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In vitro antifungal activity of polyfunctionalized 2-(hetero)arylquinolines prepared through imino Diels–Alder reactions

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ABSTRACT

Diverse polyfunctionalized quinolines, easily prepared using Lewis acid-catalyzed imino Diels–Alder reactions between corresponding aldimines, were tested for antifungal properties against standardized as well as clinical isolates of clinically important fungi. Among them, 4-pyridyl derivatives displayed the best activities mainly against dermatophytes. The activity appears not to be related neither to the lipophilicity nor to the basicity of compounds.

1. Introduction

Fungal infections have emerged as a major cause of morbidity and often of mortality in immunocompromised patients over the past two decades.[1] The limited efficacy and high toxicity of the available antifungal drugs have highlighted the need of new antifungal compounds which could constitute alternatives to the existing drugs.[2] An important requirement for new antifungal compounds is that these structures should inhibit not only standardized strains but also clinical isolates of the most clinical relevant fungal spp.[3,4] Heterocyclic systems with quinoline nucleus represent privileged moieties in medicinal chemistry, and are ubiquitous sub-structures associated with biologically active natural products. Quinolines and their derivatives have shown to display a wide spectrum of biological activities such as antiparasitical,[5] antibacterial,[6] cytotoxic and antineoplastic,[7] antimycobacterial,[8] and anti-inflammatory behavior.[9] Antifungal properties of 8-hydroxyquinoline and its derivatives[10] or substituted indoloquinolines[11] were also described. Consequently, there is great current interest in assembling quinoline ring systems from acyclic precursors and an ever-increasing demand for selective, cheap, and environmentally safe procedures for their preparation.[12] Having broad biological activity, the quinoline compounds have been considered as good starting materials for the search of novel antifungal agents.

So, in the course of our ongoing screening program for new biologically important *N*-heterocycles, we have previously reported the antifungal activity of different substituted quinolines.[13,14] These quinoline derivatives are low molecular weight heterocyclic aromatic molecules, synthetically acquired. They were easily soluble in organic solvents and showed antifungal activities mainly against opportunistic pathogenic clinically important fungi. Among them, 4-methyl-2-phenylquinoline (**A**) and 6-bromo-4-methyl-2-(β-pyridyl)quinoline (**B**) (Fig. 1) showed potent antifungal activities against dermatophytes.[13,14]

Both, **A** and **B**, have been prepared from the corresponding *N*-aldimines via sequential allylation/heterocyclization/aromatization processes that do not allow the use of commercially available anilines as principal starting materials. Moreover, this method does not offer syntheses of quinolines substituted at the C-2 position and unsubstituted at the C-3 and C-4 positions, needed in our present re-

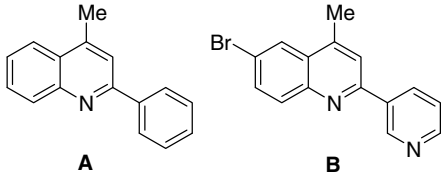

Figure 1. 2-Substituted quinolines active against dermatophytes.

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search. It seems that the emerging acid-catalyzed imino Diels–Alder cycloaddition reactions[15] and its multi-component version[16] can overcome these limitations and can be useful tools for the generation of quinoline derivatives with several degrees of structural diversity. Herein, we report the preparation, physicochemical properties, and antifungal activities of a new series of several polyfunctionalized C-2-substituted quinolines and some of their tetrahydroquinoline precursors, whose syntheses employ mainly imino Diels–Alder cycloaddition methodology that provides the generation of quinoline derivatives with structural diversity.

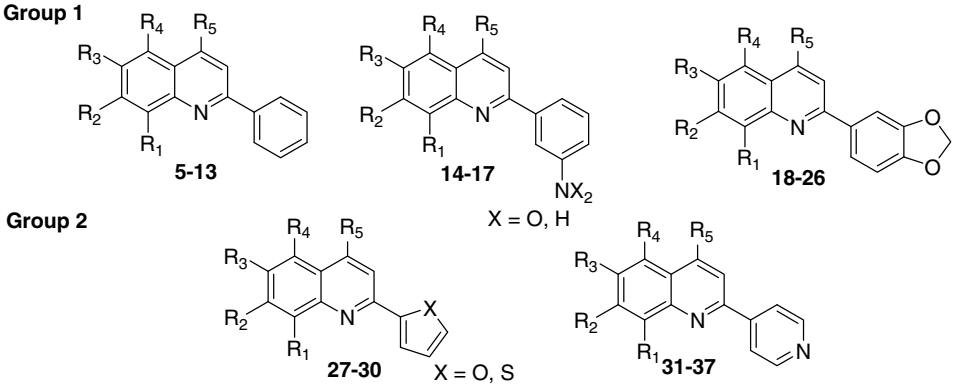
2. Results and discussion

2.1. Chemistry

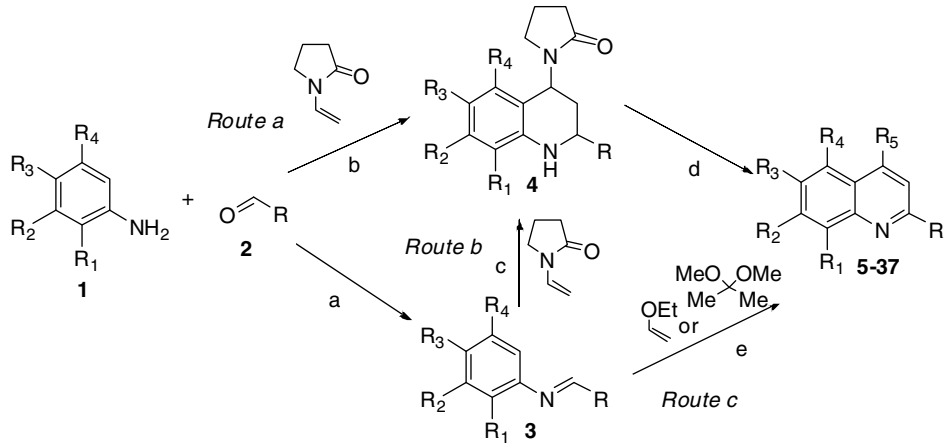
Synthesis of desired polyfunctionalized C-2-(hetero)aryl substituted quinolines **5**–**37** (Table 1) was accomplished through different two- or three-step synthetic sequences from commercially available substituted anilines **1**, aromatic aldehydes **2**: benzaldehyde and its 3-NO_2 analogue, α-furan (or α-thiophene)-carboxyaldehydes or γ-pyridinecarboxyaldehyde. *Route a* consisted in using cycloaddition reactions between in situ forming *N*-aryl aldimines and *N*-vinylpyrrolidin-2-one (NVP) (three-component imino Diels–Alder reaction). *Route b* was based on imino Diels–Alder reaction of preformed *N*-aryl aldimines **3** and NVP. Finally, *route c* involved Kametani reaction between preformed *N*-aryl aldimines and ethyl vinyl ether (EVE), or 2,2-dimethoxypropane (DMP; Scheme 1).

So, synthesis of new polyfunctionalized 2-arylquinolines **5**–**26** started with a $BiCl_3$-catalyzed three-component imino Diels–Alder reaction of various anilines, aromatic aldehydes, and NVP in MeCN at room temperature to give the corresponding isolable substituted tetrahydroquinolines **4**, whose simple fusion with elemental sulfur (220–250 °C, 10 min) allowed to obtain the required quinoline derivatives in good overall yield[17] (route a).

Table 1
Polyfunctionalized C-2-substituted quinolines prepared through imino Diels–Alder cycloaddition reactions and their molecular formula, molecular weight, pK_a, and Log*P*



