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In Vitro Antifungal Activity of New Series of Homoallylamines and Related Compounds with Inhibitory Properties of the Synthesis of Fungal Cell Wall Polymers

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Abstract—The synthesis, in vitro antifungal evaluation and SAR studies of 101 compounds of the 4-aryl-, 4-alkyl-, 4-pyridyl or -quinolinyl-4-*N*-arylamino-1-butenes series and related compounds, are reported here. Active structures showed to inhibit (1,3)-β-D-glucan and mainly chitin synthases, enzymes that catalyze the synthesis of the major fungal cell wall polymers.

Introduction

During the last two decades, coupled to the growing population of immunocompromised individuals there has been an increasing frequency of fungal infections. Among them, superficial and subcutaneous mycoses affect the skin, keratinous tissues and mucous membranes, usually giving rise to debilitating effects on a person's quality of life.[1,2]

Although amphotericin B, ketoconazole, and more recently, allylamines and triazoles have been used to treat superficial mycoses, they are very difficult to eradicate. Many of the currently available drugs are toxic, fungistatic but not fungicide thus producing recurrence or lead to the rapid development of resistance. Although a combined therapy has emerged as a good alternative for bypassing those disadvantages, there is a real need for a next generation of more potent and safer antifungal agents.[3–6]

In the course of our ongoing screening program for new and selective antifungal compounds,[7–9] we have previously reported[7] that a series of 4-aryl- or 4-alkyl-*N*-arylamino-1-butenes (Fig. 1) and related tetrahydroquinolines and quinolines display a range of antifungal properties against dermatophytes, fungi that produce most of the dermatomycoses in humans. Regarding their mode of action, active compounds showed in vitro inhibitory activities against (1,3)-β-D-glucan-synthase and mainly against chitin-synthase, enzymes that catalyze the synthesis of the major fungal cell wall polymers.[3] Since fungal but not mammalian cells possess a cell wall, these structures appeared as promissory leads for the development of selective antifungal compounds. From the early structure–activity studies of these compounds,[7] it became apparent that the R moiety on the 4-position of 4-amino-1-butenes (Fig. 1) played a crucial role in the activity, being compounds with R = aryl (compounds type C in Table 1) more active than those containing an alkyl moiety (type A in Table 1). In addition, the types of substituents on

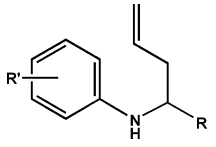

Figure 1. General structure of antifungal homoallylamines.

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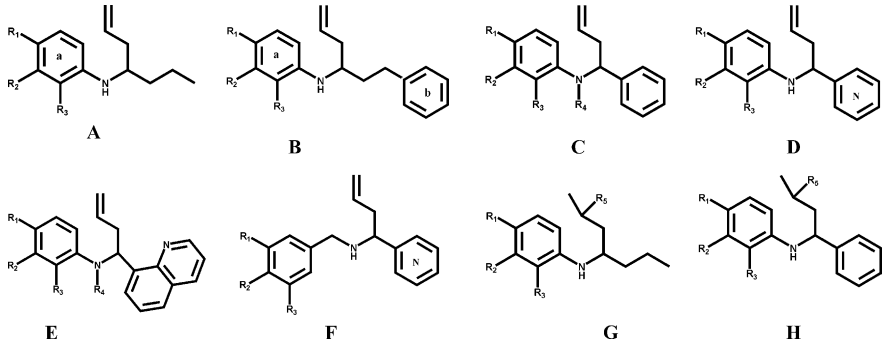
Table 1. MIC values of 4-*N*-arylamino-1-heptenes **41–46**, 4-*N*-arylamino-6-phenyl-1-hexenes **47–52**, 4-*N*-arylamino-4-phenyl-1-butenes **53–61**, 4-*N*-arylamino-4-pyridyl(8-quinolinyl)-1-butenes **62–78** 4-*N*-benzylamino-4-pyridyl-1-butenes **79,80** and related compounds against dermatophytes



Compd	Type	R_1	R_2	R_3	R_4	R_5	Pos N	*M.c.*	*M.g.*	*T.m*	*T.r.*	*E.f*
41	A	H	H	H	—	—	—	>250	>250	>250	>250	>250
42	A	H	H	CH_3	—	—	—	>250	>250	>250	>250	250
43	A	CH_3O	H	H	—	—	—	125	125	125	125	125
44	A	Cl	H	H	—	—	—	>250	>250	>250	250	250
45	A	Br	H	H	—	—	—	>250	>250	>250	125	250
46	A	F	H	H	—	—	—	250	>250	>250	>250	250
47	B	H	H	H	—	—	—	>250	>250	>250	>250	>250
48	B	CH_3	H	H	—	—	—	>250	>250	>250	>250	>250
49	B	H	H	CH_3	—	—	—	>250	>250	>250	>250	250
50	B	CH_3O	H	H	—	—	—	>250	>250	>250	>250	>250
51	B	Br	H	H	—	—	—	>250	>250	>250	>250	>250
52	B	F	H	H	—	—	—	>250	>250	>250	>250	250
53	C	H	H	H	H	—	—	30	30	30	30	12.5
54	C	CH_3	H	H	H	—	—	30	>250	>250	>250	3.12
55	C	Br	H	H	H	—	—	>250	>250	>250	>250	6.25
56	C	CH_3O	H	H	H	—	—	30	>250	30	30	3.12
57	C	H	H	$CH(CH_3)_2$	H	—	—	>250	>250	>250	>250	>250
58	C	H	CH_3O	H	H	—	—	>250	>250	>250	125	50
59	C	CH_3O	CH_3O	H	H	—	—	>250	250	>250	>250	250
60	C	CH_3O	H	CH_3O	H	—	—	>250	>250	>250	>250	250
61	C	OCH_2O		H	H	—	—	250	250	250	125	62.5
62	D	H	H	H	—	—	β	12.5	50	50	12.5	12.5
63	D	CH_3	H	H	—	—	β	6.25	50	50	6.25	6.25
64	D	CH_3	H	H	—	—	α	>250	>250	250	>250	>250
65	D	CH_3	H	H	—	—	γ	50	25	50	50	50
66	D	H	H	$CH(CH_3)_2$	—	—	β	25	50	50	25	50
67	D	CH_3O	H	H	—	—	β	25	>250	>250	50	50
68	D	OCH_2O		H	—	—	β	25	50	50	50	50
69	D	Br	H	H	—	—	β	3.12	12.5	12.5	6.25	1.5
70	D	Cl	H	H	—	—	β	6.25	12.5	25	12.5	3.12
71	D	F	H	H	—	—	β	6.25	25	12.5	6.25	1.5
72	D	F	H	F	—	—	β	6.25	25	12.5	250	250
73	D	H	H	I	—	—	β	12.5	50	25	25	12.5
74	E	CH_3	H	H	H	—	—	>250	>250	>250	>250	>250
75	E	CH_3	H	CH_3	H	—	—	>250	>250	>250	>250	25
76	E	CH_3O	H	H	H	—	—	>250	>250	>250	>250	>250
77	E	CH_3CH_2O	H	H	H	—	—	>250	>250	>250	>250	50
78	E	Cl	H	H	H	—	—	>250	>250	>250	>250	50
79	F	H	H	H	—	—	β	>250	>250	250	250	250
80	F	H	H	H	—	—	γ	>250	>250	>250	250	>250
81	C	CH_3O	H	H	$COCH_3$	—	—	250	250	250	125	250
82	C	CH_3O	H	H	Allyl	—	—	>250	>250	>250	250	250
83	E	CH_3	H	H	Allyl	—	—	>250	>250	>250	>250	>250
84	E	CH_3	H	Allyl	H	—	—	>250	>250	>250	>250	>250
85	G	Br	H	H	—	OH—	—	50	50	>250	50	50
86	H	H	H	H	H	OH	—	50	>250	>250	>250	>250
87	H	CH_3	H	H	H	OH	—	50	>250	>250	>250	>250
88	H	Br	H	H	H	OH	—	50	>100	50	12.5	50
89	H	H	H	$CH(CH_3)_2$	H	OH	—	50	125	250	50	>250
Amp.								>250	6.25	6.25	25	0.3
Terb.								0.01	0.04	0.01	0.04	0.004

M.c: *Microsporum canis* C 112. *M.g*: *Microsporum gypseum* C 115; *T.m.*: *Trichophyton mentagrophytes* ATCC 9972; *T.r.*: *Trichophyton rubrum* C113. *E.f.*: *Epidermophyton floccosum* C 114; Amp., Amphotericin B.; Terb., Terbinafine.

ring **a** showed to be important for activity. Tetrahydroquinolines or quinolines obtained by cyclization of some homoallylamines showed to be active as well.

The interesting antifungal properties displayed by these homoallylamines, tetrahydroquinolines and quinolines prompted us to synthesize new members of the previously reported series, a new one including 4-*N*-arylamino-1-butenes containing the pyridyl or quinolinyl moieties at C-4 and other related compounds, in order to find new antifungal structures with inhibitory properties of the fungal cell wall synthesis and to establish their structure–activity relationships. In this work, we report the synthesis and antifungal evaluation of 101 compounds, most of them not reported in the literature up to date.

Homoallylamines and derivatives **41–89**, tetrahydroquinolines **90–94** and **96–107**, quinolines **95**, **96**, and **108–119**, and related compounds **120–141** were tested for antifungal properties with the agar dilution method against a panel of standardized dermatophytes. Based on the results obtained in this screen, a SAR study including computational analysis was performed with the aim of explaining the influence of the different substituents on the antifungal activity. Then, to gain insight into the capacity of active compounds to interfere with the biosynthesis of fungal cell wall, active compounds were tested for their in vitro inhibitory activity on (1,3)-β-D-glucan- and chitin-synthases.

Results and Discussion

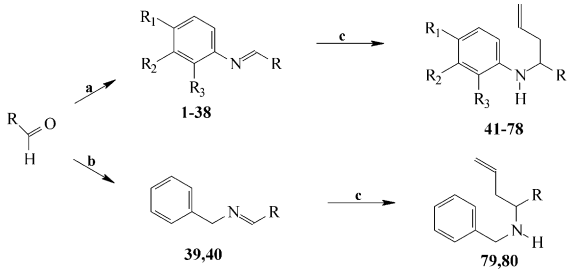
Chemistry

The starting *N*-arylaldimines 1–38 and *N*-benzylaldimines **39** and **40** needed in our investigation were readily prepared from commercially available aldehydes (butyraldehyde, cinnamaldehyde, benzaldehyde, isomeric pyridinecarboxyaldehydes or quinoline 8-carboxyaldehyde) and substituted anilines or benzylamine, according to literature procedures.[7,10] Both series of obtained aldimines were converted into the requisite *N*-substituted unsaturated amines. Using the nucleophilic addition of allylmagnesium bromide to the C=N bond of these imines, we obtained corresponding 4-*N*-arylamino-1-heptenes **41–46**, 4-*N*-arylamino-6-phenyl-1-hexenes **47–52**, 4-*N*-arylamino-4-phenyl-1-butenes **53–61**, 4-*N*-arylamino-4-pyridyl(8-quinolinyl)-1-butenes **62–78** and 4-*N*-benzylamino-1-butenes **79** and **80**, which were isolated as stable oils in 59–85% yields (Scheme 1). All these reactions were run in dry diethyl ether at 20–34 °C.

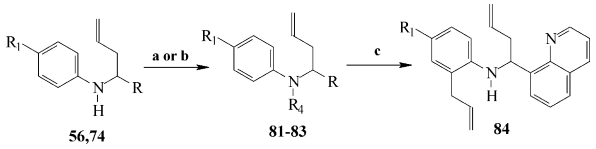
Acetamide **81** was prepared from aminobutene **56** in the usual way for amine acetylation (Ac_2O/Et_3N). *N*-Allylation of aminobutene **56** and its pyrido analogue **74**[11] was carried out with allyl bromide/K_2CO_3 in dry acetone affording derivatives **82** and **83**, respectively. Compound **83** was further used in the amino-Claisen rearrangement to afford quinoline aminobutene **84**[12] as shown in Scheme 2.

