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Antifungal properties of new series of quinoline derivatives

Robert Musiol,[a] Josef Jampilek,[b] Vladimir Buchta,[c] Luis Silva,[c] Halina Niedbala,[a] Barbara Podeszwa,[a] Anna Palka,[a] Katarzyna Majerz-Maniecka,[d] Barbara Oleksyn[d] and Jaroslaw Polanski[a,*]

[a]*Institute of Chemistry, University of Silesia, Szkolna 9, 40007 Katowice, Poland*
[b]*Zentiva a.s., U kabelovny 130, 10237 Prague 10, Czech Republic*
[c]*Department of Biological and Medical Sciences, Faculty of Pharmacy in Hradec Kralove, Charles University in Prague, Heyrovskeho 1203, 500 05 Hradec Kralove, Czech Republic*
[d]*Faculty of Chemistry, Jagiellonian University, Ingardena 3, 30060 Krakow, Poland*

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Abstract—The series of quinoline derivatives were prepared. The synthetic approach, analytical, and spectroscopic data of all synthesized compounds are presented. All the prepared derivatives were analyzed using the reversed-phase high performance liquid chromatography (RP-HPLC) method for the lipophilicity measurement. In the present study, the correlation between RP-HPLC retention parameter $\log K$ (the logarithm of capacity factor K) and various calculated $\log P$ data is shown. The relationships between the lipophilicity and the chemical structure of the studied compounds are discussed as well. The prepared compounds were tested for their in vitro antifungal activity. 2-[(3-Hydroxyphenylimino)methyl]quinolin-8-ol (**8**), 2-[(4-hydroxyphenylimino)methyl]quinolin-8-ol (**9**) and 2-[(2,5-dichloro-4-nitrophenylamino)methoxymethyl]quinolin-8-ol (**10**) showed in vitro antifungal activity comparable to or higher than that of the standard fluconazole. Structure–activity relationships among the chemical structure, the physical properties, and the biological activities of the evaluated compounds are discussed in the article.

1. Introduction

Over the last three decades there has been a dramatic increase in the incidence of fungal infections. Discovery of new drugs for the treatment of systemic mycoses is a major challenge in infectious disease research. There is an urgent need for new antifungal remedies with novel modes of action due to a decreased antifungal susceptibility of newly emerging fungi in growing setting of the immunocompromised patients (e.g., HIV-positive and neutropenic patients), the development of resistance to the present azole therapies, and high toxicity of polyenes.[1–3]

The compounds bearing a quinoline moiety are well known due to their broad biological activity.[4] In particular, 8-hydroxyquinoline and its derivatives were introduced into antifungal clinical use and novel compounds of this type are still investigated.[5–7] A series of compounds derived from 8-hydroxyquinoline as potential HIV-1 integrase inhibitors were synthesized recently.[8] These compounds show a significant similarity to some novel antifungal agents, homoallylamines, which possess potent antifungal activity.[9] Quinoline derivatives discussed in this publication can be considered as the cyclic analogues of homoallylamines illustrated in Figure 1. The aromatic substitution (R = phenyl) is an important issue, which determines antifungal activity of these compounds. The biological activity decreases with the elongation of aliphatic linker (R = propyl or phenylethyl).

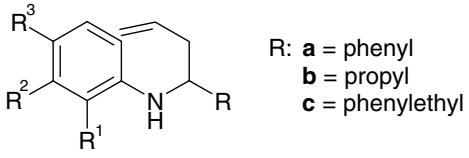

Figure 1. General structure of the evaluated antifungal homoallylamines.[9]

Keywords: Quinoline derivatives; Styrylquinoline analogues; In vitro antifungal activity; Lipophilicity measurement; Structure–activity relationships.
* Corresponding author. Tel.: +48 32 3591128; fax: +48 32 2599978; e-mail: polanski@us.edu.pl

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The model structure was modified to become more rigid replacing the basic olefinic chain by the quinoline moiety. Although the importance of the phenyl substitution (structure **a**) was demonstrated,[9] this study is based especially on the substitution by phenylethyl moiety (structure **c**). However, the resonance connection between the quinoline and phenyl ring was retained by the introduction of the styryl-like substitution to some newly synthesized compounds.