Compound	R_1	R_2	R_3	R_4	R_5	*R* (Ar or Hetaryl)	Molecular formula	Molecular weight	pK_a	Log*P*
5	H	H	H	H	H	Ph	$C_{15}H_{11}N$	205.25	4.54 ± 0.40	3.90 ± 0.25
6	H	H	Me	H	H	Ph	$C_{16}H_{13}N$	219.28	4.67 ± 0.43	4.36 ± 0.25
7	H	H	Et	H	H	Ph	$C_{17}H_{15}N$	233.31	4.65 ± 0.43	4.89 ± 0.25
8	H	H	HO	H	H	Ph	$C_{15}H_{11}NO$	221.25	4.69 ± 0.43	3.62 ± 0.49
9	H	H	NO_2	H	H	Ph	$C_{15}H_{10}N_2O_2$	250.25	2.71 ± 0.43	3.66 ± 0.27
10	H	H	F	H	H	Ph	$C_{15}H_{10}FN$	223.25	3.79 ± 0.43	3.98 ± 0.35
11	H	H	Cl	H	H	Ph	$C_{15}H_{10}ClN$	239.70	3.65 ± 0.43	4.55 ± 0.26
12	H	Me	H	Me	H	Ph	$C_{17}H_{15}N$	233.31	5.18 ± 0.50	4.82 ± 0.25
13	H	–OCH_2O–		H	H	Ph	$C_{16}H_{11}NO_2$	249.26	4.81 ± 0.20	4.10 ± 0.33
14	H	H	F	H	H	3-NO_2–Ph	$C_{15}H_9FN_2O_2$	268.24	2.48 ± 0.50	3.51 ± 0.37
15	H	H	Cl	H	H	3-NO_2–Ph	$C_{15}H_9ClN_2O_2$	284.70	2.34 ± 0.50	4.08 ± 0.28
16	H	H	Cl	H	H	3-NH_2–Ph	$C_{15}H_{11}ClN_2$	254.71	2.36 ± 0.61	2.99 ± 0.60
17	H	H	Et	H	H	3-NO_2–Ph	$C_{17}H_{14}N_2O_2$	278.31	3.35 ± 0.50	4.42 ± 0.27
18	H	H	H	H	H	(–OCH_2O–)Ph	$C_{16}H_{11}NO_2$	249.26	4.03 ± 0.61	3.76 ± 0.32
19	H	H	Me	H	H	(–OCH_2O–)Ph	$C_{17}H_{13}NO_2$	263.29	4.15 ± 0.61	4.22 ± 0.32
20	H	H	MeO	H	H	(–OCH_2O–)Ph	$C_{17}H_{13}NO_3$	279.29	3.97 ± 0.61	3.85 ± 0.34
21	H	H	F	H	H	(–OCH_2O–)Ph	$C_{16}H_{10}FNO_2$	267.25	3.26 ± 0.61	3.84 ± 0.42
22	H	H	Cl	H	H	(–OCH_2O–)Ph	$C_{16}H_{10}ClNO_2$	283.71	3.13 ± 0.61	4.41 ± 0.34
23	H	Et	H	H	H	(–OCH_2O–)Ph	$C_{18}H_{15}NO_2$	277.32	4.37 ± 0.61	4.75 ± 0.32
24	H	Me	H	Me	H	(–OCH_2O–)Ph	$C_{18}H_{15}NO_2$	277.32	4.65 ± 0.61	4.68 ± 0.32
25	Me	H	H	Me	H	(–OCH_2O–)Ph	$C_{18}H_{15}NO_2$	277.32	4.18 ± 0.61	4.68 ± 0.32
26	MeO	H	MeO	H	H	(–OCH_2O–)Ph	$C_{18}H_{15}NO_4$	309.32	2.25 ± 0.61	3.49 ± 0.40
27	H	H	MeO	H	H	2-Fu	$C_{14}H_{11}NO_2$	225.24	3.97 ± 0.50	3.30 ± 0.30
28	H	H	Cl	H	H	2-Fu	$C_{13}H_8ClNO$	229.66	3.12 ± 0.50	3.86 ± 0.29
29	H	H	MeO	H	H	2-Thie	$C_{14}H_{11}NOS$	241.31	4.38 ± 0.43	3.82 ± 0.31
30	H	H	Cl	H	H	2-Thie	$C_{13}H_8ClNS$	245.73	3.53 ± 0.43	4.37 ± 0.31
31	H	H	H	H	H	4-Py	$C_{14}H_{10}N_2$	206.24	−0.52 ± 0.10	2.51 ± 0.26
32	H	H	H	H	Me	4-Py	$C_{15}H_{12}N_2$	220.27	−0.49 ± 0.10	2.97 ± 0.26
33	Me	H	H	H	Me	4-Py	$C_{16}H_{14}N_2$	234.30	−0.47 ±0.10	3.43 ± 0.26
34	Et	H	H	H	Me	4-Py	$C_{17}H_{16}N_2$	248.32	−0.46 ± 0.10	3.97 ± 0.26
35	*i*-Pr	H	H	H	Me	4-Py	$C_{18}H_{18}N_2$	262.35	−0.51 ± 0.10	4.31 ± 0.26
36	Me	H	H	NO_2	Me	4-Py	$C_{16}H_{13}N_3O_2$	279.29	−1.08 ± 0.10	3.21 ± 0.27
37	*i*-Pr	H	H	NO_2	Me	4-Py	$C_{18}H_{17}N_3O_2$	307.35	−1.12 ± 0.10	4.09 ± 0.28



Scheme 1. Reagents and conditions: (a) EtOH, Δ; (b) 20 mol% $BiCl_3$, MeCN, Δ; (c) 1 equiv. $BF_3 \cdot OEt_2$, CH_2Cl_2, rt; (d) S_8, Δ (220–230 °C), 10–15 min; (e) excess $BF_3 \cdot OEt_2$, CH_2Cl_2, Δ.

To obtain the required C-2-hetarylquinolines **27**–**37**, the respective *N*-hetaryl imines **3** derived from anilines **1** and α-furancarboxyaldehyde (or α-thiophenecarboxyaldehyde, and γ-pyridinecarboxyaldehyde) have been easily prepared. The 2-(α-furyl)quinolines **27**, **28**, and 2-(α-thienyl)quinolines **29**,**30** have been synthesized from the respective aldimines **3** and NVP via the protocols of a $BF_3 \cdot OEt_2$-catalyzed imino Diels–Alder reaction and an aromatization process[18] (route b).

The preparation of 2-(γ-pyridyl)quinoline derivatives **31**–**35** has been realized through a modified Povarov–Kametani reaction of the respective *N*-(γ-pyridyliden)anilines **3** with EVE (quinoline **31**) or with DMP (quinolines **32**–**35**) in dichloromethane in the presence of $BF_3 \cdot OEt_2$[19] (route c). New 5-nitro substituted quinolines **36**,**37** have been obtained by regioselective nitration (nitrating mixture, 0–5 °C) of the respective quinolines **33**,**35**. The 33 synthesized quinolines have been divided into two groups according to their chemical structure, looking mainly at the chemical nature of the C-2 substituent. Group 1 includes simple phenyl substituted quinolines **5**–**17** and quinolines with a 3,4-methylenedioxyphenyl moiety **18**–**26**, alkaloid dubamine structural analogues. Group 2 includes hetaryl substituted quinolines **26**–**37** (Table 1). Molecules of group 1 can be considered as derivatives from quinoline **A**, while second group compounds as derivatives from quinoline **B**.

2.2. Antifungal assays

The minimum inhibitory concentrations (MIC) of quinolines **5**–**37** were determined in the range of concentrations from 250 to 0.98 μg/mL. The standardized microbroth dilution methods, M-27 A2 for yeasts and M-38 A for filamentous fungi, were used according to the guidelines of Clinical and Laboratory Standards Institute (CLSI, formerly National Committee for Clinical and Laboratory Standards NCCLS), which assure confident and reproducible results.[20] Table 2 summarizes the minimum concentration of each quinoline derivative necessary to completely inhibit (MIC_{100}) the growth of nine standardized opportunistic pathogenic fungi including yeasts (*Candida albicans*, *Cryptococcus neoformans*, and *Saccharomyces cerevisiae*), hialohyphomycetes (*Aspergillus* spp.) as well as dermatophytes (*Microsporum* and *Trichophyton* spp.). The structure of each quinoline is included in Table 2, allowing a better analysis of results.

Regarding the activity showed by prepared quinolines against yeasts, only compound **5** out of the 22 compounds of group 1 showed about eight times better antifungal properties (MIC = 31.2 μg/mL) than the model compound **A** (MIC = 250 μg/mL) against *C. neoformans*. Within the 11 compounds of group 2, quinolines **31** and **32** showed good activity (MIC = 25–50 μg/mL) against *C. neoformans* and, in contrast to the behavior of **B**, they did inhibit *C. albicans* and *S. cerevisiae* (MIC range = 50–100 μg/mL).

The fact that these three active quinolines inhibit *C. neoformans* is highly interesting because this fungus remains an important life-threatening complication for immunocompromised hosts. The fungus is the main cause of fatal meningoencephalitis in AIDs patients, and new compounds acting against this fungus are highly welcome.[1,21]

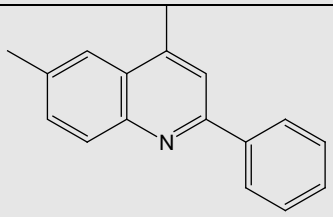
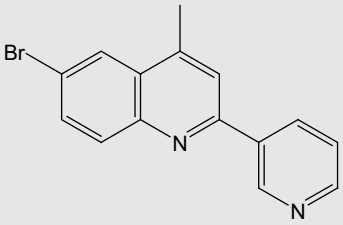
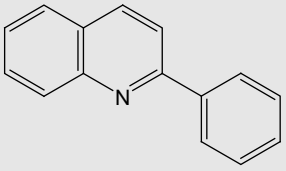
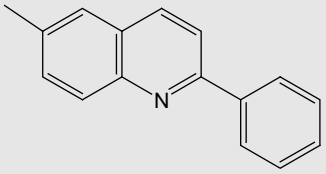
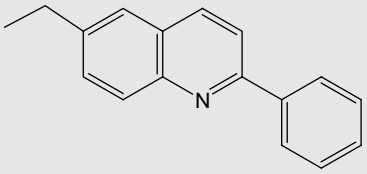
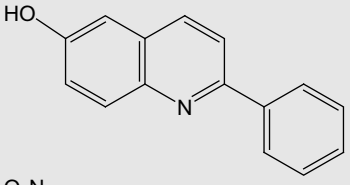
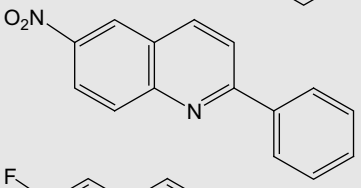
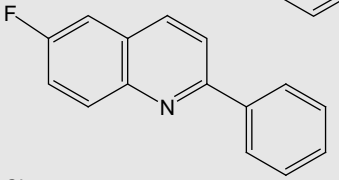
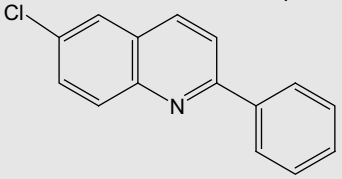
In turn, to inhibit species of *Candida* genus is also an interesting finding because candidiasis is the fourth most common nosocomial blood stream infection, *C. albicans* representing more than 60% of all isolates from clinical infections.[22]

Regarding the behavior of quinolines **5**–**37** against dermatophytes, only two molecules **33** and **35** showed very good activity (MICs = 12.5 μg/mL) against the three fungi tested, similar than that showed by compound **B**.

