de Lipinski, propenilbencenos