Synthesis and *In Vitro* Antigungal Properties of 4-Aryl-4-N-arylamine-1-butenes and Related Compounds

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Abstract: A new series of 4-aryl and 4-alkyl-4-N-arylamine-1-butenes (homoallylamines) were synthesized and some of them transformed to 4-aryl or alkylquinolines. All of them showed strong antifungal activities against human pathogenic fungi *in vitro*, being *Epidermophyton floccosum* the most susceptible species.

Introduction

As part of our project devoted to the search for antifungal agents [1-3], we synthesized a series of new 4-aryl- or 4-alkyl-N-arylamine-1-butenes and transformed some of them into biologically important 2-substituted 4-methyl-tetrahydroquinolines and quinolines [4]. We evaluated them for antifungal properties with agar dilution assays and studied their structure-activities relationships (SAR).

Experimental

Chemistry. Homoallylamines **12-22** were prepared *via* the addition of Grignard reagent to aldimines **1-11.** Electrophilic cyclization of two of them, compounds **12** and **13** under acidic conditions, led to tetrahydroquinolines **23** and **24**, which were oxidised to quinolines **25** and **26** with DDQ (Scheme 1)

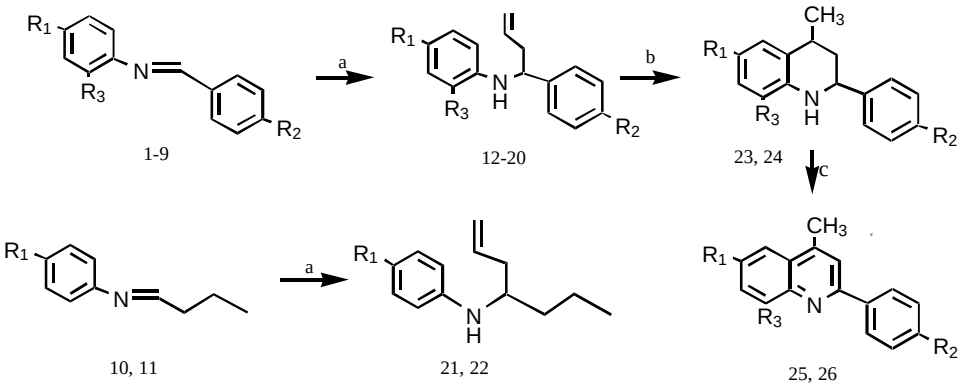
Microorganisms. We used standardized human pathogenic fungi from CEREMIC or ATCC. at concentrations up to 50 μg/mL [1,2].

*Antifungal evaluation.*The dilution agar method was used according with reported procedures [1,2].

Results and Discussion

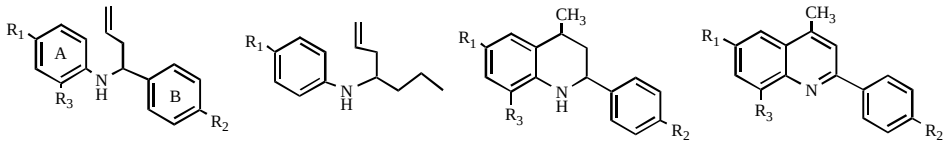
All compounds tested showed antifungal properties against dermatophytes (3.12<MIC<50 μg/mL), in particular against *Epidermophyton floccosum,* similar to those obtained with Amphotericin or Ketoconazole (Table 1). Substituents on benzene rings A or B increased four times the activity respective the non-substituted analogs. The change of an OMe from position 4 to 2 in rings A or B increased the activity twice.

Scheme 1



a)Allyl bromide+Mg/Et_2O, 1O°C; b)H_2SO_4 75% W/V; c)DDQ/Bz,

Table I. MIC values (μg/mL) of homoallylamines, tetrahydroquinolines and quinolines acting against dermatophytes.



Compd	Type	R_1	R_2	R_3	*M. c.*[a]	*M.g.*[b]	*T. m.*[c]	*T. r.*[d]	*E. f*[e]
12	C	H	H	H	30	30	30	30	12.5
13	C	CH_3	H	H	30	>50	>50	>50	3.12
14	C	OCH_3	H	H	30	>50	30	30	3.12
15	C	F	H	H	>50	>50	>50	>50	30
16	C	Cl	H	H	>50	>50	>50	>50	30
17	C	Br	H	H	>50	>50	>50	>50	30
18	C	H	OCH_3	H	30	>50	>50	>50	3.12
19	C	Cl	$N(CH_3)_2$	H	>50	>50	>50	>50	>50
20	C	H	H	CH_3	30	>50	>50	>50	3.12
21	D	H	-	-	>50	>50	>50	>50	>50
22	D	CH_3	-	-	>50	>50	>50	>50	>50
23	E	H	H	H	50	25	25	25	12.5
24	E	CH_3	H	H	50	25	25	25	12.5
25	F	H	H	H	25	12.5	12.5	25	12.5
26	F	CH_3	H	H	0.75	12.5	25	12.5	12.5
Amp.[f]					>50	6.25	6.25	25	0.3
Ket.[g]					15	6.25	12.5	15	25

[a]Microsporum canis C 112. [b]Microsporum gypseum C 115.[c]Trichophyton mentagrophytes ATCC 9972. [d]Trichophyton rubrum C 113. [e]Epidermophyton floccosum C 114. [f]Amp.= amphotericin B. [g]Ket.=ketoconazole.

References and Notes

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