From the analysis of the structures and the activities displayed, some relationships can be extracted: (a) the quinoline moiety is not by itself sufficient for antifungal activity as this is clearly suggested by the lack of activity of many compounds of groups 1 and 2; (b) within group 1, the 2-phenyl quinoline skeleton without any substituent (compound **5**) was the most active against *C. neoformans* (MIC = 31 μg/mL) and displayed a very good activity against dermatophytes (MICs = 16–25 μg/mL); (c) within the structures possessing an hetaryl substituent at C-2 position (group 2), structures with an α-furan or α-thiophene moieties (compounds **27**–**30**) appeared to be inactive. In contrast, four (**31**–**33**, **35**) out of the seven 2-(γ-pyridyl) quinolines (**31**–**37**) showed interesting antifungal activities. Those without substituents on the quinoline skeleton (compound **31**) or with a methyl in the C-4 position (compound **32**) act against all fungi tested including yeasts (MIC = 25–100 μg/mL) *Aspergillus* spp. (MIC = 50–100 μg/mL), and dermatophytes (MIC = 25–50 μg/mL). Interesting enough, 4-methyl-8-substituted (methyl or isopropyl) quinolines (**33** and **35**) displayed the best antifungal activities (MIC = 12.5 μg/mL) but with a lower spectrum of action (active only against dermatophytes).

In order to correlate the qualitative structure–activity relationships described above, with quantitative parameters, we calculated log*P* and pK_a for all 2-arylquinolines (**5**–**37**)[23] and attempted to find a relationship between these values and their MICs against two sensitive fungi, a yeast (*C. neoformans*) and a filamentous fungus (*T. mentagrophytes*), which are clinically important.

Table 2
Minimum inhibitory concentrations (MICs in μg/mL) of 2-substituted quinolines

Compound		*Ca*	*Sc*	*Cn*	*Afu*	*Afl*	*An*	*Mg*	*Tr*	*Tm*
A		>250	>250	250	>250	>250	>250	12.5	25	12.5
B		>250	>250	250	>250	>250	>250	12.5	12.5	12.5
Group 1										
5		250	125	31.2	>250	>250	>250	16	25	25
6		>250	>250	250	>250	>250	>250	250	250	250
7		>250	>250	>250	>250	>250	>250	250	250	250
8		>250	>250	>250	>250	>250	>250	125	125	250
9		>250	>250	>250	>250	>250	>250	>250	>250	>250
10		>250	>250	>250	>250	>250	>250	250	250	250
11		>250	>250	>250	>250	>250	>250	>250	>250	>250

(*continued on next page*)

Table 2 (*continued*)

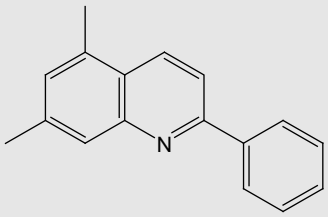
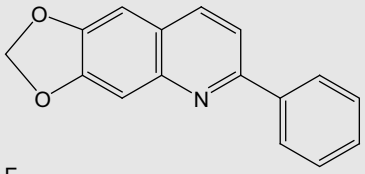
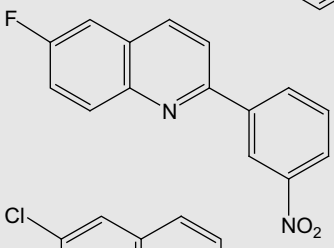
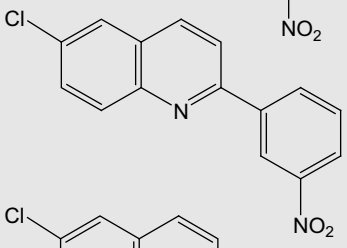
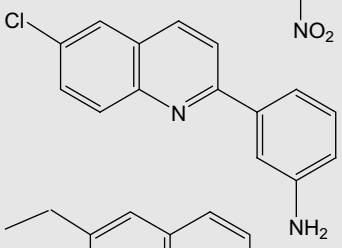
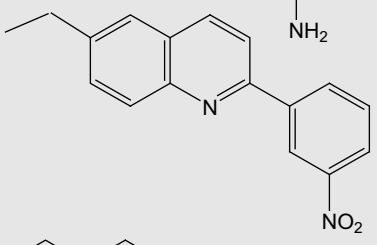
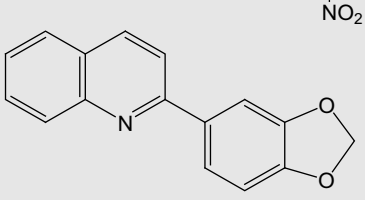
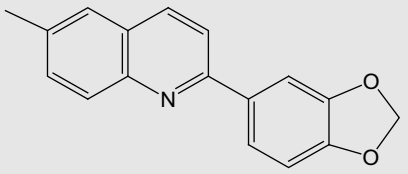
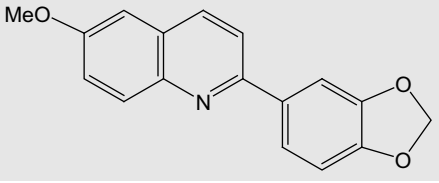
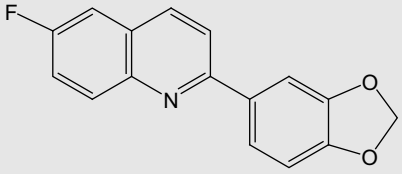
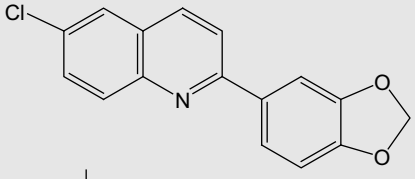
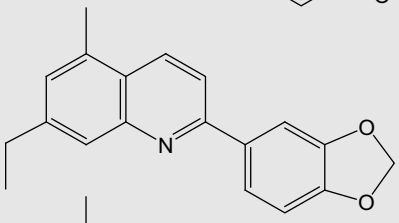
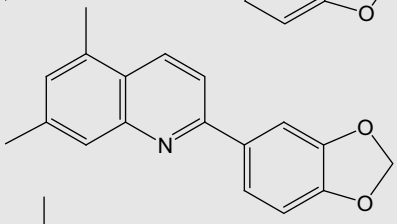
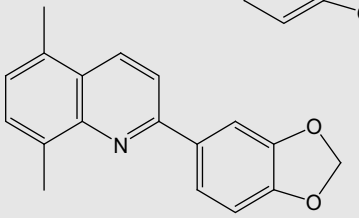
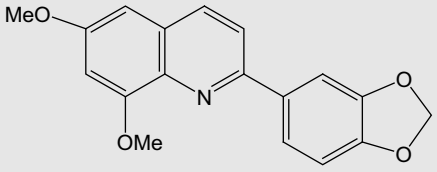
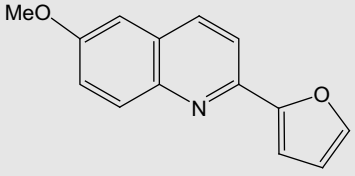
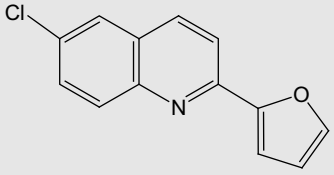
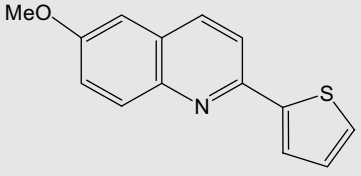
Compound		*Ca*	*Sc*	*Cn*	*Afu*	*Afl*	*An*	*Mg*	*Tr*	*Tm*
12		>250	>250	>250	>250	>250	>250	>250	>250	>250
13		>250	>250	125	>250	>250	>250	250	250	250
14		>250	>250	>250	>250	>250	>250	>250	>250	>250
15		>250	>250	>250	>250	>250	>250	>250	>250	>250
16		>250	>250	>250	>250	>250	>250	125	125	125
17		>250	>250	>250	>250	>250	>250	>250	>250	>250
18		>250	>250	>250	>250	>250	>250	>250	>250	>250
19		>250	>250	>250	>250	>250	>250	>250	>250	>250
20		>250	>250	>250	>250	>250	>250	>250	>250	>250

Table 2 (*continued*)

Compound		*Ca*	*Sc*	*Cn*	*Afu*	*Afl*	*An*	*Mg*	*Tr*	*Tm*
21		n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
22		n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
23		>250	>250	>250	>250	>250	>250	>250	>250	>250
24		n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
25		n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
26		>250	>250	>250	>250	>250	>250	>250	>250	>250
Group 2										
27		>250	>250	>250	>250	>250	>250	125	125	125
28		>250	>250	>250	>250	>250	>250	>250	>250	>250
29		>250	>250	>250	>250	>250	>250	>250	>250	>250

(*continued on next page*)

Table 2 (*continued*)