Treatment of selected unsaturated amines **41**, **42**, **45**, **46**, **53–55**, and **57** with 75% H_2SO_4 (60 °C, 8 h) had two following objectives: (1) synthesize diverse cyclic analogues (2-alkyl or aryl substituted tetrahydroquinolines) of corresponding 4-amino-1-heptenes and 4-amino-1-butenes and (2) prepare some aminoalcohols related to the same aminoalkenes. This attempt resulted in the formation of a mixture of 1,2,3,4-tetrahydroquinolines and aminoalcohols, which were separated by alumina column chromatography (Scheme 3).

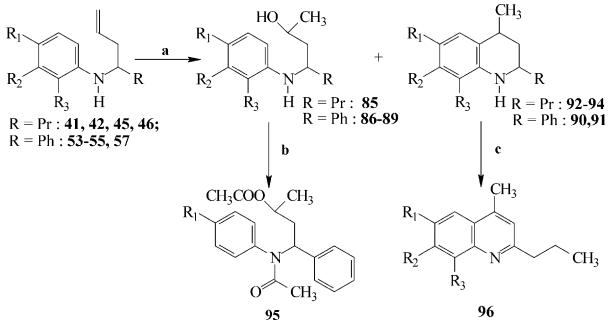
In the case of aminobutenes **53** and **54**, we were able to separate both 4-aminobutanols **86** and **87** and cyclic products **90** and **91**,[7] respectively. However, in the case of aminoalkenes **45**, **55**, and **57**, we isolated in pure form only the corresponding 4-aminobutanols **85**, **88**, and **89** in moderate yields. Finally, after the acid cyclization of aminoheptenes **41**, **42**, and **46**, the corresponding 2-*n*-propyl-tetrahydroquinolines **92–94** were obtained in **21–73**% yields. The presence of hydroxyl and amino groups in compounds **85–89** was established by both physical (mainly IR) and chemical (acetylation of compound **87** yielded derivative **95**) methods. One of the isolated tetrahydroquinolines (**92**) was aromatised with DDQ[13] affording quinoline **96** (Scheme 3).



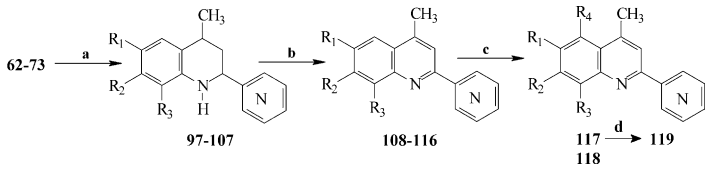
Scheme 1. Preparation of *N*-substituted aminoalkenes: (a) $ArNH_2$, EtOH (benzene or toluene), reflux; (b) $BnNH_2$, benzene, reflux; (c) allylmagnesium bromide/Et_2O, 10–24 °C, then H_2O/NH_4Cl/ice.



Scheme 2. Transformation of 4-*N*-arylamino-4-phenyl (8-quinolinyl)-1-butenes: (a) Ac_2O/Et_3N (cat), Δ; (b) allylbromide, K_2CO_3, acetone, reflux; (c) BF_3Et_2O, reflux.



Scheme 3. Transformation of aminoheptenes and aminobutenes: (a) H_2SO_4 (75%), 60 °C, 8 h; (b) Ac_2O, Et_3N (cat), Δ; (c) DDQ, benzene.



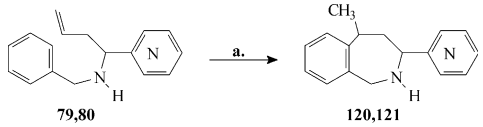
Scheme 4. Transformation of 4-methyl-(tetrahydro)quinolines. (a) H_2SO_4 (85%), $CHCl_3$, 90 °C, 10–12 h; (b) S, 270–300 °C, 10–20 min; (c) HNO_3, H_2SO_4, −8 °C; (d) $NaBH_4$, Pd/C, MeOH, rt.

Next, a series of 4-*N*-arylamino-1-butenes with a pyridine ring at C-4 **62–73** was used in the preparation of its cyclic analogues **97–107** in good yields. Tetrahydroquinolines **97–101** and **103–107** were prepared using 85% H_2SO_4 (90 °C, 10–15 h) meanwhile methoxy tetrahydroquinoline derivative **102** was obtained with PPA (95 °C, 12 h) (Scheme 4).

Since the obtained tetrahydroquinoline derivatives have two asymmetric carbons, they could contain a couple of diastereomers. GC–MS study of the crude of reaction showed that these tetrahydroquinolines are formed either as a unique diastereoisomer (**106** or **107**) or as a diastereoisomeric mixture (all other compounds), which differ in the arrangement of the methyl group at C-4 and of pyridyl ring at C-2. Its ratio varies considerably and depends on the chemical nature of *N*-arylamino fragment in the aminobutenes.[14] Based on our previous reports[15,16] and on the NMR data as well as COSY and NOESY techniques, we assume that the major isomers have the *cis* form (2e,4e orientation of groups), while minor isomers possess a 2e,4a disposition. Purification process (column chromatography on alumina) allowed us to obtain the *cis* isomer as the sole product for several tetrahydroquinolines **97**, **98**, and **100**. However, we were unable to separate diastereoisomeric mixtures for other tetrahydroquinolines. These results coincided with those found in new 2-*n*-propyl substituted tetrahydroquinolines **92–94** and reported 2-phenyl-tetrahydroquinolines **90** and **91**.[7]

Conversion of the prepared tetrahydroquinolines into the corresponding quinolines **108–116** was carried out by heating with powdered sulfur[17] in good yields. Final quinolines **109** and **110** were subjected to electrophilic nitration reaction using a nitric and sulfuric acid mixture to produce regioselectively 5-nitroquinoline derivatives **117** and **118**. Amino derivative **119** was reduced smoothly upon treatment with $NaBH_4$ with Pd/C in methanol[18] (Scheme 4).

Analogous electrophilic intramolecular cyclization of *N*-benzyl substituted 4-amino-1-butenes **79** and **80** afforded tetrahydro-[2]benzazepines **120** and **121** containing pyridyl ring[19,20] (Scheme 5).



Scheme 5. Transformation of 4-*N*-benzylamino-4-pyridyl-1-butenes. (a) H_2SO_4 concd, $CHCl_3$, 85–90 °C, 10–12 h.

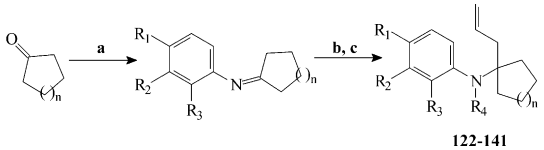
Finally, we prepared diverse series of *N*-(1-allylcycloalkyl)arylamines **122–141**. These 4,4-disubstituted analogues of 4-aryl (hetaryl)-4-*N*-arylamino-1-butenes are readily available from corresponding ketimines and allylmagnesium bromide[21–23] (Scheme 6).

Antifungal assays and structure–activity relationships

To study the structure–activity relationships, different type of structures and the effects of structural changes in different regions of the molecules were considered: (a) Change of the R substituent in the general structure of Figure 1 by alkyl (compounds type A in Table 1); phenylalkyl (type B); phenyl (type C); or alternative ring systems, pyridyl (type D) and quinolinyl (type E). (b) Introduction of a methylene between N and ring a (compounds type F). (c) Elimination of the double bond of the allyl radical (types G and H). (d) Introduction of different substituents on ring **a** and on the N atom in different type of compounds. (e) Cyclization of compounds type A, C, and D to tetrahydroquinolines types I, J, M, and quinolines types L and N.

A panel of dermatophytes including *Microsporum canis*, *Microsporum gypseum*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, and *Epidermophyton floccosum* were used for the antifungal evaluation of homoallylamines **41–84**, allyl-reduced derivatives **85–89**, tetrahydroquinolines **90–94** and **96–107**, quinolines **95**, **96**, and **108–119** and related compounds **120–141** with the agar dilution method. Concentrations up to 250 μg/mL of each compound were added to growth media according to reported procedures.[24] Compounds producing no inhibition at 250 μg/mL were considered inactive.

Results of the antifungal assays are shown in Tables 1–3. Regarding 4-alkyl- and 4-arylalkyl-4-*N*-arylamino-1-butenes (**41–52**, types A and B), results showed that they did not possess any significant antifungal activity, and that neither the presence of donor or acceptor substituents on ring **a** nor their position produced any significant variation in the activity. These results confirm our previous findings obtained with a lower number of compounds.[7]



Scheme 6. Preparation of *N*-(1-allylcycloalkyl)arylamines and their derivatives: (a) $ArNH_2$, benzene or toluene, reflux; (b) allylmagnesium bromide, Et_2O, 10–24 °C, then H_2O, NH_4Cl, ice; (c) Ac_2O, Et_3N (cat), Δ; (c) DDQ, benzene.

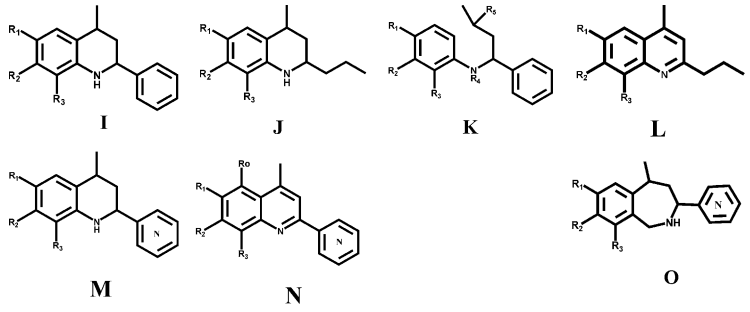
In turn, among compounds type C, those possessing none or a sole substituent in the *para* position of ring a (**53**–**56**), showed strong activity against *E. floccosum* and moderate activity against the rest of dermatophytes. The presence of a bulky substituent in the *o*-position (**57**), the change of position of a methoxy group to the *meta* position (**56**→**58**) or the presence of more than one substituent on ring **a** (**59**–**61**) drastically diminished the activity. The introduction of a substituent on the N atom (**56**→**81** or **82**) and the saturation of the allyl moiety (compare compounds **53**/**86**; **54**/**87**; **55**/**88**; **57**/**89**), rendered almost inactive compounds.

In contrast with these weak antifungal properties, the change of phenyl ring by alternative heterocycle rings such as α-, β-, or γ-pyridyl (compounds type D) or quinolinyl (type E) displayed a variety of activities, many compounds of the series inhibiting all the tested fungi at low concentrations.

Regarding the activity showed by homoallylamines with 4-β-pyridyl moieties, structures with an halogen in the *p*-position (**69**–**71**) displayed the best antifungal activities (MICs 1.5–25 μg/mL). The non-substituted and the *p*-methyl substituted compounds **62** and **63**, inhibited all the dermatophytes, with higher MICs (12.5–50 and 6.25–50 μg/mL respectively) being *M. canis, T. mentagrophytes* and *T. rubrum* the most susceptible species (MICs < 20 μg/mL). It is noteworthy that when the *p*-substituent is a methoxy or a 3,4-methylenedioxy group (structures **67** and **68**), the activity falls down, with all MICs ≥ 25 μg/mL. These results show a clear difference with 4-aryl derivatives **53**–**56**, where the *p*-OCH_3 phenyl derivative was the most active compound.