One of the major prerequisites for pharmacological screening and drug development is the prediction of absorption, for example, the transport of a molecule through cellular membranes. Drugs cross biological barriers most frequently through passive transport, which strongly depends on their lipophilicity. Therefore, hydrophobicity is one of the most important physical properties of biologically active compounds. This thermodynamic parameter describes the partitioning of a compound between an aqueous and an organic phase, and is characterized by the partition ($\log P$) or distribution ($\log D$) coefficient.[10,11] Reversed-phase high performance liquid chromatography (RP-HPLC) methods have become popular and widely used for lipophilicity measurement. The general procedure is the measurement of the directly accessible retention time under isocratic conditions with varying amounts of an organic modifier in the mobile phase using end-capped non-polar C_{18} stationary RP columns and calculating the capacity factor K; $K = (T_R - T_D)/T_D$, where T_R is the retention time of the solute, whereas T_D denotes the dead time obtained via an unretained analyte. $\log K$, calculated from the capacity factor K, is used as the lipophilicity index converted to $\log P$ scale.[12]

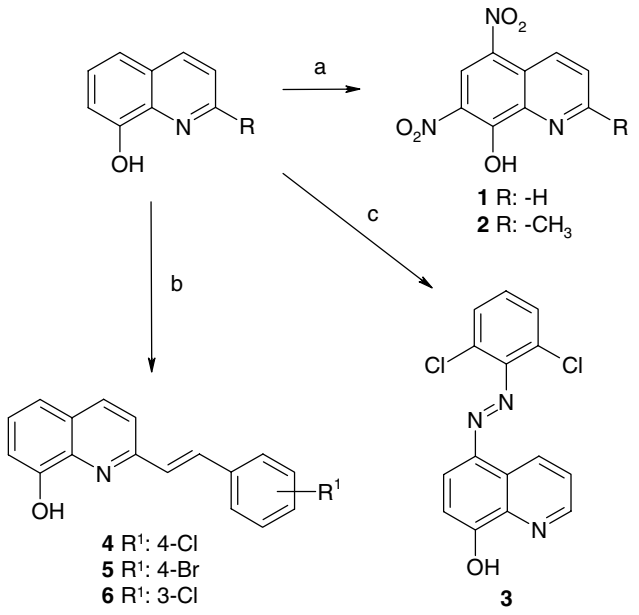
This work concentrated on the design and synthesis of new analogues containing the 8-hydroxyquinoline core. Consequently, we aimed at evaluating lipophilicity parameters in the mentioned series and at searching for the structure–activity relationships (SARs), that is, to continue studying of the substituent variability influence on the biological activity.

2. Results and discussion

2.1. Chemistry

8-Hydroxyquinoline and 8-hydroxyquinaldine were used as starting compounds. Nitration of these compounds by the mixture of H_2SO_4/HNO_3 yielded compounds **1** and **2**, respectively. The direct introduction of a diazonium salt derived from 2,6-dichloroaniline in 8-hydroxyquinaldine resulted in **3**. Compounds **4**–**6** were obtained from 8-hydroxyquinaldine and the appropriate aldehydes, see Scheme 1. Microwave-assisted terms appeared especially convenient in this case. In particular, solid-phase conditions were applied as described elswehere.[13]

Condensation of 8-hydroxyquinoline-2-carbaldehyde and the appropriate amine in dry benzene yielded compounds **7**–**9**. Compound **11** was obtained according to this procedure from 2-amino-8-hydroxyquinoline and 4-hydroxybenzaldehyde. 8-Hydroxyquinoline-2-carbaldehyde with 2,5-dichloro-4-nitroaniline in methanol generated a Schiff base, which was transformed to **10**, see Scheme 2.



Scheme 1. Synthesis of compounds **1**–**6**. Reagents and conditions: (a) HNO_3/H_2SO_4, 0 °C; (b) aldehyde, SiO_2, microwave irradiation; (c) 2, 6-dichloroaniline/$NaNO_2$/HCl, 5 °C.

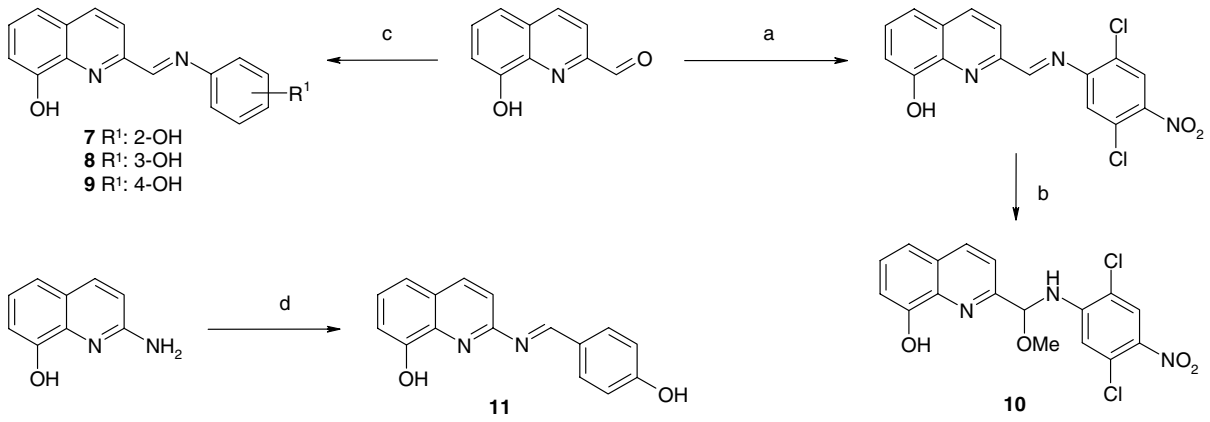
Contrary to all expectations, compound **10** retained the planarity of the system,[8] resembling the 3D structures of **1**–**9** and **11**, see Figure 2.