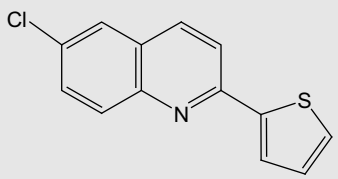
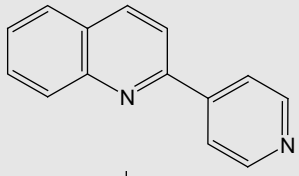
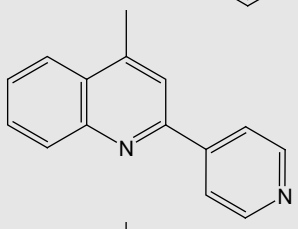
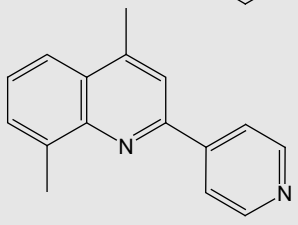
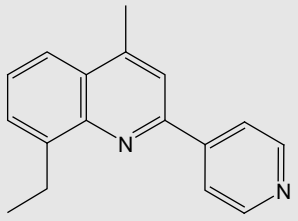
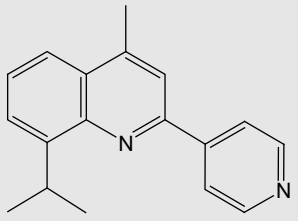
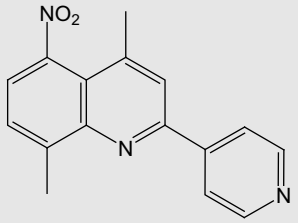
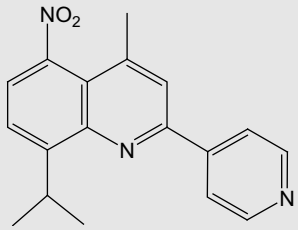
Compound		*Ca*	*Sc*	*Cn*	*Afu*	*Afl*	*An*	*Mg*	*Tr*	*Tm*
30		>250	>250	>250	>250	>250	>250	>250	>250	>250
31		100	50	50	50	50	50	50	50	50
32		100	50	25	50	100	200	25	25	25
33		>250	>250	>250	>250	>250	>250	12.5	12.5	12.5
34		>250	>250	>250	>250	>250	>250	>250	>250	>250
35		>250	>250	>250	>250	>250	>250	12.5	12.5	12.5
36		>250	>250	>250	>250	>250	>250	>250	>250	>250
37		>250	>250	>250	>250	>250	>250	>250	>250	>250

Table 2 (*continued*)

Compound	*Ca*	*Sc*	*Cn*	*Afu*	*Afl*	*An*	*Mg*	*Tr*	*Tm*
St drugs									
Amp	1	0.5	0.25	0.5	0.5	0.5	—	—	—
Keto	0.5	0.5	0.25	0.125	0.5	0.25	0.05	0.025	0.025
Terb	—	—	—	—	—	—	0.04	0.01	0.04

Amp, amphotericin B; Keto, ketoconazole; Terb, terbinafine; n.t., not tested; St, standard.

It is known that log*P* (the logarithm of the partition coefficient in a biphasic system, e.g. *n*-octanol/water) describes the macroscopic hydrophobicity of a molecule, which is a factor that determines its ability to penetrate the membranes of fungal cells and to reach the interacting sites, thus influencing the antifungal activity of compounds.[24] The comparison of log*P* values and MICs against *T. mentagrophytes* showed that the log*P* would not play a role in the antifungal activity since log*P* has similar values for active as well as for inactive compounds. As an example, active quinoline **1** and inactive quinoline derivatives **10**, **20**, **28**, and **34** possess similar log*P* values (about 3.90). Additionally, active compounds (**5**, **31**–**33**, and **35**) possess varied log*P* ranging from 2.51 (**31**) to 4.31 (**35**). The same can be concluded for the yeast *C. neoformans*.

Regarding the comparison of pK_a and MICs, the variation of basicity of quinolines did not appear to play a role in the activity neither. For example, compounds with completely different pK_a such as 2-phenylquinoline **5** (pK_a = 4.54) and 2-(γ-pyridyl)quinolines **31** or **32** (p$K_a \approx -0.50$) possess similar MICs (25–50 μg/mL) against *T. mentagrophytes* or *C. neoformans*.

From the data of both quantitative parameters pK_a and Log*P*, we can deduce that the lipophilicity or basicity of the quinolines tested would not have a direct influence into their antifungal activity.

2.3. Second-order studies with clinical isolates

In order to gain insight into the potential of active compounds not only against standardized strains but also on clinical isolates of medical important fungi, quinolines **5**, **31**, and **32** were tested against an extended panel of fungal strains isolated from patients suffering from mycoses. The % of inhibition displayed by each quinoline was determined at five concentrations: 100, 50, 25, 12.5, and 6.25 μg/mL.[25] So, compounds **5**, **31**, and **32** were tested at first against 10 isolates of *C. neoformans* and in turn structures **31** and **32** were tested against ten *Candida* strains including five clinical isolates of *C. albicans* and the rest, non-*albicans Candida* spp. These last spp. were included in the panel because there has been an increase in the percentage of non-*albicans Candida* infections in the last ten years, being *C. glabrata, C. tropicalis*, *C. parapsilosis*, and *C. krusei* the most isolated spp.[22] Results are shown in Table 3.

Results in *C. neoformans* showed that 2-(γ-pyridyl)quinolines **31** and **32** exert more than 75% inhibition on 10 out of the 11 *Cryptococcus* strains tested (that will be expressed as 10/11 in future) at 100 μg/mL, 6/11 at 50 μg/mL, 3/11 at 25 μg/mL, 2/11 at 12.5 μg/mL, and 1/11 at 6.25 μg/mL. Moreover, compounds **31** and **32** produce 50% inhibition on 11/11, 8/11, 8/11, 2/11, and 1/11 at the concentrations detailed above, respectively. In turn, quinoline **5** was active in the ten *Cryptococcus* strains tested, however with a lower effectivity, inhibiting 75 % of the growth of 6/11, 4/11, 1/11, 0/11, and 0/11 and 50 % of 10/11, 6/11, 0/11, 0/11, and 0/11 strains, at the different concentrations tested.

Regarding the activity against *Candida* isolates, it is clear that compounds **31** and **32** are better inhibitors of *C. albicans* and *C. tropicalis*, since the % of inhibition drastically drops below 100 μg/mL against *C. glabrata*, *C. parapsilosis*, and *C. krusei*. In addition, considering that compounds **33** and **35** displayed MICs as low as 12.5 μg/mL against the dermatophytes of the first panel (Table 2), they were tested against clinical isolates of *T. mentagrophytes* and *T. rubrum* (Table 4).

These two quinolines (**33** and **35**) displayed very strong activities (MICs' range: 7.8–31.25 μg/mL) against the 10 strains tested and, interesting enough, they completely inhibited 4/5 *T. rubrum* and 4/5 *T. mentagrophytes* strains at 7.8 μg/mL. These results are very encouraging since these fungi are responsible for approximately 80–93% of chronic and recurrent dermatophyte infections in human beings, which are very difficult to eradicate. They are the etiological agents of tinea unguium (producer of invasive nail infections), tinea manuum (palmar and interdigital areas of the hand infections), and tinea pedis (Athlete's foot), the last one being the most prevalent fungal infection in developed countries, and the first one accounting for 50% and 90% of all fingernail and toenail infections, respectively.[26]

3. Conclusion

We have synthesized, by a short and efficient pathway, a new series of quinoline derivatives possessing an aromatic substituent (carbocyclic or heterocyclic) at C-2 position. All of them were tested for antifungal properties against a panel of standardized fungi including yeasts, hyalohyphomycetes, and dermatophytes, at first. The most active quinoline molecules were then tested against a panel of clinical isolates in order to get an overview of their actual antifungal capacity. Results showed that the most active compounds were 2-hetaryl quinolines particularly those containing a γ-pyridyl ring. α-Furyl (α-thienyl) derivatives were devoid of antifungal properties. Nevertheless, it is clear that the activity is not due only to the 2-(γ-pyridyl) ring since quinolines **34**, **36** and **37** did not display any antifungal activity up to 250 μg/mL. The activity could be related to the C-4 and/or C-8 substitution on the quinoline ring and would not be related neither to the lipophilicity nor to the basicity of compounds. These results are important data for the design and synthesis of new quinoline derivatives, which could be hits for the development of antifungal agents.

4. Experimental

4.1. Chemistry

The melting points (uncorrected) were determined on a Fisher–Johns melting point apparatus. The IR spectra were recorded on a Lumex infralum FT-02 spectrophotometer in KBr. ^{1}H NMR spectra were recorded on Bruker AM-400 or AC-300 spectrometers. Chemical shifts are reported in ppm (δ) relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 ppm for protons). Signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; t, triplet; dt, doublet of triplets; td, triplet of doublets; q, quartet; quint., quintet; m, multiplet; br, broad. A Hewlett–Packard 5890a series II Gas Chromatograph interfaced to an HP 5972 mass selective detector (MSD) 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%-phenyl-poly(dimethyl-siloxane)]. Elemental analyses were performed on a Perkin–Elmer 2400 Series II analyzer, and were within ±0.4

Table 3
Antifungal activity (% inhibition) of selected 2-substituted quinolines against clinical isolates of *Candida* spp. and *C. neoformans*[a]