Another structure–activity feature observed in homoallylamines containing a β-pyridyl moiety is that the activity against *E. floccosum* is severely affected when ring

Table 2. MICs values of tetrahydroquinolines, quinolines and related compounds acting against dermatophyes



Compd	Type	Ro	R_1	R_2	R_3	R_4	R_5	N Position	*M.c.*	*M.g.*	*T.m*	*T.r.*	*E.f*
90	I	—	H	H	H	—		—	50	25	25	25	12.5
91	I	—	CH_3	H	H	—		—	50	25	50	25	12.5
92	J	—	H	H	H	—	—	—	125	125	125	125	62.5
93	J	—	H	H	CH_3	—	—	—	>250	250	125	250	250
94	J	—	F	H	H	—	—	—	100	125	125	125	125
95	K	—	CH_3	H	H	$COCH_3$	$COCH_3$	—	50	>250	>250	>250	>250
96	L	—	H	H	H	—	—	—	>250	>250	>250	>250	>250
97	M	—	H	H	H	—	—	β	62.5	50	62.5	62.5	50
98	M	—	CH_3	H	H	—	—	β	250	250	250	250	25
99	M	—	CH_3	H	H	—	—	β	25	25	12.5	50	50
100	M	—	CH_3	H	H	—	—	γ	50	25	25	50	50
101	M	—	H	H	$CH(CH_3)_2$	—	—	β	50	50	25	25	25
102	M	—	CH_3O	H	H	—	—	β	62.5	125	25	125	125
103	M	—	Br	H	H	—	—	β	62.5	50	125	25	25
104	M	—	Cl	H	H	—	—	β	25	25	12.5	12.5	6.25
105	M	—	F	H	H	—	—	β	25	50	25	50	25
106	M	—	F	H	F	—	—	β	62.5	50	125	50	50
107	M	—	H	H	I	—	—	β	25	50	25	12.5	25
108	N	—	H	H	H	—	—	β	50	25	50	50	50
109	N	—	CH_3	H	H	—	—	β	25	25	25	50	25
110	N	—	CH_3	H	H	—	—	α	6.25	12.5	6.25	12.5	12.5
111	N	—	CH_3	H	H	—	—	γ	62.5	62.5	25	25	12.5
112	N	—	H	H	$CH(CH_3)_2$	—	—	β	62.5	>250	>250	50	>250
113	N	—	Br	H	H	—	—	β	12.5	12.5	12.5	12.5	6.25
114	N	—	Cl	H	H	—	—	β	50	62.5	25	25	25
115	N	—	F	H	H	—	—	β	12.5	25	25	25	12.5
116	N	—	F	H	F	—	—	β	25	25	25	50	12.5
117	N	NO_2	CH_3	H	H	—	—	β	>250	>250	>250	>250	250
118	N	NO_2	CH_3	H	H	—	—	α	>250	>250	>250	>250	>250
119	N	NH_2	CH_3	H	H	—	—	β	12.5	25	25	25	12.5
120	O	—	H	H	H	—	—	β	>250	>250	250	250	125
121	O	—	H	H	H	—	—	γ	>250	>250	250	250	250

M.c: *Microsporum canis* C 112. *M.g*: *Microsporum gypseum* C 115; *T.m.*: *Trichophyton mentagrophytes* ATCC 9972; *T.r.*: *Trichophyton rubrum* C113. *E.f.*: *Epidermophyton floccosum* C 114.

a possess a substituent in the *ortho* position (compare compounds **62**/**66** and **71**/**72**).

In addition, it is interesting to note that when the β-pyridyl changes to α- or γ-pyridyl (**63**→**64** or **65**, respectively) the antifungal activity decreased and this decrease is higher in the α isomer.

The introduction of a flexible chain between ring **a** and the N atom in β- or γ-pyridyl derivatives (compounds type F, **79** and **80**) rendered inactive compounds (compare **62** with **79**).

Quinolinyl derivatives with different types of substituents in ring **a** (**74**–**78**, **83**, and **84**) were devoid of activity in all tested fungi.

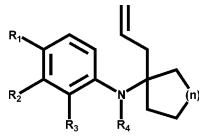
Regarding the cyclization of 4-alkyl derivatives **41**, **42**, and **46** to tetrahydroquinolines **92**–**94**, it is interesting to note an enhancement of activity against almost all dermatophytes tested although none of them possess a significative activity. The oxidation of **92** to quinoline **96** led to a complete loss of activity. The same enhancement trend is observed by cyclization of 4-aryl derivatives **53** and **54** to tetrahydroquinolines **90** and **91**, with the difference that the activity in this type of compounds was enhanced when tetrahydroquinolines were oxidized to quinolines (see ref 7).

In turn, α-pyridyl tetrahydroquinoline **99** showed better activities than the corresponding open derivative **64** and 4-γ-pyridyl derivative **100** showed similar activities than the corresponding homoallylamine **65**. Compounds **120** and **121**, analogues of tetrahydroquinolines but with a bigger saturated ring, did not show any significative activity neither. α-Pyridyl quinoline **110** displayed better activities than tetrahydroquinoline **99**, and the activities of γ-pyridyl quinoline **64** were similar than those of tetrahydroquinoline **53**.

In contrast, when the most active homoallylamines possessing a 4-β-pyridyl moiety in their structures were cyclised to tetrahydroquinolines, less active structures were obtained in most cases (compare MICs of compounds **62**/**97**; **63**/**98**; **69**/**103**; **70**/**104**; **71**/**105**). The oxidation of β-pyridyl substituted tetrahydroquinolines to the corresponding quinolines did not introduce homogenous changes in the antifungal properties, although an enhancement in the activity was observed in most compounds (compare **97**/**108**; **98**/**109**; **103**/**113**; **105**/**115**; **106**/**116**). Quinolines **117**–**119**, obtained by introducing a nitro group to structures **98** and **99** were devoid of activity, this effect having been already observed in homoallylamines.

Another type of homoallylamines, possessing a spiro atom (**122**–**141**), were tested in order to widen the insight about activities of homoallyamines. Although with low MICs, compounds **122**–**125** and **137**–**141** displayed antifungal activities and some interesting SAR could be extracted: Unsubstituted compounds (**122**–**125**) were the most active of this series and within them, the size of the spiro ring seemed to play a role in the antifungal activity, (**123**) with $n=2$ (MICs = 50–125 μg/mL) or **124** with $n=3$ (MICs = 50–250 μg/mL) being the most active compounds. Within substituted compounds with $n=2$,

Table 3. MICs values of *N*-(1-allylcycloalkyl)arylamines **122**–**141**



P

Compd	Type	R_1	R_2	R_3	R_4	n	*M.c.*	*M.g.*	*T.m*	*T.r.*	*E.f*
122	P	H	H	H	H	1	100	125	62.5	62.5	250
123	P	H	H	H	H	2	50	50	125	50	125
124	P	H	H	H	H	3	62.5	50	125	25	250
125	P	H	H	H	H	4	100	250	>250	>250	>250
126	P	H	H	CH_3	H	1	250	>250	>250	250	250
127	P	CH_3O	H	H	H	1	250	>250	125	250	250
128	P	CH_3O	CH_3O	H	H	2	>250	>250	125	250	250
129	P	OCH_2O	H	H	2	250	>250	250	250	250	
130	P	Cl	H	H	H	2	>250	>250	>250	>250	>250
131	P	H	H	F	H	2	>250	>250	>250	>250	>250
132	P	Cl	H	H	H	3	>250	>250	>250	>250	>250
133	P	H	H	F	H	3	>250	>250	>250	>250	>250
134	P	H	H	CH_3	H	4	>250	>250	>250	>250	>250
135	P	CH_3O	H	H	H	4	100	125	>250	100	250
136	P	Cl	H	H	H	4	>250	>250	>250	>250	>250
137	P	CH_3CH_2O	H	H	H	2	100	100	100	100	250
138	P	CH_3O	H	H	H	2	100	125	100	100	100
139	P	CH_3O	H	H	H	3	100	125	100	100	100
140	P	CH_3O	H	H	$COCH_3$	2	100	100	125	50	50
141	P	CH_3CH_2O	H	H	$COCH_3$	2	>250	250	>250	100	100

M.c: *Microsporum canis* C 112. *M.g*: *Microsporum gypseum* C 115; *T.m.*: *Trichophyton mentagrophytes* ATCC 9972; *T.r.*: *Trichophyton rubrum* C113. *E.f.*: *Epidermophyton floccosum* C 114.

the activity lowers down according with the following order of substitution of ring **a**: compounds with donor substituents in the 4-position (**137** and **138**) displayed better activities than structures with donor substituents in the 3,4 positions (**128** and **129**), which in turn are better than compounds with acceptor substituents (**130–133**). In contrast, substitution in the N atom (**140** and **141**) seems not to play an important role in the activity.

To a better understanding of experimental antifungal results, we conducted a computer-assisted conformational and electronic study on the most representative molecules which could aid in the finding of the potentially reactive centers for these compounds. Before computing its electronic properties, it was necessary to define the three-dimensional geometry of the relevant conformation of the molecules which could be a low-energy one or that topographically congruent with other active compounds in this series.

Once obtained the relevant conformations for the different homoallylamines and derivatives, we evaluated the electronic aspects of the molecules using Molecular Electrostatic Potentials (MEPs) in an attempt to find the potentially reactive sites. MEPs are of particular value for this purpose, since they allow the visualization of the electron density of a molecular system, strongly depending on the molecule conformation. Indeed, each three-dimensional arrangement of atoms in a molecule correspond to a different electronic distribution and hence a different MEP.

Conformational analysis were conducted according with the Computational Analysis Section within the

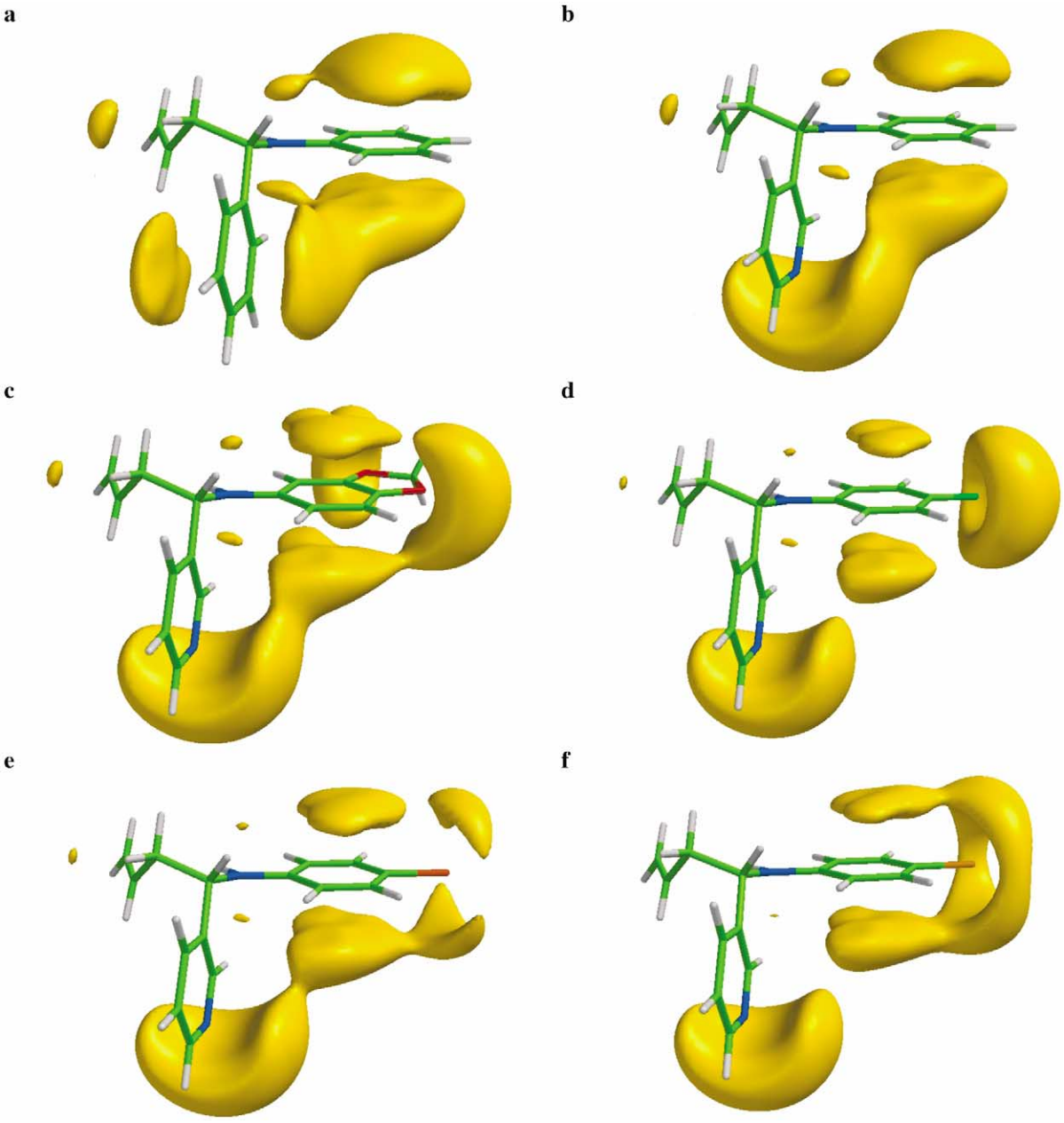


Figure 2. MEPS calculated using the RHF/3-21G optimized geometries for compounds: (a) **53**, (b) **62**, (c) **68**, (d) **69**, (e) **70**, and (f) **71**.