2.2. Lipophilicity

Hydrophobicities ($\log P$/C$\log P$ values) of the studied compounds were calculated using two commercially available programs and measured by means of RP-HPLC determination of capacity factors K with a subsequent calculation of $\log K$. The results are shown in Table 1 and illustrated in Figure 3.

This shows that the experimentally determined $\log K$ values correlate approximately with calculated $\log P$/C$\log P$ data, see Figure 3. As expected, the dependence between $\log K$ and the length of the alkyl substituents in compounds **1**, **2** (H, CH_3) takes a form of a linear plot. The experimental lipophilicity parameters specify lipophilicity within individual series of compounds **4**–**6** (3-Cl, 4-Cl, and 4-Br), as well as **7**–**9** (2-OH, 3-OH, and 4-OH). 2-[(2-Hydroxyphenylimino)methyl]quinolin-8-ol (**7**) is much less lipophilic than indicated by the calculated lipophilicity. This fact is probably caused by the interaction of the imine nitrogen with the phenolic moiety.

A large difference between the experimental and calculated lipophilicity parameters could be observed for compound **3**. Azoderivative **3** is situated between



Scheme 2. Synthesis of compounds **7**–**11**. Reagents and conditions: (a) 2,5-dichloro-4-nitroaniline, MeOH, piperidine; (b) MeOH; (c) amine, benzene, reflux 2 h; (d) 4-hydroxybenzaldehyde, benzene, reflux 2 h.

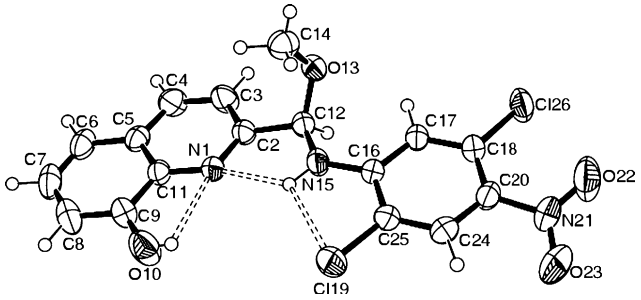


Figure 2. 3D structure of compound **10**.[8,16]

Table 1. Comparison of the determined log*K* values with the calculated lipophilicities (log*P*/C log*P*) of the prepared compounds and fluconazole (FLU)

Compound	log*K*	log*P*/C log*P* ChemOffice	log*P* ACD/log*P*
1	0.7154	1.80/1.91868	2.18 ± 0.34
2	0.7292	2.50/2.41769	2.64 ± 0.35
3	0.9633	5.28/5.5695	4.72 ± 0.79
4	1.5558	4.90/5.4825	5.08 ± 0.32
5	1.5802	5.17/5.6325	5.26 ± 0.38
6	1.5395	4.90/5.4825	5.08 ± 0.32
7	0.4308	3.63/2.43151	1.09 ± 0.79
8	0.8860	3.63/2.43151	1.51 ± 0.79
9	1.0911	3.63/2.43151	1.32 ± 0.79
10	1.1766	4.08/4.66098	4.44 ± 0.43
11	0.8353	3.92/3.5685	1.24 ± 1.05
FLU	—	0.99/−0.440	0.31 ± 0.74

8 and **9** according to log*K* and shows medium lipophilicity, but according to the calculated data it seems to be much more hydrophobic. In contrast, for compound **11** calculated lipophilicity parameters are higher than the experimentally measured log*K* value. Compound **11** is an isostere of compound **9**. Thus, the differences between experimental and calculated lipophilicity data are caused by the opposite position of the nitrogen atoms in the C=N linker between quinoline core and phenyl moiety and consequently by different intramolecular interactions.

2.3. Antifungal activity

Eleven prepared compounds were tested for their in vitro antifungal activity. All experiments were performed in comparison with fluconazole, a known antifungal agent (Fig. 4).[14,15] Some compounds were not sufficiently soluble in the testing medium RPMI 1640 and precipitated during the testing period, therefore their MICs could not be determined accurately.

Compound **2** showed only a moderate activity. Ten other evaluated compounds showed medium or high antifungal activity against all evaluated fungal strains. Their MICs ranged from 0.24 to 250 μmol/L. The activities of the compounds are shown in Table 2.