	Strain	Compound **5**					Compound **31**					Compound **32**					Amp (μg/mL)	Keto (μg/mL)
		Concentrations (μg/mL)					Concentrations (μg/mL)					Concentrations (μg/mL)					(μg/mL)	(μg/mL)
		100	50	25	12.5	6.25	100	50	25	12.5	6.25	100	50	25	12.5	6.25	6.25	6.25
Ca	ATCC 10231	0	0	0	0	0	100	73 ± 3	63 ± 3	41 ± 4	19 ± 3	100	73 ± 3	63 ± 3	41 ± 4	19 ± 3	100	100
Ca	C 126	—	—	—	—	—	69 ± 5	32 ± 4	0	0	0	69 ± 5	32 ± 4	0	0	0	100	100
Ca	C 127	—	—	—	—	—	80 ± 6	65 ± 5	0	0	0	80 ± 6	65 ± 5	0	0	0	100	100
Ca	C 128	—	—	—	—	—	88 ± 4	15 ± 3.6	0	0	0	88 ± 4	15 ± 3.6	0	0	0	100	100
Ca	C 129	—	—	—	—	—	85 ± 3	82 ± 4	50 ± 4	3 ± 0.2	0	85 ± 3	82 ± 4	50 ± 4	3 ± 0.2	0	100	100
Ca	C 130	—	—	—	—	—	84 ± 5	84 ± 4	48 ± 3	2 ± 0.7	0	84 ± 5	84 ± 4	48 ± 3	2 ± 0.7	0	100	100
Cg	C 115	—	—	—	—	—	75 ± 4	4 ± 1	4 ± 2	1 ± 0.1	0	75 ± 4	4 ± 1	4 ± 2	1 ± 0.1	0	100	100
Ct	C 131	—	—	—	—	—	100	75 ± 8	60 ± 7	54 ± 5	22 ± 3	100	75 ± 8	60 ± 7	54 ± 5	22 ± 3	100	100
Cp	C 124	—	—	—	—	—	55 ± 3	5 ± 3	0	0	0	55 ± 3	5 ± 3	0	0	0	100	100
Ck	C 117	—	—	—	—	—	66 ± 6	3 ± 2	0	0	0	66 ± 6	3 ± 2	0	0	0	100	100
Cn	ATCC 32264	100	100	77 ± 9	32 ± 4	0	100	100	100	90 ± 5	83 ± 6	100	100	100	90 ± 5	83 ± 6	100	100
Cn	IM 983040	50 ± 3	29 ± 3	13 ± 2	4 ± 1	0	45 ± 5	34 ± 6	12 ± 3	0	0	45 ± 5	34 ± 6	12 ± 3	0	0	100	100
Cn	IM 972724	99 ± 4	87 ± 8	35 ± 4	13 ± 1	0	74 ± 5	23 ± 4	8 ± 1	0	0	74 ± 5	23 ± 4	8 ± 1	0	0	100	100
Cn	IM 042074	84 ± 7	77 ± 4	33 ± 3	7 ± 1	0	92 ± 10	87 ± 12	87 ± 9	76 ± 7	68 ± 6	92 ± 10	87 ± 12	87 ± 9	76 ± 7	68 ± 6	100	100
Cn	IM 983036	32 ± 4	12 ± 3	0	0	0	79 ± 8	69 ± 9	45 ± 12	20 ± 2	0	79 ± 8	69 ± 9	45 ± 12	20 ± 2	0	100	100
Cn	IM 00319	47 ± 10	34 ± 2	14 ± 2	0	0	92 ± 3	80 ± 10	52 ± 3	32 ± 6	12 ± 1	92 ± 3	80 ± 10	52 ± 3	32 ± 6	12 ± 1	100	100
Cn	IM 972751	83 ± 9	54 ± 5	22 ± 4	0	0	98 ± 7	20 ± 3	9 ± 2	0	0	98 ± 7	20 ± 3	9 ± 2	0	0	100	100
Cn	IM 031631	74 ± 5	34 ± 3	15 ± 3	5 ± 2	0	100	75 ± 6	57 ± 12	36 ± 2	12 ± 3	100	75 ± 6	57 ± 12	36 ± 2	12 ± 3	100	100
Cn	IM 031706	67 ± 6	46 ± 4	17 ± 2	0	0	100	69 ± 4	57 ± 7	41 ± 5	21 ± 5	100	69 ± 4	57 ± 7	41 ± 5	21 ± 5	100	100
Cn	IM 961951	45 ± 4	32 ± 7	10 ± 3	0	0	97 ± 2	89 ± 8	78 ± 9	34 ± 3	4 ± 1	97 ± 2	89 ± 8	78 ± 9	34 ± 3	4 ± 1	100	100
Cn	IM 052470	88 ± 7	76 ± 11	35 ± 5	21 ± 3	0	99 ± 4	75 ± 5	53 ± 6	24 ± 2	0	99 ± 4	75 ± 5	53 ± 6	24 ± 2	0	100	100

Ca, *Candida albicans*; *Cg*, *C. glabrata*; *Ct*, *C. tropicalis*; *Cp*, *C. parapsilosis*; Ck, C. krusei; *Cn*, *Cryptococcus neoformans*; IM, Instituto Malbrán, Buenos Aires; ATCC, American Type Culture Collection, Manassas, USA; C, Reference Center in Mycology, Rosario, Argentina. Amp B, amphotericin B; Keto, ketoconazole.

[a] For the aim of comparison, standardized strains of *C. albicans* and *C. neoformans* are included in the table.

Table 4
Minimum inhibitory concentration (MIC_{100}, μg/mL) of quinolines **33** and **35** against clinical isolates of *Trichophyton* genus

Strain	Voucher sp.	Compound **33**	Compound **35**	Terb
T. rubrum	C 110	7.8	7.8	0.006
T. rubrum	C 133	15.6	15.6	0.006
T. rubrum	C 135	7.8	7.8	0.006
T. rubrum	C 136	7.8	7.8	0.006
T. rubrum	C 137	7.8	7.8	0.012
T mentagrophytes	C 131	31.25	15.6	0.006
T mentagrophytes	C 132	7.8	7.8	0.006
T mentagrophytes	C 364	7.8	7.8	0.006
T mentagrophytes	C 539	7.8	7.8	0.006
T mentagrophytes	C 943	7.8	7.8	0.006

C, Reference Center in Mycology (Rosario, Argentina); Terb, Terbinafine.

of theoretical values. The reaction progress was monitored using thin layer chromatography on a silufol UV254 TLC aluminum sheet.

4.1.1. Group 1. General procedure for synthesis of 2-arylquinolines 5–13, 18–26

To a solution of the appropriate aniline (1.00 mmol) and aldehyde (benzaldehyde or piperonal) (1 mmol) in anhydrous CH_3CN (15 mL) under N_2, 20 mol% $BiCl_3$ was added, and to the resulting mixture was added *N*-vinylpyrrolidone (2.0 mmol). The reaction mixture was stirred at gentle reflux for 4 h and then quenched with a solution of Na_2CO_3. The organic layer was separated, and dried with Na_2SO_4. The organic solvent was removed in vacuo to afford the respective 2-aryl-1,2,3,4-tetrahydroquinolines, which were purified or used in subsequent synthetic step without careful purification. The corresponding tetrahydroquinolines were heated quickly (10–15 min) in the presence of elemental sulfur S_8 to 220–230 °C, the reaction mixture was adsorbed under silica gel and separated by chromatography column to afford the 2-arylquinolines **5**–**13** and **18**–**20**.

4.1.1.1. 2-Phenylquinoline (5). White solid. Mp 67–69 °C. Yield 54 %. IR (KBr): *ν* 1589, 1473, 1439, 849, 748 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): *δ* 8.22 (1H, d, *J* = 8.6 Hz, 3-H), 8.19–8.16 (1H, m, 8-H), 8.19–8.16 (2H, m, 2′-H_{Ph} and 6′-H_{Ph}), 7.88 (1H, d, *J* = 8.6 Hz, 4-H), 7.83 (1H, d, *J* = 8.1 Hz, 5-H), 7.73 (1H, ddd, *J* = 7.2, 7.2, 0.7 Hz, 6-H), 7.55–7.52 (1H, m, 7-H), 7.55–7.52 (2H, m, 3′-H_{Ph} and 5′-H_{Ph}), 7.47 (1H, t, *J* = 7.2 Hz, 4′-H_{Ph}); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 157.3, 148.3, 139.7, 136.7, 129.7, 129.6, 129.2, 128.9 (2C), 127.5 (2C), 127.4, 127.1, 126.2, 118.9. MS *m*/*z* (EI) 205 (M^+). Found: C, 87.55; H, 5.67; N, 6.79. Calcd for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82.

4.1.1.2. 6-Methyl-2-phenylquinoline (6). Yellow solid. Mp 70–72 °C. Yield 62 %. IR (KBr): *ν* 2898, 1490, 1460, 1246, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): *δ* 8.16 (2H, dt, *J* = 7.2, 1.5 Hz, 2′-H_{Ph} and 6′-H_{Ph}), 8.11 (1H, d, *J* = 8.8 Hz, 3-H), 8.08 (1H, d, *J* = 8.37 Hz, 8-H), 7.83 (1H, d, *J* = 8.6 Hz, 4-H), 7.57 (1H, s, 5-H), 7.55–7.51 (1H, m, 7-H), 7.55–7.51 (2H, m, 3′-H_{Ph} and 5′-H_{Ph}), 7.46 (1H, tt, *J* = 7.3, 1.3 Hz, 4′-H_{Ph}), 2.55 (3H, s, 6-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 156.4, 146.8, 139.8, 136.1, 136.0, 131.9, 129.4, 129.1, 128.7 (2C), 127.4 (2C), 127.1, 126.3, 118.9, 21.5. MS *m*/*z* (EI) 219 (M^+). Found: C, 87.53; H, 6.14; N, 6.21. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39.