Experimental. Electronic studies were carried out from MEPs using ab initio RHF/3-21G calculations. As seen above and in a previous paper,[7] experimental results showed that the most active homoallylamines possessed aryl or mainly β-pyridyl **b**-rings. Compounds possessing only an aromatic ring (**a**) were inactive (**41**–**52**) or displayed very low activity (**122**–**141**).

In accordance with these results, computational studies were carried out with the active homoallylamines **53**, **62**, and **68**–**71** (Fig. 2a–f).

The analyses of MEPs showed four regions with negative potential for all compounds: (1) a region generated by the aryl **a**; (2) a region generated by ring **b**; and (3 and 4) two small regions generated by both the NH group and the double bond of the allyl moiety, which are shallower than those due to aromatic rings.

Figure 2 showed that (a) all compounds possessing both aromatic rings **a** and **b** (Fig. 2a–f) showed negative regions around them, which seems to be necessary but not sufficient by itself to produce antifungal effect (a great number of compounds having two aromatic rings were devoid of antifungal activity). (b) Negative potential in zones 3 and 4 seemed not to contribute to the activity: Compounds possessing electro-donating groups such as methylenedioxy (**68**) (Fig. 2c) show clear negative zones 3 and 4. In contrast, the most active compounds (**69**–**71**) (Fig. 2d–f, respectively) show a neat diminution of the negative potential on zones 3 and 4, suggesting that the characteristic electronic features for compounds of these series to display antifungal activities would be both the presence of negatives zones around rings **a** and mainly **b**, and a very weak negative potential in zones 3 and 4.

Mode of action studies

To gain insight into the mode of action of the most active compounds, we tested 4-*N*-arylamino-4-β-pyridyl-1-butenes **62**, **63**, and **69**–**71** for their capacity of in vitro inhibiting the *Saccharomyces cerevisiae* (1,3)-β-D-glucan synthase[25] or chitin synthase-1,[26] enzymes that catalyze the synthesis of the major polymers of the fungal cell-wall, (1,3)-β-D-glucan and chitin, respectively. Results on the in vitro assays are listed in Table 4.

Table 4. (1,3)-β-D-glucan and chitin synthase inhibitory capacity expressed as % of inhibition and IC_{50} values (μg/μL)

Compd	(1,3)-β-D-Glucan synthase assay		Chitin synthase assay	
	% I[a]	IC^{b}_{50}	% I[c]	IC^{b}_{50}
62	43.44±1.6	>0.50	40.00±2.0	>0.50
63	73.00±2.28	0.21	92.44±2.8	0.17
69	93.83±0.1	0.17	91.25±1.7	0.09
70	75.65±0.04	0.14	89.1±0.06	0.06
71	76.30±3.97	0.27	96.52±2.3	0.04
104	98.83±1.94	0.02	98.59±2.0	0.01
Pap		0.10		
Nik				0.0006[d]

Pap, Papulacandin B; Nik, Nikkomicin.
[a]% of inhibition at 20 μg/assay (total volume: 40 μL): mean±SEM.
[b]Concentration (μg/μL) that produces 50% of inhibition.
[c]% of inhibition at 20 μg/assay (total volume: 50 μL): mean±SEM.
[d]Value obtained from ref 39.

Regarding the activity against chitin synthase-1, homoallylamines **63** and **69**–**71**, substituted in ring **a**, exhibited strong inhibitory activities at 20 μg/assay (inhibition ranging from 89 to 96%). Serial dilutions of them (1, 2, 5, 10, and 20 μg/assay) were tested for enzyme inhibition and their average inhibitory effects were calculated (Fig. 3). The IC_{50} values were all ≤0.17 μg/μL, possessing compound **63**, with a donor substituent, a higher IC_{50} value (=0.17 μg/μL) than compounds with acceptor subsituents **69**–**71** (IC_{50}=0.04–0.09 μg/μL). Compound **62**, without any substituent on ring **a**, was a very weak inhibitor of chitin synthase with 40% inhibition at 20 μg/assay.

Results obtained from (1,3)-β-D-glucan synthase assays showed the same pattern of activity, with non-sub-

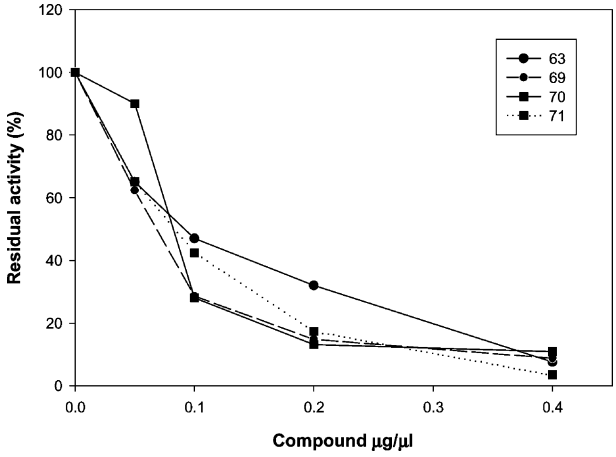


Figure 3. Effect of different concentrations of 4-*N*-arylamino-4-pyridyl-1-butenes **63** and **69**–**71** on the in vitro incorporation of [^{14}C]-*N*-acetylglucosamine into insoluble chitin, expressed as % of residual activity of the enzyme chitin synthase-1.

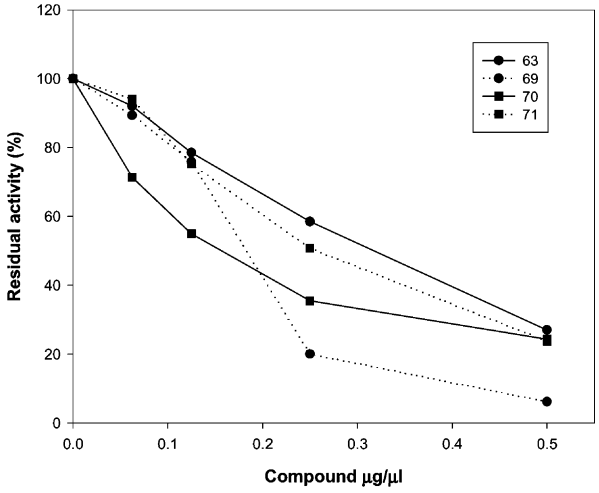


Figure 4. Effect of different concentrations of 4-*N*-arylamino-4-pyridyl-1-butenes **63** and **69**–**71** on the in vitro incorporation of [^{14}C]-glucose into insoluble (1,3)-β-D-glucan, expressed as % of residual activity of the enzyme (1,3)-β-D-glucan synthase.

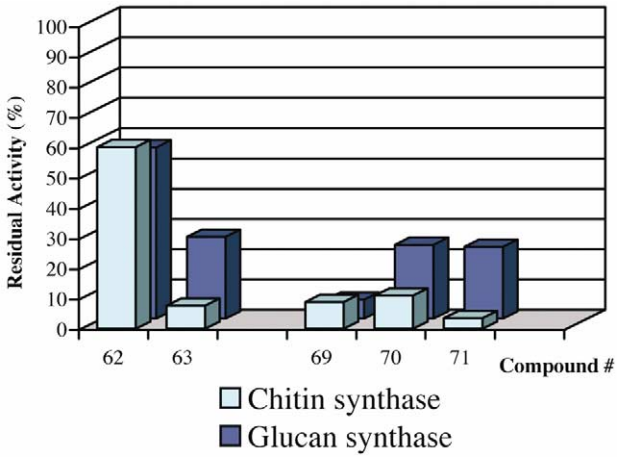


Figure 5. Comparative values of the inhibitory activities of antifungal 4-*N*-arylamino-4-pyridyl-1-butenes **63** and **69–71**, against (1,3)-β-D-glucan synthase and chitin synthase-1, expressed as % of residual activity.

stituted homoallylamine **62** possessing a weak capacity of inhibiting the enzyme with a IC_{50} >0.50 μg/μL. In contrast, compounds **63** and **69–71** were very good inhibitors of this enzyme (IC_{50} between 0.14 and 0.27 μg/μL) (Fig. 4).

From these results, we can deduce that substituted homoallylamines with β-pyridyl moieties might act by inhibiting the biosynthesis of the major polymers of the fungal cell wall as one of their antifugal mechanism of action. They inhibit both (1,3)-β-D-glucan and mainly chitin synthases as it is clearly shown in the comparative Figure 5.

In contrast, although active in cellular assays, non-substituted homoallylamine **62** seems not to act by this mechanism.

Conclusions

In this article, we report the synthesis and fungistatic effects of new series of homoallylamines and related compounds acting against dermatophytes, the structure–activity relationships and studies of their mechanism of action. Among compounds tested, homoallyalmines with a 4-β-pyridyl as ring **b** and an halogen in the *p*-position of ring **a**, displayed the best antifungal activities (MICs 1.5–25 μg/mL). When the most active homoallylamines were cyclized to tetrahydroquinolines, less active structures were obtained in most cases. The oxidation of β-pyridyl substituted tetrahydroquinolines to the corresponding quinolines, did not introduce homogenous changes in the antifungal properties, although an enhancement in the activity was observed in most compounds.

The analyses of Molecular Electrostatic Potential (MEPs) strongly suggested that the characteristic electronic features for compounds of these series to display antifungal activities would be both the presence of negatives zones around rings **a** and **b**, and a very weak negative potential in the zones of the NH group and the double bond of the allyl moiety.

Regarding their mode of action, substituted homoallylamines with β-pyridyl moieties might act by inhibiting the biosynthesis of the major polymers of the fungal cell wall as one mechanism of action. They inhibit both (1,3)-β-D-glucan and mainly chitin synthases. In contrast, although active in cellular assays, non-substituted homoallylamine with β-pyridyl ring **b**, seems not to act by this mechanism.

Experimental

Chemistry

All reagents were purchased from Aldrich, commercial grade. IR spectra were recorded on a Nicolet Avatar 360-FT spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AM-400, Bruker AC-300, or on a Bruker AC-200 spectrometer. Chemical shifts are reported in ppm (δ) relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.26 ppm for protons and at 77.0 ppm for carbons). 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; quin., quintet; quin-d, quintet double; sext., sextet; sept, septet; 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%-phenylpoly(dimethylsiloxane)]. Elemental analyses were performed on a Leco CHN-600 or on a Perkin-Elmer 2400 Series II analyzers. Column chromatography was carried out on columns packed with SiO_2 or Al_2O_3.

The aldimine formation was performed according to literature reports.[7,10] Aldimines were obtained with nearly quantitative yields. The imine structure was confirmed by IR spectroscopy. Starting imines were used in subsequent synthesis without further purification. General procedure for the synthesis of *N*-arylaminoalquenes (**41–78**) have been reported in ref 7.

4-*N*-Arylamino-1-heptenes (41–46)

Compound **41** has been reported previously in ref 7.

4-*N*-(2-Methylphenyl)amino-1-heptene (42). Yellowish oil. Yield 87%. IR (film) ν 3430 cm^{-1} (s, NH). ^{1}H NMR (400 MHz) δ0.81 (3H, t, J = 7.1 Hz, 7-H), 1.22–1.42 (4H, m, 5- and 6-H), 1.99 (3H, s, CH_3), 2.19 (2H, sept., J = 5.7 Hz, 3-H), 3.23 (1H, br. s., H-N), 3.36 (1H, t, J = 6.0 Hz, 4-H), 4.94 (1H, dd, J = 5.4, 1.3 Hz, 1-H_A), 4.97 (1H, s, 1-H_B), 5.64–5.76 (1H, m, 2-H), 6.47 (1H, d, J = 7.8 Hz, 6-H_{Ar}), 6.50 (1H, d, J = 7.1 Hz, 4-H_{Ar}), 6.89 (1H, d, J = 7.2 Hz, 3-H_{Ar}) 6.99 (1H, td, J = 8.3, 1.2 Hz, 5-H_{Ar}); ^{13}C NMR (100 MHz) δ 14.0, 17.3, 19.1, 36.6, 38.5, 51.5, 109.9, 116.2, 117.3, 121.4, 126.7, 130.1, 134.9, 145.4. MS *m*/*z* (EI) 203 (M^+, 10%), 162 (M−C_3H_5,

100%). Found: C, 82.57; H, 10.68; N, 6.65; calcd for $C_{14}H_{21}N$: C, 82.76; H, 10.34; N, 6.90.