The studied compounds could be divided into two groups according to their chemical structural properties, see Schemes 1 and 2. Group 1 includes compounds **1**–**3**. Group 2 includes compounds **4**–**11**. Figure 5 describes the dependence between in vitro antifungal activity (log $1/IC_{80}$) and the logarithm of the retention factor (log*K*) of all studied compounds **1**–**11**. The sum of the activities of the studied compounds against the fungal strains *Candida albicans* ATCC 44859, *Candida tropicalis* 156, and *Candida glabrata* 20/I after 24 h incubation was selected to illustrate this dependence due to the fact that the activity of all evaluated compounds was exactly determined.

Generally, group 1 showed medium or moderate in vitro antifungal activity. While compound **1**, which is substituted by two nitro groups in the $C_{(5)}$ and $C_{(7)}$ positions of quinoline, showed medium activity against all tested strains, consequent methylation in $C_{(2)}$ (compound **2**) resulted in the loss of the antifungal effect. Compound **3** substituted by dichlorophenylazo moiety in the $C_{(5)}$ position of quinoline showed moderate activity. It could be assumed that the increase in lipophilicity (Log*K*) of the compounds within the series **1**–**3** results in the decrease of antifungal activity. 5,7-Dinitroquinolin-8-ol (**1**) is the most active compound of Group 1, see Figure 5.

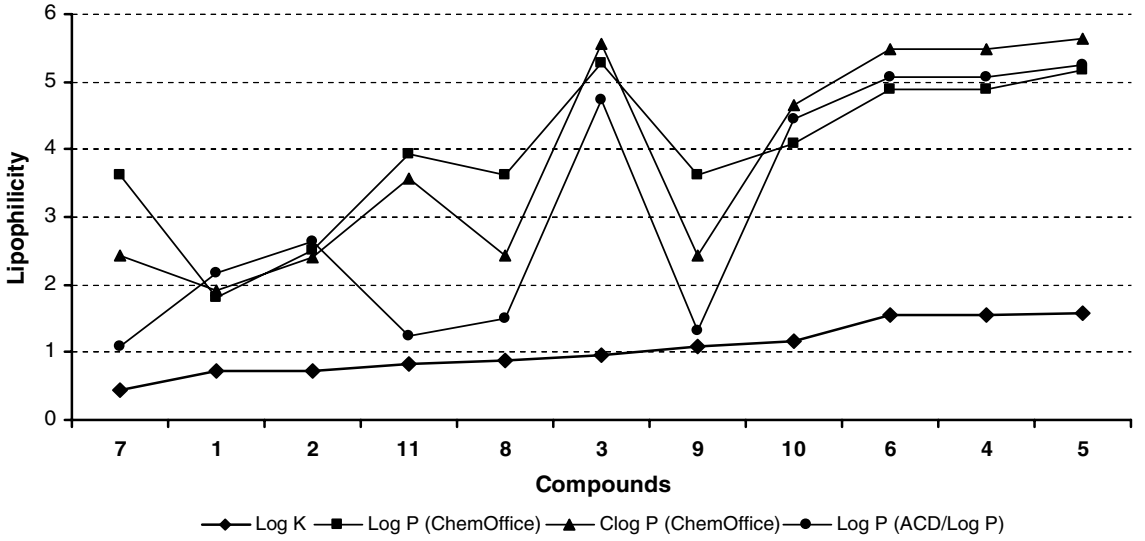


Figure 3. Comparison of the calculated log *P*/C log *P* data using the two programs with the experimentally found log *K* values.

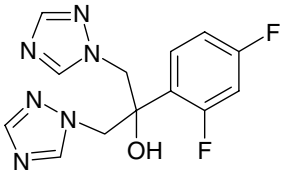


Figure 4. Chemical structure of fluconazole.

Group 2 showed high biological activity. Phenolic moiety in the $C_{(4)}$ position of phenyl ring, which is conjugated with quinoline nucleus (compounds **9**, **11**), seems to be the most advantageous in terms of their effect against all tested fungal strains. The substitution in $C_{(4)}$ by bromine (compound **5**) or chlorine (compound **4**) resulted in decreasing activity, probably due to lower solubility of these compounds in DMSO that allowed to test these compounds in a maximum concentration of 62.5 μmol/L (Table 2). Substitution in the $C_{(2)}$ or $C_{(3)}$ position of phenyl ring by phenolic or chlorine moiety (compounds **6**–**8**) resulted in a considerable decrease of the activity, see Figure 5. Antifungal activity is also influenced by the inclusion and position of nitrogen in the olefinic linker; its presence providing the best results. The position of the iminic nitrogen is important as well. 2-[(4-Hydroxy-

Table 2. In vitro antifungal activity (IC_{80}) of the selected compounds compared with the standard fluconazole (FLU)