4.1.1.3. 6-Ethyl-2-phenylquinoline (7). White solid. Mp 63–66 °C. Yield 51%. IR (KBr): *ν* 2960, 2895, 1493, 1443 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): *δ* 8.17–8.13 (2H, m, 2′-H_{Ph} and 6′-H_{Ph}), 8.15–8.13 (1H, m, 3-H), 8.11 (1H, d, *J* = 9.3 Hz, 8-H), 7.84 (1H, d, *J* = 8.6 Hz, 4-H), 7.61–7.59 (1H, m, 5-H), 7.61–7.59 (1H, m, 7-H), 7.53 (2H, t, *J* = 7.1 Hz, 3′-H_{Ph} and 5′- H_{Ph}), 7.46 (1H, t, *J* = 7.3 Hz, 4′-H_{Ph}), 2.85 (2H, q, *J* = 7.6 Hz, CH_3-*CH_2*–), 1.36 (3H, t, *J* = 7.6 Hz, *CH_3*–CH_2–); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 156.5, 147.1, 142.3, 139.8, 136.2, 130.8, 129.5, 129.0, 128.7 (2C), 127.4 (2C), 127.2, 124.9, 118.9, 28.8, 15.3. MS *m*/*z* (EI) 233 (M^+). Found: C, 87.41; H, 6.33; N, 6.25. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00.

4.1.1.4. 6-Hydroxy-2-phenylquinoline (8). White solid. Mp 112–115 °C. Yield 56%. IR (KBr): *ν* 3456, 1592, 1537, 1476, 873 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): *δ* 8.01–8.10 (1H, m, 8H), 8.01–8.10 (2H, m, 2′-H_{Ph} and 6′-H_{Ph}), 7.83 (1H, d, *J* = 8.9 Hz, 3H), 7.75 (1H, d, *J* = 8.9 Hz, 4H), 7.53–7.54 (1H, m, 3′-H_{Ph} and 5′-H_{Ph}), 7.46 (1H, s, 5H), 7.45–7.48 (1H, m, 4′-H_{Ph}), 6.90 (1H, s, –OH); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 160.5, 149.6, 143.0, 139.2, 129.7, 128.2, 127.1, 126.6 (2C), 126.4, 124.8 (2C), 123.6, 118.7, 113.7. MS *m*/*z* (EI) 221 (M^+). Found: C, 81.15; H, 5.34; N, 6.12. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33.

4.1.1.5. 6-Nitro-2-phenylquinoline (9). Brown solid. Mp 175–178 °C. Yield 56%. IR (KBr): *ν* 3456, 1592, 1537, 1476, 873 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): *δ* 8.78 (1H, d, *J* = 2.4 Hz, 6-H), 8.47 (1H, dd, *J* = 9.2, 2.5 Hz, 7-H), 8.37 (1H, d, *J* = 8.7 Hz, 3-H), 8.26 (1H, d, *J* = 9.2 Hz, 8-H), 8.22–8.20 (2H, m, 2′-H_{Ph} and 6′-H_{Ph}), 7.56–7.54 (2H, m, 3′-H_{Ph} and 5′-H_{Ph}), 7.48–7.50 (1H, m, 4′-H_{Ph}); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 160.6, 150.4, 138.4, 131.4, 130.5, 129.0 (2C), 127.8 (2C), 127.5, 127.4, 124.3, 123.2, 120.6, 77.0. MS *m*/*z* (EI) 250 (M^+). Found: C, 71.78; H, 4.27; N, 11.05. Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19.

4.1.1.6. 6-Fluoro-2-phenylquinoline (10). Beige solid. Mp 128–131 °C. Yield 58 %. IR (KBr): *ν* 1484, 1231, 831, 750, 686 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): *δ* 8.19–8.15 (1H, m, 8-H), 8.19–8.15 (2H, m, 2′-H_{Ph} and 6′-H_{Ph}), 8.15–8.13 (1H, m, 3-H), 7.86 (1H, d, *J* = 8.7 Hz, 4-H), 7.56–7.52 (2H, m, 3′-H_{Ph} and 5′- H_{Ph}), 7.50–7.46 (1H, m, 7-H), 7.50–7.46 (1H, m, 5-H), 7.43 (1H, dd, *J* = 8.8, 2.8 Hz, 4′-H_{Ph}); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 161.7, 156.7, 145.5, 139.4, 135.9, 132.2, 129.4, 128.8 (2C), 127.4 (2C), 119.8, 119.6, 110.5, 110.3. MS *m*/*z* (EI) 223 (M^+). Found: C, 80.66; H, 4.75; N, 6.39. Calcd for $C_{15}H_{10}FN$: C, 80.70; H, 4.51; N, 6.27.

4.1.1.7. 6-Chloro-2-phenylquinoline (11). Beige solid. Mp 134–137 °C. Yield 50%. IR (KBr): *ν* 1495, 1223, 835, 752, 687 cm^{-1}. ^1H NMR ($CDCl_3$, $CDCl_3$, 400 MHz): *δ* 8.16–8.14 (1H, m, 3-H), 8.16–8.14 (1H, m, 8-H), 8.11 (2H, d, *J* = 7.8 Hz, 2′-H_{Ph} and 6′-H_{Ph}), 7.89 (1H, d, *J* = 8.5 Hz, 4-H), 7.80 (1H, d, *J* = 2.3 Hz, 6-H), 7.65 (1H, dd, *J* = 9.0, 2.3 Hz, 7-H), 7.53 (2H, t, *J* = 7.5 Hz, 3′-H_{Ph} and 5′-H_{Ph}), 7.47 (1H, t, *J* = 7.2 Hz, 4′-H_{Ph}); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 157.5, 146.6, 139.2, 135.8, 131.9, 131.3, 130.5, 129.5, 128.9 (2C), 127.7 (2C), 127.5, 126.1, 119.7. MS *m*/*z* (EI) 239 (M^+). Found: C, 75.01; H, 4.44; N, 5.82. Calcd for $C_{15}H_{10}ClN$: C, 75.16; H, 4.21; N, 5.84.

4.1.1.8. 5,7-Dimethyl-2-phenylquinoline (12). White solid. Mp 71–74 °C. Yield 70%. IR (KBr): *ν* 3014, 2974, 1589, 1473, 1439 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): *δ* 8.32 (1H, d, *J* = 8.8 Hz, 3-H), 8.17 (2H, dd, *J* = 7.2 Hz, 2′-H_{Ph} and 6′-H_{Ph}), 7.83 (1H, s, 8-H), 7.81 (1H, d, *J* = 8.8 Hz, 4-H), 7.53 (2H, t, *J* = 7.0 Hz, 3′-H_{Ph} and 5′-H_{Ph}), 7.46 (1H, t, *J* = 7.1 Hz, 4′-H_{Ph}), 7.19 (1H, s, 6-H), 2.66 (3H, s, 7-CH_3), 2.53 (3H, s, 5-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 156.7, 148.8, 139.8, 139.4, 133.9, 132.9, 129.1, 129.0, 128.7 (2C), 127.4 (2C), 127.0, 124.5, 117.6, 21.8, 18.4. MS *m*/*z* (EI) 233 (M^+). Found: C, 87.33; H, 6.60; N, 6.13. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00.

4.1.1.9. 6,7-(Methylenedioxy)-2-phenylquinoline (13). Beige solid. Mp 109–111 °C. Yield 54%. IR (KBr): *ν* 1457, 1228, 1029, 849, 748 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): *δ* 8.11 (2H, dd, *J* = 7.1, 1.5 Hz, 2′-H_{Ph} and 6′-H_{Ph}), 7.98 (1H, d, *J* = 8.5 Hz, 3-H), 7.69 (1H, d, *J* = 8.5 Hz, 4-H), 7.51 (2H, dd, *J* = 7.1, 1.7 Hz, 3′-H_{Ph} and 5′-H_{Ph}),

7.46 (1H, s, 8-H), 7.03 (1H, s, 5-H), 6.08 (2H, s, –OCH_2O–); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.2, 150.7, 147.6, 146.4, 139.7, 135.4, 128.8, 128.7 (2C), 127.1 (2C), 124.0, 117.1, 106.1, 102.4, 101.6. MS *m*/*z* (EI) 249 (M^+). Found: C, 77.18; H, 4.55; N, 5.54. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62.

4.1.1.10–4.1.1.13 Quinolines **14**–**17** were prepared by our published protocol.[17]

4.1.1.14. 2-(3′,4′-Methylenedioxyphenyl)quinoline (18) (alkaloid dumanine). Yellow solid. Mp 90–92 °C. Yield 50%. IR (KBr): ν 2884, 1594, 1495, 1248, 1042 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.16 (1H, d, *J* = 8.6 Hz, 3-H), 8.12 (1H, d, *J* = 8.5 Hz, 4-H), 7.80 (1H, m, 8-H), 7.77 (1H, m, 5-H), 7.74 (1H, d, *J* = 1.7 Hz, 2′-H_{Ph}), 7.70 (1H, ddd, *J* = 8.4, 8.4, 1.5 Hz, 7-H), 7.65 (1H, dd, *J* = 8.0, 1.7 Hz, 6′-H_{Ph}), 7.50 (1H, ddd, *J* = 8.1, 8.0, 1.1 Hz, 6-H), 6.95 (1H, d, *J* = 8.1 Hz, 5′-H_{Ph}), 6.03 (2H, s, —OCH_2O—); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.6, 148.8, 148.4, 148.2, 136.6, 134.1, 129.6, 129.5, 127.4, 127.0, 126.0, 121.7, 118.5, 108.4, 107.9, 101.3. MS *m*/*z* (EI) 249 (M^+). Found: C, 77.24; H, 4.60; N, 5.49. Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62.