4-*N*-(4-Methoxylphenyl)amino-1-heptene (43). Yellowish oil. Yield 75%. IR (film) ν 3399 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 0.80 (3H, t, $J=7.0$ Hz, 7-H), 1.28–1.35 (4H, m, 5- and 6-H), 2.15 (2H, td, $J=4.2$, 0.9 Hz, 3-H), 3.05 (1H, br. s., H–N), 3.21 (1H, t, $J=5.8$ Hz, 4-H), 3.57 (3H, s, CH_3O), 4.93 (1H, dt, $J=6.5$, 2.2 Hz, 1-H_A), 4.96 (1H, s, 1-H_B), 5.66–5.72 (1H, m, 2-H), 6.41 (2H, d, $J=8.9$ Hz, 2(6)-H_{Ar}), 6.64 (2H, d, $J=8.9$ Hz, 3(5)-H_{Ar}); ^{13}C NMR (100 MHz) d 14.0, 19.0, 36.5, 38.3, 52.9, 55.4, 114.2 (2C), 114.7 (2C), 117.1, 134.9, 141.9, 151.6. MS *m*/*z* (EI) 219 (M^+, 9%), 178 (M−C_3H_5, 100%). Found: C, 76.43; H, 9.96; N, 6.21; calcd for $C_{14}H_{21}NO$: C, 76.71; H, 9.59; N, 6.39.

4-*N*-(4-Chlorophenyl)amino-1-heptene (44). Dark yellowish oil. Yield 86%. IR (film) ν 3418 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 0.78 (3H, t, $J=7.5$ Hz, 7-H), 1.24–1.29 (4H, m, 5- and 6-H), 1.92–1.98 (2H, m, 3-H), 3.29 (1H, t, $J=6.1$ Hz, 4-H), 4.96–5.02 (2H, m, 1-H), 5.62–5.76 (1H, m, 2-H), 6.39 (2H, d, $J=8.8$ Hz, 2(6)-H_{Ar}), 6.99 (2H, d, $J=8.8$ Hz, 3(5)-H_{Ar}); ^{13}C NMR (100 MHz) δ 13.7, 19.2, 36.5, 38.4, 52.3, 114.4 (2C), 117.6, 126.7, 128.7 (2-C), 134.6, 146.4. MS *m*/*z* (EI) 223 (M^+ for ^{35}Cl, 8%), 182 (M−C_3H_5, 100%). Found: C, 69.60; H, 8.29; N, 6.20; calcd for $C_{13}H_{18}ClN$: C, 69.80; H, 8.05; N, 6.27.

4-*N*-(4-Bromophenyl)amino-1-heptene (45). Yellowish oil. Yield 91%. IR (film) ν 3412 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 0.79 (3H, t, $J=7.1$ Hz, 7-H), 1.20–1.41 (4H, m, 5- and 6-H), 2.09–2.18 (2H, m, 3-H), 3.23 (1H, t, $J=5.9$ Hz, 4-H), 3.33 (1H, br. s., H–N), 4.94 (1H, ddd, $J=8.4$, 3.2, 1.5 Hz, 1-H_A), 4.96 (1H, s, 1-H_B), 5.60–5.71 (1H, m, 2-H), 6.29 (2H, d, $J=8.8$ Hz, 2(6)-H_{Ar}), 7.07 (2H, d, $J=8.8$ Hz, 3(5)-H_{Ar}); ^{13}C NMR (100 MHz) δ 14.0, 19.0, 38.3, 40.8, 52.0, 107.9, 114.5 (2C), 117.2, 131.7 (2C), 134.5, 146.7. MS *m*/*z* (EI) 267 (M^+ for ^{79}Br, 9%), 226 (M−C_3H_5, 100%). Found: C, 58.05; H, 6.85; N, 5.36; calcd for $C_{13}H_{18}BrN$: C, 58.21; H, 6.72; N, 5.22.

4-*N*-(4-Fluorophenyl)amino-1-heptene (46). Dark yellowish oil. Yield 82%. IR (film) ν 3414 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ0.79 (3H, t, $J=7.1$ Hz, 7-H), 1.26–1.34 (4H, m, 5- and 6-H), 2.10–2.14 (2H, m, 3-H), 3.20 (1H, t, $J=5.8$ Hz, 4-H), 4.92 (1H, ddd, $J=9.0$, 3.0, 1.5 Hz, 1-H_A), 4.96 (1H, d, $J=0.9$ Hz, 1-H_B), 5.62–5.73 (1H, m, 2-H), 6.35 (2H, dd, $J=8.3$, 4.5 Hz, 2(6)-H_{Ar}), 6.72 (2H, t, $J=8.3$ Hz, 3(5)-H_{Ar}); ^{13}C NMR (100 MHz) δ 13.7, 19.0, 39.5, 39.6, 52.6, 113.9 (2C), 115.3 (2C), 117.3, 134.7, 144.2, 156.5 (d, $J=-8$ Hz). MS *m*/*z* (EI) 207 (M^+, 6%), 166 (M−, 100%). Found: C, 75.66; H, 8.86; N, 6.45; calcd for $C_{13}H_{18}FN$: C, 75.36; H, 8.70; N, 6.76.

4-*N*-Arylamino-6-phenyl-1-hexenes (47–52)

6-Phenyl-4-*N*-phenylamino-1-hexene (47). Yellowish oil. Yield 67%. IR (film) ν 3410 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 1.65 (1H, m, 5-H_A), 1.77 (1H, m, 5-H_B), 2.19 (2H, m, 3-H), 2.70 (2H, t, $J=7.3$ Hz, 6-H), 3.40 (1H, m, 4-H), 4.89 (2H, m, 1-H), 5.65 (1H, m, 1-H), 6.09–7.15 (10H, m, H_{Ar}); ^{13}C NMR (100 MHz) δ 32.3, 35.9, 38.5, 51.6, 113.1 (2C), 116.8, 117.4, 125.7, 128.1 (2C), 128.5 (2C), 129.2 (2C), 134.5, 141.6, 147.3. MS *m*/*z* (EI) 251 (M^+, 5%), 91 (M−$C_{11}H_{14}N$, 100%). Found: C, 86.23; H, 8.65; N, 5.23; calcd for $C_{18}H_{21}N$: C, 86.05; H, 8.37; N, 5.58.

4-*N*-(4-Methylphenyl)amino-6-phenyl-1-hexene (48). Yellowish oil. Yield 79%. IR (film) ν 3403 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 1.54–1.63 (1H, m, 5-H_A), 1.67–1.74 (1H, m, 5-H_B), 2.09 (3H, s, CH_3), 2.11–2.17 (2H, m, 3-H), 2.48–2.62 (2H, m, 6-H), 3.10 (1H, br. s., H–N), 3.24 (1H, td, $J=6.4$, 1.6 Hz, 4-H), 4.89 (2H, dd, $J=7.9$, 1.7 Hz, 1-H_A), 4.93 (1H, s, 1-H_B), 5.58–5.69 (1H, m, 2-H), 6.30 (2H, d, $J=8.3$ Hz, 2(6)-H_{Ar}), 6.81 (2H, d, $J=8.3$ Hz, 3(5)-H_{Ar}), 6.99 (1H, d, $J=8.1$ Hz, 4-H_{Ph}), 7.02 (2H, dd, $J=7.0$, 1.0 Hz, 2(6)-H_{Ph}), 7.10 (2H, dd, $J=7.0$, 1.5 Hz, 3(5)-H_{Ph}); ^{13}C NMR (100 MHz) δ 20.3, 32.2, 35.8, 38.4, 51.9, 113.4 (2C), 117.5, 125.7, 125.9, 127.9 (2C), 128.6 (2C), 129.7 (2C), 134.6, 141.9, 145.2. MS *m*/*z* (EI) 265 (M^+, 10%), 224 (M−C_3H_5, 100%). Found: C, 85.67; H, 8.96; N, 5.35; calcd for $C_{19}H_{23}N$: C, 86.04; H, 8.68; N, 5.28.

4-*N*-(2-Methylphenyl)amino-6-phenyl-1-hexene (49). Transparent oil. Yield 89%. IR (film) ν 3430 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 2.01–2.09 (2H, m, 5-H), 2.28 (3H, s, CH_3), 2.53–2.55 (2H, m, 3–H), 2.87–2.95 (2H, m, 6-H), 3.71 (1H, t, $J=7.6$ Hz, 4-H), 5.25 (2H, d, $J=8.4$ Hz, 1-H_A), 5.29 (2H, s, 1-H_B), 5.96–6.03 (1H, m, 2-H), 6.72 (1H, d, $J=7.6$ Hz, 6-H_{Ar}), 6.81 (1H, t, $J=7.3$ Hz, 4-H_{Ar}), 7.22–7.47 (7H, m, 3(5)-H_{Ar} and H_{Ph}); ^{13}C NMR (100 MHz) δ 17.4, 32.3, 36.0, 38.4, 51.4, 110.0, 116.3, 117.7, 121.7 (2C), 125.8, 127.0 (2C), 128.3 (2C), 130.3, 134.6, 141.8, 145.3. MS *m*/*z* (EI) 265 (M^+, 8%). Found: C, 85.79; H, 8.96; N, 5.19; calcd for $C_{19}H_{23}N$: C, 86.04; H, 8.68; N, 5.28.

4-*N*-(4-Methoxyphenyl)amino-6-phenyl-1-hexene (50). Brown oil. Yield 90%. IR (film) ν 3400 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 1.78–2.67 (6H, m, 3-, 5- and 6-H), 3.18 (1H, br. s., H–N), 3.31 (1H, br. t, $J=8.9$ Hz, 4-H), 3.58 (3H, s, CH_3O), 4.81–4.88 (2H, m, 1-H), 5.47–5.59 (1H, m, 2-H), 6.32 (2H, d, $J=8.7$ Hz, 2(6)-H_{Ar}), 6.34 (2H, d, $J=8.7$ Hz, 3(5)-H_{Ar}), 6.59–7.14 (5H, m, H_{Ph}); ^{13}C NMR (100 MHz) δ 32.3, 35.8, 36.4, 52.6, 55.5, 114.6 (2C), 114.9 (2C), 117.6, 125.9, 128.1 (2C), 128.4 (2C), 134.6, 141.6, 142.0, 151.6. MS *m*/*z* (EI) 281 (M^+, 11%), 240 (M−C_3H_5, 100%). Found: C, 81.38; H, 8.48; N, 4.67; calcd for $C_{19}H_{23}NO$: C, 81.14; H, 8.19; N, 4.98.

4-*N*-(4-Bromophenyl)amino-6-phenyl-1-hexene (51). Yellowish oil. Yield 79%. IR (film) ν 3410 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 1.58–1.66 (1H, m, 5-H_A), 1.69–1.78 (1H, m, 5-H_B), 2.14–2.17 (2H, m, 3-H), 2.50–2.62 (2H, m, 6-H), 3.23 (1H, td, $J=6.4$, 1.2 Hz, 4-H), 3.38 (1H, br. s., H-N), 4.91–4.99 (2H, m, 1-H), 5.58–5.69 (1H, m, 2-H), 6.23 (2H, dd, $J=6.8$, 2.0 Hz, 2(6)-H_{Ar}), 7.05 (2H, dd, $J=6.8$, 2.0 Hz, 3(5)-H_{Ar}), 7.01–7.17 (5H, m, H_{Ph}); ^{13}C NMR (100 MHz) δ 32.1, 35.8, 38.7, 51.6, 108.2, 114.7 (2C), 117.7, 125.9, 128.2 (2C), 128.7 (2C),

131.9 (2C), 134.2, 141.6, 146.5. MS *m/z* (EI) 331 (M^+ for ^{81}Br, 3%). Found: C, 65.23; H, 6.35; N, 4.13; calcd for $C_{18}H_{20}BrN$: C, 65.46; H, 6.06; N, 4.24.