Compound	MIC/IC_{80} (μmol/L)							
	CA 24h 48h	CT 24h 48h	CK 24h 48h	CG 24h 48h	TB 24h 48h	AF 24h 48h	AC 24h 48h	TM 72h 120h
1	1.95 7.81	15.63 31.25	15.63 31.25	15.63 31.25	7.81 15.63	3.91 3.91	31.25 62.50	7.81 15.63
2	62.50 250	500 1000	500 500	500 1000	500 500	125 250	500 500	250 250
3	31.25 125	31.25 62.50	62.50 62.50	15.63 31.25	125 >125	31.25 62.50	>125 >125	31.25 31.25
4	3.91 >62.5	7.81 >62.5	>62.5 >62.5	3.91 62.5	>62.5 >62.5	>62.5 >62.5	31.25 >62.5	>62.5 >62.5
5	3.91 >62.5	7.81 >62.5	125 >125	3.91 >62.5	125 >125	>62.5 >62.5	7.81 >62.5	>62.5 >62.5
6	7.81 15.63	15.63 15.63	15.63 31.25	7.81 15.63	31.25 62.50	15.63 31.25	7.81 7.81	15.63 15.63
7	31.25 62.50	125 125	62.50 125	62.50 125	125 250	62.50 125	31.25 62.50	62.50 125
8	31.25 125	15.63 62.50	125 250	3.91 15.63	>250 >250	125 >250	>250 >250	15.63 >250
9	1.95 31.25	0.49 3.91	15.63 31.25	0.24 0.49	62.50 250	7.81 62.50	31.25 62.50	7.81 15.63
10	1.95 62.50	7.81 31.25	62.50 125	1.95 7.81	>500 >500	3.91 >500	>500 >500	>500 >500
11	3.91 15.63	3.91 7.81	3.91 7.81	1.95 3.91	31.25 125	3.91 125	31.25 125	15.63 15.63
FLU	0.06 0.12	0.12 >125	3.91 15.62	0.98 3.91	0.24 0.48	>125 >125	>125 >125	1.95 3.91

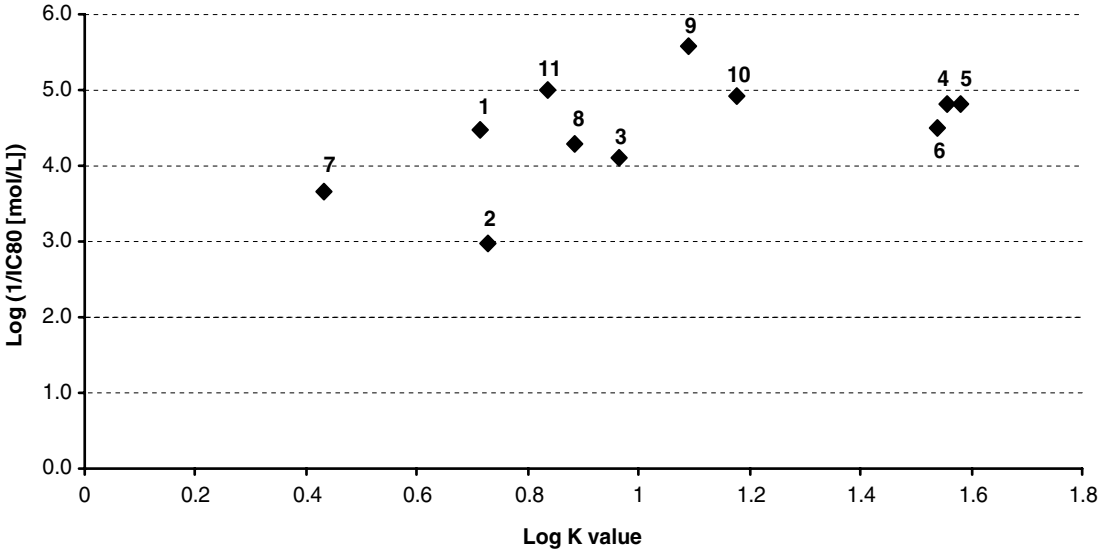


Figure 5. Dependence between the sum of the values of in vitro antifungal activities against the fungal strains *Candida albicans* ATCC 44859, *Candida tropicalis* 156, and *Candida glabrata* 20/I {$\log(1/IC_{80}$ [mol/L])} and the logarithm of the retention factor ($\log K$) of the studied compounds **1**–**11**.

phenolimino)methyl]quinolin-8-ol (**9**), derived from aniline, appeared to be the most active compound that was obtained in this study.

The activity of compound **10** is very promising, especially against *C. albicans* ATCC 44859, *C. glabrata* 20/I, and *Aspergillus fumigatus* 231. The X-ray analysis indicated a planar structure for this compound, see Figure 2.[8,16] Thus, it seems that the mode of action of compound **10** should not be very different from other planar styrylquinolines. Consequently, resonance connection between the quinoline and phenyl ring is probably not the most important condition for antifungal activity, as expected.