4.1.1.15. 2-(3′,4′-Methylenedioxyphenyl)-6-methylquinoline (19). Yellow solid. Mp 166–168. Yield 41%. IR (KBr): ν 2898, 1587, 1490, 1460, 1246 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.07 (1H, d, *J* = 8.6 Hz, 3-H), 8.00 (1H, d, *J* = 8.6 Hz, 4-H), 7.74 (1H, d, *J* = 8.6 Hz, 8-H), 7.72 (1H, d, *J* = 1.7 Hz, 2′-H_{Ph}), 7.63 (1H, dd, *J* = 8.3, 1.7 Hz, 6′-H_{Ph}), 6.92 (1H, d, *J* = 8.3 Hz, 5′-H_{Ph}), 7.54 (1H, m, 7-H), 7.52 (1H, d, *J* = 1.7 Hz, 5-H), 6.03 (2H, s, —OCH_2O—), 2.53 (3H, s, 6-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 148.7, 148.4, 146.8, 136.0, 135.9, 134.3, 131.9, 129.3, 127.0, 126.3, 121.6, 118.6, 108.4, 107.9, 101.3, 21.5. MS *m*/*z* (EI) 263 (M^+). Found: C, 77.36; H, 5.11; N, 5.22. calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32.

4.1.1.16. 2-(3′,4′-Methylenedioxyphenyl)-6-methoxyquinoline (20). Brown solid. Mp 139–141. Yield 59 %. IR (KBr): ν 2960, 2037, 1612, 1588, 1489 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.06 (1H, d, *J* = 8.6 Hz, 3-H), 8.02 (1H, d, *J* = 9.2 Hz, 4-H), 7.69 (1H, d, *J* = 1.7 Hz, 2′-H_{Ph}), 7.61 (1H, dd, *J* = 8.1, 1.7 Hz, 6′-H_{Ph}), 7.74 (1H, d, *J* = 8.6 Hz, 8-H), 7.36 (1H, dd, *J* = 9.3, 2.8 Hz, 7-H), 7.07 (1H, d, *J* = 2.8 Hz, 5-H), 6.93 (1H, d, *J* = 8.1 Hz, 5′-H_{Ph}), 6.03 (2H, s, —OCH_2O—), 3.94 (3H, s, 6-OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.3, 151.3, 150.1, 146.2, 145.9, 133.0, 127.4, 127.3, 126.5, 126.4, 124.1, 115.6, 114.6, 113.7, 113.4, 101.1, 55.4. MS *m*/*z* (EI) 279 (M^+). Found: C, 73.27; H, 4.83; N, 4.88. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02.

4.1.1.17. 2-(3′,4′-Methylenedioxyphenyl)-6-fluoroquinoline (21). Yellow solid. Mp 153–155. Yield 56 %. IR (KBr): ν 2899, 1585, 1236, 833, 752 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (1H, dd, *J* = 9.3, 5.4 Hz, 8-H), 8.07 (1H, d, *J* = 8.4 Hz, 3-H), 7.77 (1H, d, *J* = 8.6 Hz, 4-H), 7.71 (1H, d, *J* = 1.7 Hz, 2′-H_{Ph}), 7.62 (1H, dd, *J* = 8.1, 1.8 Hz, 6′-H_{Ph}), 7.46 (1H, ddd, *J* = 8.8, 8.8, 2.9 Hz, 7-H), 7.38 (1H, dd, *J* = 8.8, 2.8 Hz, 5-H), 6.93 (1H, d, *J* = 8.1 Hz, 5′-H_{Ph}), 6.03 (2H, s, —OCH_2O—); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.8, 148.4, 145.2, 135.9, 133.7, 131.9, 127.3, 121.5, 119.8, 119.5, 119.2, 110.5, 110.2, 108.4, 107.7, 101.3. MS *m*/*z* (EI) 267 (M^+). Found: C, 71.69; H, 3.94; N, 5.15. Calcd for $C_{16}H_{10}FNO_2$: C, 71.91; H, 3.77; F, N, 5.24.

4.1.1.18. 2-(3′,4′-Methylenedioxyphenyl)-6-chloroquinoline (22). Yellow solid. Mp 150–152. Yield 54 %. IR (KBr): ν 2957, 1584, 833, 757, 685 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.08 (1H, d, *J* = 8.8 Hz, 3-H), 8.04 (1H, d, *J* = 9.0 Hz, 8-H), 7.81 (1H, d, *J* = 8.7 Hz, 4-H), 7.78 (1H, d, *J* = 2.3 Hz, 6-H), 7.72 (1H, d, *J* = 1.7 Hz, 2′-H_{Ph}), 7.65–7.62 (2H, m, 7-H and 6′-H_{Ph}), 6.94 (1H, d, *J* = 8.1 Hz, 5′-H_{Ph}), 6.04 (2H, s, —OCH_2O—); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.4, 150.0, 146.2, 144.2, 133.0, 130.5, 131.0, 128.8, 127.4, 127.1, 126.4, 125.5, 124.4, 113.7, 113.4, 101.1. MS *m*/*z* (EI) 283 (M^+). Found: C, 67.59; H, 3.76; N, 4.75. Calcd for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; Cl, 12.50; N, 4.94.

4.1.1.19. 2-(3′,4′-Methylenedioxyphenyl)-7-ethylquinoline (23). Yellow solid. Mp 175–177. Yield 40 %. IR (KBr): ν 2959, 2898, 1585, 1490, 1442 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.16 (1H, d, *J* = 8.6 Hz, 3-H), 8.12 (1H, d, *J* = 8.7 Hz, 4-H), 7.8 (1H, d, *J* = 1.8 Hz, 2′-H_{Ph}), 7.77 (1H, d, *J* = 8.0 Hz, 5-H), 7.68 (1H, dd, *J* = 8.1, 1.74 Hz, 6′-H_{Ph}), 7.50 (1H, d, *J* = 1.6 Hz, 8-H), 7.49 (1H, dd, *J* = 8.0, 1.4 Hz, 6-H), 7.08 (1H, d, *J* = 8.1, 5′- H_{Ph}), 5.94 (2H, s, —OCH_2O—), 1.84 (2H, q, *J* = 8.0 Hz, 8-CH_2CH_3–), 1.18 (3H, t, *J* = ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.4, 150.0, 146.2, 144.2, 133.0, 130.5, 131.0, 128.8, 127.4, 127.1, 126.4, 125.5, 124.4, 113.7, 113.4, 101.1. Hz, 8-CH_2CH_3–). MS *m*/*z* (EI) 277 (M^+). Found: C, 77.75; H, 5.67; N, 5.18. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05.

4.1.1.20. 2-(3′,4′-Methylenedioxyphenyl)-5,8-dimethylquinoline (24). Yellow solid. Mp 170–173. Yield 58 %. IR (KBr): ν 2896, 1591, 1487, 1463, 1251 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.28 (1H, d, *J* = 8.8 Hz, 3-H), 7.88 (1H, d, *J* = 1.7 Hz, 2′-H_{Ph}), 7.81 (1H, d, *J* = 8.8 Hz, 4-H), 7.73 (1H, dd, *J* = 8.2, 1.7 Hz, 6′-H_{Ph}), 7.44 (1H, d, *J* = 7.1 Hz, 7-H), 7.20 (1H, d, *J* = 7.1 Hz, 6-H), 6.95 (1H, d, *J* = 8.1 Hz, 5′-H_{Ph}), 6.04 (2H, s, —OCH_2O—), 2.84 (3H, s, 5-CH_3), 2.64 (3H, s, 8-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.3, 147.6, 147.4, 146.2, 140.6, 136.9, 135.9, 132.9, 132.3, 127.4, 126.4, 125.7, 124.4, 113.7, 113.3, 101.1, 28.1, 15.5. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.2, 148.6, 148.3, 147.2, 135.3, 134.4, 133.2, 131.8, 129.2, 126.2, 126.1, 121.4, 117.1, 108.3, 107.8, 101.2, 18.3, 17.8. MS *m*/*z* (EI) 277 (M^+). Found: C, 77.94; H, 5.66; N, 4.93. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05.

4.1.1.21. 2-(3′,4′-Methylenedioxyphenyl)-5,7-dimethylquinoline (25). Yellow solid. Mp 115–117. Yield 60 %. IR (KBr): ν 2896, 1590, 1480, 1436, 1244 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.27 (1H, d, *J* = 8.8 Hz, 3-H), 7.77 (1H, br.s, 8-H), 7.74–7.72 (1H, m, 2′-H_{Ph} and 5′-H_{Ph}), 7.65 (1H, dd, *J* = 8.1, 1.7 Hz, 6′-H_{Ph}), 7.17 (1H, br.s, 6-H), 6.95 (1H, d, *J* = 8.1 Hz, 4-H), 6.03 (2H, s, —OCH_2O—), 2.65 (3H, s, 7-CH_3), 2.52 (3H, s, 5-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.3, 148.8, 147.3, 146.2, 144.5, 143.8, 132.9, 129.2, 127.8, 126.4, 125.1, 123.8, 123.6, 113.7, 113.3, 101.1, 21.5, 20.1. MS *m*/*z* (EI) 277 (M^+). Found: C, 77.88; H, 5.63; N, 5.10. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05.

4.1.1.22. 2-(3′,4′-Methylenedioxyphenyl)-6,8-dimethoxyquinoline (26). Yellow solid. Mp 146–148. Yield 62 %. IR (film): ν 2955, 2899, 1607, 1478, 1451 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.02 (1H, d, *J* = 8.7 Hz, 3-H), 7.76 (1H, d, *J* = 8.6 Hz, 4-H), 7.71 (1H, d, *J* = 1.7 Hz, 2′-H_{Ph}), 7.62 (1H, dd, *J* = 8.1, 1.8 Hz, 6′-H_{Ph}), 6.91 (1H, d, *J* = 8.07 Hz, 5′-H_{Ph}), 6.71 (1H, d, *J* = 2.5 Hz, 5-H), 6.65 (1H, d, *J* = 2.5 Hz, 7-H), 6.01 (2H, s, —OCH_2O—), 4.05 (1H, s, 8-OCH_3), 3.92 (1H, s, 6-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.0, 156.4, 153.3, 148.3, 148.2, 136.6, 135.5, 134.4, 128.6, 121.3, 119.4, 108.3, 107.8, 101.5, 101.2, 96.8, 56.1, 55.5. MS *m*/*z* (EI) 309 (M^+). Found: C, 69.55; H, 4.99; N, 4.32. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53.