4-*N*-(4-Fluorophenyl)amino-6-phenyl-1-hexene (52). Yellowish oil. Yield 69%. IR (film) ν 3411 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 1.58–1.65 (1H, m, 5-H_A), 1.68–1.78 (1H, m, 5-H_B), 2.13 (1H, dd, *J* = 13.5, 7.0 Hz, 3-H_A), 2.16 (1H, dd, *J* = 13.5, 7.9 Hz, 3-H_B), 2.50–2.62 (2H, m, 6-H), 3.20 (1H, quin., *J* = 5.6 Hz, 4-H), 4.90–4.99 (2H, m, 1-H), 5.59–5.69 (1H, m, 2-H), 6.29 (2H, dd, *J* = 8.7, 4.5 Hz, 2(6)-H_{Ar}), 6.71 (2H, t, *J* = 8.7 Hz, 3(5)-H_{Ar}), 7.00 (1H, d, *J* = 8.2 Hz, 4-H_{Ph}), 7.06 (2H, d, *J* = 7.6 Hz, 2(6)-H_{Ph}), 7.13 (2H, t, *J* = 7.6 Hz, 3(5)-H_{Ph}); ^{13}C NMR (100 MHz) δ 32.7, 35.9, 38.3, 52.3, 114.1 (2C), 115.7 (2C), 117.7, 125.8, 128.0 (2C), 128.6 (2C), 134.4, 141.8, 143.9, 156.6 (d, *J* = −233.0 Hz). MS *m/z* (EI) 269 (M^+, 5%). Found: C, 80.11; H, 7.63; N, 5.31; calcd for $C_{18}H_{20}FN$: C, 80.30; H, 7.44; N, 5.20.

4-Aryl-4-*N*-arylamino-1-butenes (53–61)

Compounds **53–56** have been previously reported.[7]

4-Phenyl-4-*N*-(2-isopropylphenyl)amino-1-butene (57). Dark yellowish oil. Yield 85%. IR (film) ν 3439 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 1.18 (3H, d, *J* = 6.8 Hz, CH_3-*i*-Pr), 1.22 (3H, d, *J* = 6.8 Hz, CH'_3-*i*-Pr), 2.40 (1H, m, 3-H_A), 2.52 (1H, m, 3-H_B), 2.84 (1H, quin., *J* = 6.8 Hz, H–C-*i*-Pr), 4.25 (1H, br. s., H–N), 4.30 (1H, dd, *J* = 8.1, 4.7 Hz, 4-H), 5.04 (1H, td, *J* = 7.8, 1.5 Hz, 1-H_A), 5.11 (1H, t, *J* = 1.5 Hz, 1-H_B), 5.61–5.72 (1H, m, 2-H), 6.20 (1H, dd, *J* = 8.0, 0.8 Hz, 6-H_{Ar}), 6.54 (1H, td, *J* = 7.5, 1.1 Hz, 4-H_{Ar}), 6.77 (1H, td, *J* = 7.8, 1.5 Hz, 5-H_{Ar}), 7.00 (1H, dd, *J* = 7.5, 1.5 Hz, 3-H_{Ar}), 7.06–7.25 (5H, m, H_{Ph}); ^{13}C NMR (100 MHz) δ 22.4, 27.4, 43.7, 56.7, 111.8, 117.1, 118.3, 124.7, 126.1, 126.5, 126.8 (2C), 128.5 (2C), 131.9 (2C), 134.9, 143.6, 143.7. MS *m/z* (EI) 265 (M^+, 4%), 224 (M−C_3H_5, 100%). Found: C, 85.77; H, 8.93; N, 5.31; calcd for $C_{19}H_{23}N$: C, 86.04; H, 8.68; N, 5.28.

4-*N*-(3-Methoxyphenyl)amino-4-phenyl-1-butene (58). Yellowish oil. Yield 94%. IR (film) ν 3410 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 2.48–2.56 (1H, m, 3-H_A), 2.59–2.68 (1H, m, 3-H_B), 3.83 (3H, s, OCH_3), 4.48 (1H, dd, *J* = 7.8, 5.3 Hz, 4-H), 5.19 (1H, d, *J* = 17.2 Hz, 1-H_A), 5.20 (1H, d, *J* = 10.3 Hz, 1-H_B), 5.75–5.84 (1H, m, 2-H), 6.11 (1H, br.t, *J* = 2.1 Hz, 2-H_{Ar}), 6.24 (1H, br.dd, *J* = 8.1, 1.7 Hz, 6-H_{Ar}), 6.32 (1H, d, *J* = 1.6 Hz, 4-H_{Ar}), 7.17 (1H, t, *J* = 8.1 Hz, 5-H_{Ar}), 6.29–6.38 and 7.25–7.43 (5H, m, H_{Ph}); ^{13}C NMR (100 MHz) δ 43.0, 54.8, 57.1, 99.3, 102.4, 106.4, 118.2, 126.1, 126.9 (2C), 128.5 (2C), 129.7, 134.5, 143.4, 148.6, 160.4. MS *m/z* (EI) 253 (M^+, 4%), 212 (M−C_3H_5, 100%). Found: C, 80.78; H, 7.43; N, 5.38; calcd for $C_{17}H_{19}NO$: C, 80.63; H, 7.51; N, 5.53.

4-*N*-(3,4-Dimethoxyphenyl)amino-4-phenyl-1-butene (59). Pink oil. Yield 44%. IR (film) ν 3392 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 2.48–2.65 (2H, m, 3-H), 3.54 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.31 (1H, dd, *J* = 7.4, 4.8 Hz, 4-H), 4.36 (1H, br. s., H–N), 5.15–5.21 (1H, m, 1-H), 5.73–5.86 (1H, m, 2-H), 5.80 (1H, d, *J* = 8.1 Hz, 6-H_{Ar}), 6.10 (1H, s, 2-H_{Ar}), 6.52 (1H, d, *J* = 8.1 Hz, 5-H_{Ar}), 7.23–7.45 (5H, m, H_{Ph}). MS *m/z* (EI) 283 (M^+, 4%), 242 (M−C_3H_5, 100%). Found: C, 76.29; H, 7.47 N, 5.31; calcd for $C_{18}H_{21}NO_2$: C, 76.33; H, 7.42; N, 4.95.

4-*N*-(2,4-Dimethoxyphenyl)amino-4-phenyl-1-butene (60). Reddish oil. Yield 93%. IR (film) ν 3421 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 2.55–2.68 (2H, m, 3-H), 3.56 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 4.20 (1H, dd, *J* = 7.6, 5.5 Hz, 4-H), 4.35 (1H, br. s., H–N), 5.16 (1H, d, *J* = 10.3 Hz, 1-H_A), 5.22 (1H, d, *J* = 17.1 Hz, 1-H_B), 5.78–5.88 (1H, m, 2-H), 6.10 (2H, s, 3(5)-H_{Ar}), 6.33 (1H, s, 6-H_{Ar}), 7.24–7.41 (5H, m, H_{Ph}); ^{13}C NMR (100 MHz) δ 43.3, 55.4, 55.5, 57.8, 99.0, 103.5, 111.2, 117.9, 126.3, 126.8 (2C), 128.4 (2C), 131.6, 134.7, 143.9, 147.8, 151.6. MS *m/z* (EI) 283 (M^+, 9%), 242 (M−C_3H_5, 100%). Found: C, 76.34; H, 7.50; N, 4.78; calcd for $C_{18}H_{21}NO_2$: C, 76.33; H, 7.42; N, 4.95.

4-*N*-(3,4-Methylenedioxyphenyl)amino-4-phenyl-1-butene (61). Dark oil. Yield 79%. IR (film) ν 3409 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 2.34–2.41 (1H, m, 3-H_A), 2.47–2.53 (1H, m, 3-H_B), 3.89 (1H, br. s., H–N), 4.20 (1H, dd, *J* = 8.0, 4.0 Hz, 4-H), 5.05 (2H, t, *J* = 8.0 Hz, 1-H), 5.69 (2H, s, O–CH_2–O), 5.83 (1H, d, *J* = 8.0 Hz, 6-H_{Ar}), 6.05 (1H, s, 2-H_{Ar}), 6.46 (1H, d, *J* = 8.0 Hz, 5-H_{Ar}), 7.13–7.27 (5H, m, H_{Ph}); ^{13}C NMR (100 MHz) δ 43.3, 57.9, 96.4, 100.4, 105.1, 108.4, 118.3, 126.2, 126.7 (2C), 128.6 (2C), 134.6, 139.4, 143.1, 143.5, 148.0. MS *m/z* (EI) 267 (M^+, 5%), 226 (M–C_3H_5, 100%). Found: C, 76.19.; H, 6.63.; N, 5.12; calcd for $C_{17}H_{17}NO_2$: C, 76.40; H, 6.37; N, 5.24.

4-*N*-Arylamino-4-pyridyl-1-butenes (62–74).

4-*N*-Phenylamino-4-(3-pyridyl)-1-butene (62). Beige crystals. Mp 57 °C. Yield 88%. IR (KBr) ν 3257 cm^{-1} (s, NH). ^1H NMR (300 MHz) δ 2.51 (1H, quin., *J* = 5.6 Hz, 3-H_B), 2.61 (1H, quin., *J* = 4.9 Hz, 3-H_A), 4.18 (1H, br.s, H–N), 4.44 (1H, br.s, 4-H), 5.17 (1H, s, 1-H_{trans}), 5.21 (1H, d, *J* = 7.1 Hz, 1-H_{cis}), 5.70–5.80 (1H, dddd, *J* = 15.4, 7.1, 7.1, 5.5 Hz, 2-H), 6.48 (2H, d, *J* = 5.8 Hz, 2(6)-H_{Ar}), 6.67 (1H, t, *J* = 5.3 Hz, 4-H_{Ar}), 7.09 (2H, t, *J* = 5.3 Hz, 3(5)-H_{Ar}), 7.23 (1H, t, *J* = 5.8 Hz, 5-H_{Py}), 7.67 (1H, d, *J* = 5.8 Hz, 4-H_{Py}), 8.50 (1H, d, *J* = 3.0 Hz, 6-H_{Py}), 8.65 (1H, s, 2-H_{Py}); ^{13}C NMR (75 MHz) δ 43.1, 55.0, 113.6 (2C), 118.0, 119.2, 123.7, 129.3 (2C), 133.8, 134.0, 139.0, 146.8, 148.7, 148.8. MS *m/z* (EI) 224 (M^+, 3%), 183 (M−C_3H_5, 100%). Found: C, 80.09; H, 7.35; N, 12.56; calcd for $C_{15}H_{16}N_2$: C, 80.36; H, 7.14; N, 12.50.

4-*N*-(4-Methylphenyl)amino-4-(3-pyridyl)-1-butene (63). Yellow crystals. Mp 84–85 °C. Yield 94%. IR (KBr) ν 3256 cm^{-1} (s, NH). ^1H NMR (300 MHz) δ 2.20 (3H, s, CH_3), 2.50 (1H, quin., *J* = 5.8 Hz, 3-H_B), 2.57–2.65 (1H, m, 3-H_A), 4.10 (1H, br.s, H–N), 4.41 (1H, t, *J* = 4.7 Hz, 4-H), 5.17 (1H, d, *J* = 0.6 Hz, 1-H_{trans}), 5.20 (1H, dd, *J* = 6.3, 1.1 Hz, 1-H_{cis}), 5.70–5.81 (1H, m, 2-H), 6.42 (2H, dt, *J* = 6.3, 1.9 Hz, 2(6)-H_{Ar}), 6.91 (2H, d, *J* = 6.3 Hz, 3(5)-H_{Ar}), 7.23 (1H, dd, *J* = 5.8, 3.6 Hz, 5-H_{Py}), 7.68 (1H, dt, *J* = 5.8, 1.4 Hz, 4-H_{Py}), 8.50 (1H, dd, *J* = 3.6, 1.4

Hz, 6-H_{Py}), 8.65 (1H, d, J = 1.7 Hz, 2-H_{Py}); ^{13}C NMR (75 MHz) δ 20.5, 43.2, 55.3, 113.7 (2C), 119.1, 123.7, 127.1, 129.8 (2C), 134.0, 134.0, 139.2, 144.6, 148.6, 148.8. MS m/z (EI) 238 (M^+, 4%), 197 (M-C_3H_5, 100%). Found: C, 80.77; H, 7.80; N, 11.43; calcd for $C_{16}H_{18}N_2$: C, 80.67; H, 7.56; N, 11.77. Compound **64** has been reported previously in ref 16.