The comparison of antifungal activity with the hydrophobicity indicated an optimal value of $\log K$ around 1, see Figure 5. Compound **9** ($\log K = 1.0911$) showed the highest antifungal activity against all strains tested. Generally, the activity decreases both with the decrease and the increase of the lipophilicity value of $\log K$ around 1 (compounds **10**, **11**). Thus, some trends in individual structural types of the evaluated compounds **4**–**6** and **7**–**9** could be described. It could be assumed, according to Figure 5, that the activity of compounds **4**–**6**, in fact, does not depend on lipophilicity but only on the position of the substitution of phenyl ring. The activity of compounds **7**–**9** demonstrates an exponential increase with the lipophilicity increase to $\log K$ around 1, see Figure 5.

3. Conclusion

A series of quinoline derivatives were prepared and tested for their in vitro antifungal activity against the eight strains of human pathogenic fungi. The lipophilicity ($\log K$) was measured by means of RP-HPLC. Six compounds of the obtained series showed high in vitro antifungal activity. 2-[(4-Hydroxyphenolimino)methyl]quinolin-8-ol (**9**), 2-[(2,5-dichloro-4-nitrophenylamino)methoxymethyl]quinolin-8-ol (**10**), and 2-[(4-hydroxybenzylidene)amino]quinolin-8-ol (**11**) indicated in vitro antifungal activity comparable to or higher than that of fluconazole. The substitution in the $C_{(4)}$ position of the phenyl ring by polar group (phenolic or nitro moiety) seems to be very important for antifungal effect, as well as the presence and the position of the nitrogen atom in the connecting linker between the quinoline and phenyl ring. The optimal parameter of lipophilicity ($\log K$) concerning the biological effect of these compounds ranges around 1.

4. Experimental

4.1. General

All reagents were purchased from Aldrich. Kieselgel 60, 0.040–0.063 mm (Merck, Darmstadt, Germany) was used for column chromatography. TLC experiments were performed on alumina-backed silica gel 40 F_{254} plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and evaluated in iodine vapor. Melting points were determined on Boetius PHMK 05 (VEB Kombinat Nagema, Radebeul, Germany) and are uncorrected. Elemental analyses were carried out on an automatic Perkin-Elmer 240 microanalyser (Boston, USA). All ^{1}H NMR spectra were recorded on a Bruker AM-500 (499.95 MHz for ^{1}H), Bruker BioSpin Corp., Germany. Chemicals shifts are reported in ppm (δ) to internal $Si(CH_3)_4$, when diffused easily exchangeable signals are omitted. Signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; br s, broad singlet.

4.2. Synthesis

4.2.1. 5,7-Dinitro-8-hydroxyquinoline (1) and 5,7-dinitro-8-hydroxy-2-methylquinoline (2). The appropriate quinoline (2.0 g) was added slowly in small quantities to the mixture HNO_3/H_2SO_4 7:3 (20 mL) in an ice bath. After 2 h the mixture was poured on 50 g of ice. A yellow powder was filtered, washed with hot EtOH, and crystallized from nitrobenzene.

(**1**) Yield 70%. Mp 315 °C; lit. Mp 314–315 °C.[17]
(**2**) Yield 75%. Mp 260 °C; lit. Mp 260 °C.[18]

4.2.2. 5-(2,6-Dichlorophenylazo)quinolin-8-ol (3). 2,6-Dichloroaniline (1.3 g) was dissolved in 5% HCl (30 mL) and cooled to 5 °C. Then 10% aqueous solution of $NaNO_2$ (10 mL), was added dropwise. 8-Hydroxyquinoline (1.6 g) was dissolved in a solvent consisting from 5% NaOH (40 mL) and EtOH (10 mL) and cooled on an ice bath. While stirring, this solution was added to the mixture of diazo compound. Stirring was continued up to 15 min. The mixture was evaporated under reduced pressure, and the residue was washed twice with CH_2Cl_2 (15 mL). Column chromatography (acetone) gave a brick red crystalline compound. Yield 20%. Mp 180 °C (dec). Anal. Calcd for $C_{15}H_9Cl_2N_3O \cdot \frac{1}{2}H_2O$ (327.16): C, 55.07; H, 3.08. Found: C, 55.04; H, 2.81. ^{1}H NMR (DMSO-d_6), δ: 7.25 (t, J = 9.00 Hz, 1H), 7.50–7.65 (m, 2H), 7.8 (t, J = 7.90 Hz, 1H), 7.85–8.00 (m, 2H), 8.05 (d, J = 7.50 Hz, 1H), 9.00 (s, 1H), 9.40 (d, J = 8.10 Hz, 1H).

Compounds **4**–**6** were obtained in the reaction of 8-hydroxyquinaldine with the appropriate aldehyde using microwave irradiation as described previously.[13]

4.2.3. 2-[(2-Hydroxyphenylimino)methyl]quinolin-8-ol (7). 8-Hydroxyquinoline-2-carbaldehyde (0.18 g) and 2-aminophenol (0.12 g) were mixed thoroughly with montmorillonite K-10 (0.5 g) and microwaved at 750 W for 3.5 min. After the reaction, crude **7** was extracted from the mixture with CH_2Cl_2 (2×20 mL). The solvent was removed under reduced pressure. The crude product was purified by crystallization from EtOH, and a bright yellow crystalline compound was obtained. Yield 65%. Mp 168–169 °C; lit. Mp 168–169 °C.[19]

Compounds **8**, **9**, and **11** were obtained in the reaction of 8-hydroxyquinoline-2-carbaldehyde with the appropriate amine in dry benzene. Substrates were refluxed under Dean–Stark apparatus for 2 h. The product was purified by crystallization in ethanol.