4.1.2. Group 2

4.1.2.1–4.1.2.4. Quinolines **27**–**30** were prepared by our published protocol.[18]

4.1.2.5. 2-(Pyridin-4-yl)quinoline (31). To a solution of the appropriate aldimine **3** (1.00 mmol) in anhydrous CH_2Cl_2 (15 mL) was cooled to 0 °C. Over a period of 20 min, $BF_3 \cdot OEt_2$(0.39 g;

2.8 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature, and EVE (0.70 g; 9.8 mmol) in CH_2Cl_2 (10 mL) was then rapidly added with vigorous stirring. The reaction mixture was stirred at gentle reflux for 10 h and then quenched with a solution of Na_2CO_3. The organic layer was separated, and dried with Na_2SO_4. The organic solvent was removed in vacuo. The residue was purified by chromatography column (silica gel) to afford the respective 2-pyridylquinoline **31** as a yellow solid. Mp 90–93 °C. Yield 73 %. IR (KBr): ν 3038, 2947 cm^{-1}. ^1H RMN ($CDCl_3$, 400 MHz) δ 8.83 (2H, d, J = 4.6 Hz, $H_{\alpha\text{-Py}}$ and $H_{\alpha'\text{-Py}}$), 8.31 (1H, d, J = 8.6 Hz, 3-H), 8.21 (2H, dd, J = 4.8, 1.3 Hz, $H_{\beta\text{-Py}}$ and $H_{\beta'\text{-Py}}$), 7.98 (1H, d, J = 8.3 Hz, 4-H), 7.75 (1H, br. d, J = 8.1 Hz, 5-H), 7.67 (1H, br. d, J = 6.8 Hz, 7-H), 7.53 (1H, t, J = 7.6 Hz, 6-H), 2.97 (3H, s, 8-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.4 (2C), 150.6, 149.1, 142.0, 134.3, 129.9, 128.5, 125.4, 125.1, 124.7, 123.2, 120.4 (2C). MS m/z (EI) 206 (M^+). Found: C, 81.54; H, 4.91; N, 13.62. Calcd for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58.

4.1.2.6–4.1.2.9. 4-Methyl-2-(pyridin-4-yl)quinolines **32**–**35** were prepared by our published protocol.[19]

General procedure for synthesis of 4-methyl-5-nitroquinolines 36, 37. To a solution of the corresponding 4-methylquinolines **33**,**35** (1.00 mmol) in H_2SO_4 (15 mL) was added KNO_3. The resulting mixture was stirred at room temperature for 24 h and then neutralized with a solution of NaOH 1 N. The organic layer was separated with CH_2Cl_2, and dried with Na_2SO_4. The organic solvent was removed in vacuo. The residue was purified by chromatography column (silica gel) to afford the respective 4-methyl-5-nitroquinolines **36**,**37**.

4.1.2.10. 4,8-Dimethyl-5-nitro-2-(pyridin-4-yl)quinoline (36). Yellow solid. Mp 169–172 °C.; IR (KBr): 1354, 1510 cm^{-1}. ^1H RMN ($CDCl_3$, 400 MHz) δ 8.85 (2H, dd, J = 4.5, 1.5 Hz, $H_{\alpha-Py}$ and $H_{\alpha'\text{-Py}}$), 8.21 (2H, dd, J = 4.5, 1.5 Hz, $H_{\beta\text{-Py}}$ and $H_{\beta'\text{-Py}}$), 7.92 (1H, d, J = 0.8 Hz, 3-H), 7.74 (1H, d, J = 7.8 Hz, 6-H), 7.66 (1H, dd, J = 7.7, 1.0 Hz, 7-H), 2.99 (3H, d, J = 0.8 Hz, 4-CH_3), 2.69 (3H, d, J = 0.8 Hz, 8-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.4 (2C), 151.1, 151.0, 145.6, 144.1, 143.2, 139.6, 134.8, 130.2, 123.5, 119.6 (2C), 113.8, 19.4, 18, 0. MS m/z (EI) 279 (M^+). Found: C, 68.77; H, 4.83; N, 15.13. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05.

4.1.2.11. 8-Isopropyl-5-nitro-2-(pyridin-4-yl)quinoline (37). Yellow solid. Mp 177–180 °C. IR (KBr): 1352, 1592 cm^{-1}. ^1H RMN ($CDCl_3$, 400 MHz) δ 8.87 (2H, dd, J = 4.5, 1.5 Hz, $H_{\alpha-Py}$ and $H_{\alpha'\text{-Py}}$), 8.24 (2 H, dd, J = 4.9, 1.9 Hz, $H_{\beta\text{-Py}}$ and $H_{\beta'\text{-Py}}$), 7.93 (1H, d, J = 0.8 Hz, 3-H), 7.81 (1H, d, J = 7.9 Hz, 6-H), 7.70 (1H, d, J = 8.1 Hz, 7-H), 4.56 (1H, sep, J = 6.7 Hz, 8-$CH(CH_3)_2$), 2.70 (3H, d, J = 0.8, 4-CH_3), 1.48 (6H, d, J = 6.9 Hz, 8-$CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.0, 151.9, 151.4 (2C), 145.1, 144.3, 144.0, 142.8, 132.1, 129.8, 123.3, 119.8 (2C), 112.5, 31.6, 23.5 (2C), 19.4. MS m/z (EI) 307 (M^+). Found: C, 70.15; H, 5.87; N, 13.58. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67.

4.2. Antifungal evaluation

4.2.1. Microorganisms and media

For the antifungal evaluation, standardized strains from the American Type Culture Collection (ATCC), Rockville, MD, USA, and Reference Center in Mycology (CEREMIC, C, Rosario, Argentina) were used. *Candida albicans* ATCC 10231, *S. cerevisiae* ATCC 9763, *C. neoformans* ATCC 32264, *Aspergillus flavus* ATCC 9170, *A. fumigatus* ATTC 26934, *A. niger* ATCC 9029, *Trichophyton rubrum* C 110, *T. mentagrophytes* ATCC 9972, and *M. gypseum* C 115.

Clinical isolates were provided by CEREMIC and Malbrán Institute [(IM), Av. Velez Sarsfield 563, Buenos Aires]. The isolates included nine strains of *Candida* genus, 10 strains of each *C. neoformans* and *Trichophyton* genus, which *voucher specimens* are presented in Tables 3 and 4. Strains were grown on Sabouraud-chloramphenicol agar slants for 48 h at 30 °C, and were maintained on slopes of Sabouraud-dextrose agar (SDA, Oxoid) and sub-cultured every 15 days to prevent pleomorphic transformations. Inocula were obtained according to reported procedures and adjusted to $1–5 \times 10^3$ cells/spores with colony forming units (CFU)/mL.[20]

4.2.2. Antifungal susceptibility testing

4.2.2.1. MIC determinations. Minimum inhibitory concentration of each quinoline was determined by using broth microdilution techniques according to the guidelines of CLSI (formerly NCCLS).

MIC values were determined in RPMI-1640 (Sigma, St. Louis, Mo, USA) buffered to pH 7.0 with MOPS. Microtiter trays were incubated at 35 °C in a moist, dark chamber, and MICs were visually recorded at 48 h. For the assay, stock solutions of pure compounds were twofold diluted with RPMI from 250 to 0.98 μg/mL (final volume = 100 μL) and a final DMSO concentration $\leqslant$ 2%. A volume of 100 μL of inoculum suspension was added to each well with the exception of the sterility control where sterile water was added to the well instead. Ketoconazole, Amphotericin B (Sigma Chemical Co, St Louis, MO, USA), and Terbinafine (Novartis, Buenos Aires) were used as positive controls.

Endpoints were defined as the lowest concentration of drug resulting in total inhibition (MIC_{100}) of visual growth compared to the growth in the control wells containing no antifungal.

4.2.2.2. Determination of percentages of fungal growth inhibition. The test was performed in 96-wells microplates. Quinoline test wells (QTW) were prepared with stock solutions of each quinoline in DMSO ($\leqslant$ 2%), diluted with RPMI-1640 to final concentrations 100–6.25 μg/mL. Inoculum suspension (100 μL) was added to each well (final volume in the well = 200 μL). A growth control well (GCW) (containing medium, inoculum, the same amount of DMSO used in QTW, but compound-free) and a sterility control well (SCW) (sample, medium, and sterile water instead of inoculum) were included for each strain tested. Microtiter trays were incubated in a moist, dark chamber at 35 °C, 24 or 48 h for *Candida* spp or *Cryptococcus* sp., respectively. Microplates were read in a VERSA Max microplate reader (Molecular Devices, Sunnyvale, CA, USA). Amphotericin B and Ketoconazole were used as positive controls (100% inhibition at the concentration tested). Tests were performed by triplicate. Reduction of fungal growth due to each quinoline concentration was calculated as follows: % of inhibition: $100 - (OD_{405}\,PTW - OD_{405}\,SCW)/OD_{405}\,GCW - OD_{405}\,SCW$.

4.2.2.3. Statistical analysis. Data were statistically analyzed by one-way analysis of variance. A $p < 0.05$ was considered significant.

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