4-*N*-(4-Methylphenyl)amino-4-(4-pyridyl)-1-butene (65). White crystals. Mp 95 °C. Yield 73%. IR (KBr) ν 3273 cm^{-1} (s, NH). ^{1}H NMR (400 MHz) δ 2.18 (3H, s, CH_3), 2.45 (1H, quin., J = 7.6 Hz, 3-H_B), 2.56 (1H, quin-d, J = 5.0, 1.0 Hz, 3-H_A), 4.07 (1H, br.s, H–N), 4.32 (1H, dd, J = 7.6, 5.0 Hz, 4-H), 5.16 (1H, s, 1-H_{trans}), 5.19 (1H, d, J = 8.1 Hz, 1-H_{cis}), 5.66–5.74 (1H, m, 2-H), 6.36 (2H, d, J = 8.1 Hz, 2(6)-H_{Ar}), 6.89 (2H, d, J = 8.1 Hz, 3(5)-H_{Ar}), 7.29 (2H, d, J = 5.5 Hz, 3(5)-H_{Py}), 8.53 (2H, dd, J = 5.5, 1.5 Hz, 2(6)-H_{Py}); ^{13}C NMR (100 MHz) δ 20.3, 42.4, 56.4, 113.4 (2C), 119.1, 121.6 (2C), 127.1, 129.6 (2C), 133.6, 144.3, 150.0 (2C), 152.9. MS m/z (EI) 238 (M^+, 100%), 197 (M−C_3H_5, 100%). Found: C, 80.44; H, 7.87; N, 11.69; calcd for $C_{16}H_{18}N_2$: C, 80.67; H, 7.56; N, 11.77.

4-*N*-(2-Isopropylphenyl)amino-4-(3-pyridyl)-1-butene (66). Yellow transparent oil. Bp 195–200 °C/10 mm Hg. n_D^{20} 1.5704. Yield 78%. IR (film) ν 3434 cm^{-1} (s, NH). ^{1}H NMR (400 MHz) δ 1.30 (3H, d, J = 6.6 Hz, CH_3-*i*-Pr), 1.33 (3H, d, J = 6.6 Hz, CH'_3-*i*-Pr), 2.54 (1H, quin., J = 8.1 Hz, 3-H_B), 2.69 (1H, quin., J = 5.0 Hz, 3-H_A), 2.96 (1H, sept., J = 6.6 Hz, H-C-*i*-Pr), 4.28 (1H, s, H–N), 4.49 (1H, dd, J = 8.1, 5.0 Hz, 4-H), 5.23 (1H, s, 1-H_{cis}), 5.25 (1H, d, J = 26.4 Hz, 1-H_{trans}), 5.73–5.84 (1H, m, 2-H), 6.25 (1H, d, J = 8.1 Hz, 6-H_{Ar}), 6.70 (1H, t, J = 7.5 Hz, 4-H_{Ar}), 6.92 (1H, ddd, J = 8.1, 7.6, 1.5 Hz, 5-H_{Ar}), 7.15 (1H, d, J = 7.5 Hz, 3-H_{Ar}), 7.22 (1H, dd, J = 7.6, 4.5 Hz, 5-H_{Py}), 7.66 (1H, dt, J = 7.6, 1.5 Hz, 4-H_{Py}), 8.49 (1H, dd, J = 4.5, 1.5 Hz, 6-H_{Py}), 8.66 (1H, d, J = 2.0 Hz, 2-H_{Py}); ^{13}C NMR (100 MHz) δ 22.1, 22.4, 27.4, 43.4, 54.6, 111.7, 117.7, 119.2, 123.6, 124.9, 126.5, 132.3, 133.9, 134.0, 139.0, 143.2, 148.4, 148.5. MS m/z (EI) 266 (M^+, 5%), 225 (M−C_3H_5, 100%). Found: C, 81.34; H, 8.45; N, 10.17; calcd for $C_{18}H_{22}N_2$: C, 81.20; H, 8.27; N, 10.53.

4-*N*-(4-Methoxyphenyl)amino-4-(3-pyridyl)-1-butene (67). Red crystals. Mp 57–58 °C. Yield 60%. IR (KBr) ν 3255 cm^{-1} (s, NH). ^{1}H NMR (300 MHz) δ 2.47 (1H, quin., J = 6.0 Hz, 3-H_B), 2.56 (1H, quin-d, J = 4.1, 1.1 Hz, 3-H_A), 3.65 (3H, s, CH_3O), 3.95 (1H, br.s, H–N), 4.34 (1H, dd, J = 6.0, 4.1 Hz, 4-H), 5.13 (1H, s, 1-H_{trans}), 5.18 (1H, dd, J = 4.7, 1.1 Hz, 1-H_{cis}), 5.66–5.78 (1H, m, 2-H), 6.41 (2H, dd, J = 6.6, 1.7 Hz, 2(6)-H_{Ar}), 6.66 (2H, dd, J = 6.6, 1.7 Hz, 3(5)-H_{Ar}), 7.02 (1H, dd, J = 5.8, 3.6 Hz, 5-H_{Py}), 7.65 (1H, dt, J = 5.8, 1.1 Hz, 4-H_{Py}), 8.46 (1H, dd, J = 3.6, 1.1 Hz, 6-H_{Py}), 8.60 (1H, d, J = 1.7 Hz, 2-H_{Py}); ^{13}C NMR (75 MHz) δ 43.2, 55.8, 55.8, 114.9 (4C), 119.1, 123.7, 134.0, 134.2, 139.2, 144.2, 148.5, 148.7, 152.3. MS m/z (EI) 254 (M^+, 7%), 213 (M−C_3H_5, 100%). Found: C, 75.28; H, 7.24; N, 11.31; calcd for $C_{16}H_{18}N_2O$: C, 75.59; H, 7.09; N, 11.02.

4-*N*-(3,4-Methylenedioxyphenyl)amino-4-(3-pyridyl)-1-butene (68). Red crystals. Mp 55–56 °C. bp 165–170 °C/10 mm Hg. Yield 12%. IR (KBr) ν 3297 cm^{-1} (s, NH). ^{1}H NMR (400 MHz) δ 2.39 (1H, quin., J = 8.1 Hz, 3-H_B), 2.61 (1H, quin., J = 6.0 Hz, 3-H_A), 3.98 (1H, br.s, H–N), 4.30 (1H, dd, J = 8.1, 5.5 Hz, 4-H), 5.10 (1H, s, 1-H_{trans}), 5.14 (1H, d, J = 4.5 Hz, 1-H_{cis}), 5.64–5.70 (1H, m, 2-H), 5.74 (2H, d, J = 1.2 Hz, O–CH_2–O), 5.84 (1H, dd, J = 8.6, 2.0 Hz, 6-H_{Ar}), 6.07 (1H, d, J = 2.0 Hz, 2-H_{Ar}), 6.50 (1H, d, J = 8.6 Hz, 5-H_{Ar}), 7.18 (1H, dd, J = 7.6, 4.5 Hz, 5-H_{Py}), 7.62 (1H, d, J = 7.6 Hz, 4-H_{Py}), 8.44 (1H, d, J = 4.5 Hz, 6-H_{Py}), 8.57 (1H, s, 2-H_{Py}); ^{13}C NMR (100 MHz) δ 42.8, 55.6, 96.5, 100.5, 105.1, 108.4, 119.0, 123.5, 133.7, 134.0, 138.9, 139.7, 142.6, 148.1, 148.4, 148.5. MS m/z (EI) 268 (M^+, 8%), 227 (M−C_3H_5, 100%). Found: C, 71.57; H, 6.34; N, 10.56; calcd for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.45.

4-*N*-(4-Bromophenyl)amino-4-(3-pyridyl)-1-butene (69). Yellow crystals. Mp 79–80 °C. Yield 32%. IR (KBr) ν 3255 cm^{-1} (s, NH). ^{1}H NMR (400 MHz) δ 2.40 (1H, quin., J = 6.5 Hz, 3-H_B), 2.47 (1H, quin-d, J = 5.8, 0.9 Hz, 3-H_A), 3.52 (1H, br.s, H–N), 4.28 (1H, d, J = 6.5 Hz, 4-H), 5.02 (1H, t, J = 1.0 Hz, 1-H_{trans}), 5.06 (1H, dd, J = 3.1, 1.0 Hz, 1-H_{cis}), 5.54–5.63 (1H, m, 2-H), 6.23 (2H, dt, J = 8.9, 2.0 Hz, 2(6)-H_{Ar}), 7.02 (2H, dd, J = 8.9, 2.0 Hz, 3(5)-H_{Ar}), 7.10 (1H, dd, J = 7.9, 4.8 Hz, 5-H_{Py}), 7.50 (1H, dt, J = 7.9, 1.6 Hz, 4-H_{Py}), 8.37 (1H, dd, J = 4.9, 1.6 Hz, 6-H_{Py}), 8.49 (1H, d, J = 2.1 Hz, 2-H_{Py}); ^{13}C NMR (100 MHz) δ 42.5, 54.7, 109.1, 116.4 (2C), 119.0, 123.6, 131.6 (2C), 133.2, 133.7, 138.1, 145.5, 148.2, 148.3. MS m/z (EI) 302 (M^+ for ^{79}Br, 4%), 261 (M−C_3H_5, 100%). Found: C, 59.11; H, 5.05; N, 9.43; calcd for $C_{15}H_{15}BrN_2$: C, 59.41; H, 4.95; N, 9.24.

4-*N*-(4-Chlorophenyl)amino-4-(3-pyridyl)-1-butene (70). Yellow crystals. Mp 84–86 °C. Yield 69%. IR (KBr) r 3305 cm^{-1} (s, NH). ^{1}H NMR (400 MHz) δ 2.42 (1H, quin., J = 7.5 Hz, 3-H_B), 2.53 (1H, quin., J = 5.9 Hz, 3-H_A), 4.16 (1H, s, H–N), 4.31 (1H, quin., J = 4.8 Hz, 4-H), 5.08 (1H, s, 1-H_{trans}), 5.12 (1H, d, J = 4.1 Hz, 1-H_{cis}), 5.60–5.68 (1H, m, 2-H), 6.30 (2H, dt, J = 8.9, 3.1 Hz, 2(6)-H_{Ar}), 6.93 (2H, dt, J = 8.8, 3.0 Hz, 3(5)-H_{Ar}), 7.16 (1H, dd, J = 7.5, 4.8 Hz, 5-H_{Py}), 7.55 (1H, dt, J = 7.5, 1.5 Hz, 4-H_{Py}), 8.42 (1H, dd, J = 4.8, 1.5 Hz, 6-H_{Py}), 8.53 (1H, d, J = 2.0 Hz, 2-H_{Py}); ^{13}C NMR (100 MHz) δ 42.8, 55.0, 114.5 (2C), 119.2, 122.4, 123.5, 128.9 (2C), 133.8, 133.8, 138.2, 145.2, 148.5, 148.6. MS m/z (EI) 258 (M^+ for ^{35}Cl, 4%), 217 (M−C_3H_5, 100%). Found: C, 69.55; H, 5.97; N, 10.95; calcd for $C_{15}H_{15}ClN_2$: C, 69.63; H, 5.80; N, 10.83.

4-*N*-(4-Fluorophenyl)amino-4-(3-pyridyl)-1-butene (71). Orange crystals. Mp 67–68 °C. Yield 73%. IR (KBr) ν 3264 cm^{-1} (s, NH). ^{1}H NMR (300 MHz) δ 2.48 (1H, quin., J = 6.1 Hz, 3-H_B), 2.60 (1H, quin-d, J = 4.7, 0.8 Hz, 3-H_A), 4.08 (br.s, 1H, H–N), 4.36 (1H, t, J = 4.7 Hz, 4-H), 5.16 (1H, s 1-H_{trans}), 5.19 (2H, dd, J = 12.7, 1.1 Hz, 1-H_{cis}), 5.67–5.79 (1H, m, 2-H), 6.39 (2H, dd, J = 6.8, 3.3 Hz, 2(6)-H_{Ar},), 6.77 (2H, t, J = 6.8 Hz, 3(5)-H_{Ar}), 7.23 (1H, dd, J = 5.8, 3.6 Hz, 5-H_{Py}), 7.64 (1H, dt, J = 5.8, 1.1 Hz, 4-H_{Py}), 8.49 (1H, dd, J = 3.6, 1.1 Hz, 6-H_{Py}), 8.61 (1H, d, J = 1.7 Hz, 2-H_{Py},); ^{13}C NMR (75 MHz) δ 43.2, 55.6, 114.4 (2C, d, J = 5.15 Hz), 115.7 (2C, d, J = 16.6 Hz), 119.3, 123.7, 133.7, 134.0, 138.7,

143.1, 148.7, 148.8, 155.0 (d, $J=-225.0$ Hz). MS m/z (EI) 242 (M^+, 3%), 201 ($M-C_3H_5$, 100%). Found: C, 74.11; H, 6.46; N, 11.34; calcd for $C_{15}H_{15}FN_2$: C, 74.38; H, 6.20; N, 11.57.