4.2.4. 2-[(3-Hydroxyphenylimino)methyl]quinolin-8-ol (8). A dark red crystalline compound. Yield 66%. Mp 240 °C (dec). Anal. Calcd for $C_{16}H_{12}N_2O_2 \cdot \frac{1}{2}H_2O$ (273.29): C, 70.32; H, 4.79. Found: C, 69.98; H, 4.60. ^{1}H NMR (DMSO-d_6), δ: 6.72 (s, 1H), 7.12 (t, 1H), 7.20–7.25 (m, 2H), 7.40–7.48 (m, 2H), 7.50 (d, J = 7.60 Hz, 1H), 8.23 (d, J = 8.50 Hz, 1H), 8.41 (d, J = 8.50 Hz, 1H), 8.71 (t, 1H), 9.66 (s, 1H), 10.05 (br s, 1H).

4.2.5. 2-[(4-Hydroxyphenylimino)methyl]quinolin-8-ol (9). A yellow crystalline compound. Yield 75%. Mp 243 °C. Anal. Calcd for $C_{16}H_{12}N_2O_2$ (264.29): C, 72.72; H, 4.58. Found: C, 72.53; H, 4.68. ^{1}H NMR (DMSO-d_6), δ: 6.83 (dd, J = 7.50 Hz, 2H), 7.11 (dd, J = 7.50 Hz, 2H), 7.31 (d, J = 8.30 Hz, 1H), 7.40 (d, J = 7.90 Hz, 1H), 7.45 (t, 1H), 8.19 (d, J = 7.90 Hz, 1H), 8.34 (d, J = 7.80 Hz, 1H), 8.74 (s, 1H), 9.67 (s, 1H), 9.88 (br s, 1H).

4.2.6. 2[(4-Hydroxybenzylidene)amino]quinolin-8-ol (11). A brown crystalline compound. Yield 20%. Mp 150 °C. Anal. Calcd for $C_{16}H_{12}N_2O_2$ (264.29): C, 72.72; H, 4.58. Found: C, 72.80; H, 4.60. ^{1}H NMR (DMSO-d_6), δ: 6.66–6.73 (m, 2H), 6.81 (d, J = 9.00 Hz, 1H), 6.95 (d, J = 7.40 Hz, 2H), 7.10 (s, 1H), 7.20–7.25 (m, 2H), 7.70 (d, J = 7.40 Hz, 2H), 7.82 (br s, 1H), 7.88 (d, J = 8.70 Hz, 1H).

4.2.7. 2-[(2,5-Dichloro-4-nitrophenylamino)methoxymethyl]quinolin-8-ol (10). 8-Hydroxyquinoline-2-carbaldehyde (0.6 g) and 2,5-dichloro-4-nitroaniline (0.7 g) were added to methanol (40 mL) with five drops of piperidine and refluxed for 2 h. A yellow crystalline compound. Yield 35%. Mp 170–175 °C. More comprehensive discussion on the synthesis and structure of this compound has been reported elsewhere.[8,16]

4.3. Lipophilicity HPLC determination (capacity factor *K*/calculated log *K*)

The HPLC separation module Waters Alliance 2695 XE and Waters Photodiode Array Detector 2996 (Waters Corp., Milford, MA, USA) were used. The chromatographic column Symmetry® C_{18} 5 μm, 4.6×250 mm, Part No. WAT054275 (Waters Corp., Milford, MA, USA), was used. The HPLC separation process was monitored by Millennium32® Chromatography Manager Software, Waters 2004 (Waters Corp., Milford, MA, USA). The mixture of MeOH p.a. (55.0%) and H_2O-HPLC—Mili-Q Grade (45.0%) was used as a mobile phase. The total flow of the column was 0.9 mL/min, injection 30 μL, column temperature 25 °C, and sample temperature 10°C. The detection wavelength 240 nm was chosen. The KI methanolic solution was used for the dead time (T_D) determination.

The capacity factors K were calculated using the Millennium32® Chromatography Manager Software. The log K values of the individual compounds are shown in Table 1.

4.4. Lipophilicity calculations

Log P, that is, the logarithm of the partition coefficient for *n*-octanol/water, was calculated using the programs CS ChemOffice Ultra ver. 7.0 (CambridgeSoft, Cambridge, MA, USA) and ACD/Log P ver. 1.0 (Advanced Chemistry Development Inc., Toronto, Canada). C log P values (the logarithm of *n*-octanol/water partition coefficient based on established chemical interactions) were generated by means of CS ChemOffice Ultra ver. 7.0 (CambridgeSoft, Cambridge, MA, USA) software. The results are shown in Table 1.

4.5. In vitro antifungal susceptibility testing

The broth microdilution test[20] was used for the assessment of in vitro antifungal activity of the synthesized compounds against *C. albicans* ATCC 44859 (CA), *C. tropicalis* 156 (CT), *Candida krusei* ATCC 6258 (CK), *C. glabrata* 20/I (CG), *Trichosporon beigelii* 1188 (TB), *Aspergillus fumigatus* 231 (AF), *Absidia corymbifera* 272 (AC), and *Trichophyton mentagrophytes* 445 (TM). Fluconazole (FLU) was used as the standard of a clinically used antimycotic drug. The procedure was performed with twofold dilution of the compounds in RPMI 1640 (Sevapharma a.s., Prague, Czech Republic) buffered to pH 7.0 with 0.165 mol of 3-morpholino-propane-1-sulfonic acid (MOPS, Sigma, Germany). The final concentrations of the compounds ranged from 500 to 0.975 μmol/L. Drug-free controls were included. The MIC was defined as 80% (IC_{80}) and a higher reduction of growth in comparison with control. The values of MICs were determined after 24 and 48 h of static incubation at 35 °C. For *T. mentagrophytes*, the final MICs were determined after 72 and 120 h of incubation. The results are summarized in Table 2.

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References and notes

1. Rees, J. R.; Pinner, R. W.; Hajjeh, R. A. *Clin. Infect. Dis.* **1998**, *27*, 1138.
2. Polak, A. *Mycoses* **1999**, *42*, 355.
3. Fostel, J. M.; Lartey, P. A. *Drug Discovery Today* **2000**, *5*, 25.
4. Roth, H. J.; Fenner, H. In *Arzneistoffe*, 3rd ed.; Deutscher Apotheker Verlag, Stuttgart, 2000; pp 51–114.
5. Gershon, H.; Gershon, M.; Clarke, D. D. *Mycopathologia* **2004**, *158*, 131.
6. Dardari, Z.; Lemrani, M.; Bahloul, A.; Sebban, A.; Hassar, M.; Kitane, S.; Berrada, M.; Boudouma, M. *Farmaco* **2004**, *59*, 195.
7. Jampilek, J.; Dolezal, M.; Kunes, J.; Buchta, V.; Kralova, K. *Med. Chem.* **2005**, *1*, 591.
8. Majerz-Maniecka, K.; Oleksyn, B.; Musiol, R.; Podeszwa, B.; Polanski J. *Abstracts of Papers*, Joint Meeting on Medicinal Chemistry, Vienna, Austria, June 20–23, 2005; In *Sci. Pharm.* **2005**, *73* (*Suppl. 1*), 194.
9. Vargas, L. Y.; Castelli, M. V.; Kouznetsov, V. V.; Urbina, J. M.; Lopez, S. N.; Sortino, M.; Enriz, R. D.; Ribas, J. C.; Zacchino, S. *Bioorg. Med. Chem.* **2003**, *11*, 1531.
10. Avdeef, A. *Curr. Top. Med. Chem.* **2001**, *1*, 277.
11. Pliska, V. In *Lipophilicity in Drug Action and Toxicology*; Pliska, V., Testa, B., van der Waterbeemd, H., Eds.; Wiley-VCH: Weinheim, 1996; pp 1–6.
12. Valko, K. *J. Chromatogr., A* **2004**, *1037*, 299.
13. Polanski, J.; Niedbala, H.; Musiol, R.; Tabak, D.; Podeszwa, B.; Gieleciak, R.; Bak, A.; Palka, A.; Magdziarz, T. *Acta Pol. Pharm. Drug Res.* **2005**, *61*, 3.
14. Odds, F. C.; Cheesman, S. L.; Abbott, A. B. *J. Antimicrob. Chemother.* **1986**, *18*, 473.
15. Hoban, D. J.; Zhanel, G. G.; Karlowsky, J. A. *Antimicrob. Agents Chemother.* **1999**, *43*, 1463.
16. Majerz-Maniecka, K. A.; Musiol, R.; Nitek, W.; Oleksyn, B. J.; Polanski, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1005.
17. Bennett, G. M.; Grove, J. F. *J. Chem. Soc.* **1945**, 378.
18. Behforouz, M.; Haddad, J.; Cai, W.; Arnold, M. B.; Mohammadi, F.; Sousa, A. C.; Horn, M. A. *J. Org. Chem.* **1996**, *61*, 6552.
19. Hata, T.; Uno, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 477.
20. National Committee for Clinical Laboratory Standards: Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeats: Proposed Standard M 27-P, National Committee for Clinical Laboratory Standards, Villanova, PA 1992.