4-*N*-(2,4-Difluorophenyl)amino-4-(3-pyridyl)-1-butene (72). Red oil. Yield 58%. IR (film) ν 3425 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 2.48 (1H, quin., $J=6.0$ Hz, 3-H_B), 2.56 (1H, quin., $J=8.1$ Hz, 3-H_A), 4.28 (1H, s, H–N), 4.31 (1H, s, 4-H), 5.10 (1H, s, 1-H_{trans}), 5.13 (1H, d, $J=8.1$ Hz, 1-H_{cis}), 5.68 (1H, m, 2-H), 6.19 (1H, sext, $J_{HF}=9.1$ Hz, 3-H_{Ar}), 6.48 (1H, t, $J_{HH}=8.1$ Hz, 6-H_{Ar}), 6.66 (1H, ddd, $J_{HF}=11.1$, $J_{HH}=8.1$, 3.0 Hz, 5-H_{Ar}), 7.20 (1H, dd, $J=8.1$, 4.0 Hz, 5-H_{Py}), 7.59 (1H, d, $J=8.1$ Hz, 4-H_{Py}), 8.43 (1H, d, $J=4.0$ Hz, 6-H_{Py}), 8.56 (1H, s, 2-H_{Py}); ^{13}C NMR (100 MHz) δ 42.7, 55.1, 103.3 (dd, $J=23.0$, 22.3 Hz), 110.2 (dd, $J=21.6$, 3.4 Hz), 112.9 (dd, $J=8.8$, 8.8 Hz), 119.1, 123.5, 131.6 (dd, $J=11.5$, 3.4 Hz), 133.1, 133.7, 138.1, 148.2, 148.5, 150.7 (dd, $J=-242.0$, 11.5 Hz), 154.2 (dd, $J=-238.0$, 11.5 Hz). MS m/z (EI) 260 (M^+, 2%), 219 ($M-C_3H_5$, 100%). Found: C, 69.02; H, 5.68; N, 10.43; calcd for $C_{15}H_{14}F_2N_2$: C, 69.23; H, 5.38; N, 10.77.

4-*N*-(2-Iodophenyl)amino-4-(3-pyridyl)-1-butene (73). Red crystals. Mp 46–47 °C. Yield 25%. IR (KBr) ν 3406 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 2.50 (1H, quin., $J=8.1$ Hz, 3-H_B), 2.60 (1H, quin., $J=6.0$ Hz, 3-H_A), 4.17 (1H, s, H–N), 4.42 (1H, s, 4-H), 5.15 (1H, s, 1-H_{trans}), 5.19 (1H, d, $J=9.1$ Hz, 1-H_{cis}), 5.68–5.78 (1H, m, 2-H), 6.46 (2H, d, $J=8.1$ Hz, 4(6)-H_{Ar}), 6.66 (1H, t, $J=8.1$ Hz, 5-H_{Ar}), 7.07 (1H, t, $J=8.1$ Hz, 3-H_{Ar}), 7.22 (1H, t, $J=5.0$ Hz, 5-H_{Py}), 7.65 (1H, d, $J=8.1$ Hz, 4-H_{Py}), 8.48 (1H, d, $J=5.0$ Hz, 6-H_{Py}), 8.55 (1H, s, 2-H_{Py}); ^{13}C NMR (100 MHz) δ 43.0, 54.9, 113.4, 117.8, 119.0, 123.5, 129.1, 133.6, 133.9, 138.8, 146.7, 148.4, 148.5. MS m/z (EI) 350 (M^+, 3%), 309 ($M-C_3H_5$, 100%). Found: C, 51.73; H, 4.11; N, 8.20; calcd for $C_{15}H_{15}IN_2$: C, 51.43; H, 4.29; N, 8.00.

4-*N*-Arylamino-4-(8-quinolinyl)-1-butenes (74–78)

Have been reported previously in refs 11 and 12.

4-*N*-Benzylamino-4-pyridyl-1-butenes (79 and 80). Have been reported in refs 19 and 20.

***N*-(1-Phenyl-3-buten-1-yl)-N-(4-methoxyphenyl)acetamide (81).** Compound **56** (0.70 g, 2.8 mmol) was heated under reflux for 9 h in acetic anhydride (1.0 mL, 10.5 mmol). The reaction was monitored via TLC. At the end of the reaction the pH was brought to 7–8 with sodium bicarbonate. The organic products were extracted with ethyl acetate (3×10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The oily residue was purified by column chromatography (silica gel) with ethyl acetate and heptene (1:10) to give 81 as brownish oil. Yield 96% (0.78 g). IR (film) ν 1652 cm^{-1} (s, CO). ^1H NMR (400 MHz) δ 1.74 (3H, s, CH_3), 2.58 (2H, dd, $J=16.0$, 8.0 Hz, 3-H), 3.77 (3H, s, OCH_3), 5.11 (1H, t, $J=12.0$ Hz, 1-H_B), 5.18 (1H, s, 1-H_A), 5.81–5.85 (1H, m, 2-H), 6.27 (1H, t, $J=8.0$ Hz, 4-H), 7.14–7.23 (7H, m, H_{Ar}); ^{13}C NMR (100 MHz) δ 23.1, 34.9, 55.1, 55.8, 113.7, 117.2, 127.4, 127.9 (2C), 128.6 (2C), 131.1 (2C), 131.2, 134.9 (2C), 139.5, 158.9, 170.8. MS m/z (EI) 295 (M^+, 4%). Found: C, 77.08; H, 7.35; N, 4.55; calcd for $C_{19}H_{21}NO_2$: C, 77.29; H, 7.12; N, 4.74.

***N*-(1-Phenyl-3-buten-1-yl)-*N*-(4-methoxyphenyl)allylamine (82).** A suspension of **56** (0.70 g, 2.8 mmol) in 10 mL acetone with allyl bromide (0.67 g, 5.5 mmol) and potassium carbonate (1.53 g, 11.0 mmol) was allowed to reflux for 24 h. The mixture was treated with water. The products were extracted with ether (3×10 mL), the organic layer was dried (Na_2SO_4) and the residue purified by a short chromatographic column (silica gel) to give **82** as brown oil. Yield 15% (0.12 g). IR (film) ν 916 cm^{-1} (s, =C–H). ^1H NMR (200 MHz) δ 2.40–2.67 (2H, m, 3-H), 3.73 (3H, s, OCH_3), 4.28–4.37 (3H, m, 4-H and N–CH_2), 4.94–5.06 (2H, m, 1-H), 5.13–5.22 (2H, m, =CH_2), 5.57–5.90 (1H, m, 2-H), 5.95–6.05 (1H, m, CH=), 6.16 (2H, d, $J=2.6$ Hz, 2(6)-H_{Ar}), 6.62 (2H, dd, $J=8.8$, 2.6 Hz, 3(5)-H_{Ar}), 7.21–7.36 (5H, m, H_{Ph}). MS m/z (EI) 293 (M^+, 9%), 252 (M-C_3H_5, 100%). Found: C, 81.73; H, 7.87; N, 4.89; calcd for $C_{20}H_{23}NO$: C, 81.91; H, 7.85; N, 4.78.

Compound **83** has been reported previously in ref 10 and compound **84** in ref 11.

General procedure for the synthesis of aminoalcohols (85–89) and tetrahydroquinolines (90–94)

Sulfuric acid 75% w/v (2.0 mL) was added to 1.0 g of the aminobutenes (**41**, **42**, **45**, **46**, **53–55**, and **57**) and the mixture was heated to 60 °C for 8 h while stirring vigorously. The reaction progress was monitored via TLC (heptane, chromatoplates of Silufol UV_{254}). After the reaction was completed, the mixture was cooled down to room temperature and a concentrated ammonium hydroxide solution was added (pH 8–9). Two 30-mL extractions with Et_2O were performed. The organic layers were combined and dried with anhydrous Na_2SO_4. The residue after ether evaporation was purified by column chromatography over silica to give 4-aminobutanols (**85–89**) and tetrahydroquinolines (**90–94**).

4-*N*-(4-Bromophenyl)amino-2-heptanol (85). Reddish oil. Yield 63%. IR (film) ν 3371 cm^{-1} (s, NH, OH). ^1H NMR (400 MHz) δ 0.85–0.90 (3H, m, 7-CH_3), 1.17 (3H, d, $J=4.0$ Hz, 1-CH_3), 1.22–1.35 (2H, m, 3-H), 1.40–1.55 (4H, m, 5- and 6-H), 1.60–1.70 (1H, m, 4-H), 3.45 (1H, quin., $J=4.0$ Hz, $_I$2-$H_{Isomer\ A}$), 3.55 (1H, quin., $J=8.0$ Hz, 2-$H_{Isomer\ B}$), 3.97 (1H, br. s., H–N), 6.48–6.58 (2H, m, 2(6)-H_{Ar}), 7.19–7.24 (2H, m, 3(5)-H_{Ar}); ^{13}C NMR (100 MHz) δ 14.0, 18.7/19.1, 23.9/24.1, 37.5, 43.1/43.5, 50.3/53.5, 64.8/67.7, 110.0, 114.7 (2C), 131.8 (2C), 147.1; GC: two isomers (t_R A = 23.96, t_R B = 24.08 min). MS m/z (EI) for isomer A: 285 (M^+ for ^{79}Br, 30%); for isomer B: 287 (M^+ for ^{81}Br, 31%). Found: C, 54.78; H, 6.44; N, 5.06; calcd for $C_{13}H_{20}BrNO$: C, 54.55; H, 6.99; N, 4.90.

4-Phenyl-4-*N*-phenylamino-2-butanol (86). Brownish solid. Yield 7%. Mp 130 °C. IR (KBr) ν 3272 cm^{-1} (s,

NH), δ cm^{-1} (s). ^1H NMR (300 MHz) δ 1.22 (3H, d, $J=6.2$ Hz, 1-CH_3), 1.81–1.95 (2H, m, 3-H), 4.00 (1H, sext., $J=6.2$ Hz, 2-H), 4.55 (1H, dd, $J=8.8$, 5.1 Hz, 4-H), 6.59 (2H, dd, $J=7.7$, 0.8 Hz, 2(6)-H_{Ar}), 6.89 (1H, t, $J=7.7$ Hz, 4-H_{Ar}), 7.10 (2H, t, $J=7.7$ Hz, 3(5)-H_{Ar}), 7.21–7.35 (5H, m, H_{Ph}); ^{13}C NMR (75 MHz) δ 24.5, 47.3, 58.4, 67.8, 114.6 (2C), 118.2, 126.4, 127.2 (2C), 128.8 (2C), 129.2 (2C), 143.9, 147.2. MS *m/z* (EI) 241 (M^+, 8%). Found: C, 79.55; H, 8.00; N, 5.97; calcd for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81.

4-*N*-(4-Methylphenyl)amino-4-phenyl-2-butanol (87). Brownish solid. Yield 21%. Mp 140 °C. IR (KBr) ν 3274 cm^{-1} (s, NH). ^1H NMR (300 MHz) δ 1.22 (3H, d, $J=4.7$ Hz, 1-CH_3), 1.84–1.96 (2H, m, 3-H), 2.18 (3H, s, CH_{3Ar}), 4.03 (1H, sept., $J=2.5$ Hz, 2-H), 4.52 (1H, dd, $J=6.8$, 3.8 Hz, 4-H), 6.53 (2H, d, $J=6.3$ Hz, 2(6)-H_{Ar}), 6.92 (2H, d, $J=6.3$ Hz, 3(5)-H_{Ar}), 7.22–7.38 (5H, m, H_{Ph}); ^{13}C NMR (75 MHz) δ 20.5, 24.4, 47.2, 58.9, 68.0, 114.9 (2C), 126.2, 127.2, 128.7 (2C), 128.8 (2C), 129.7 (2C), 143.9, 144.7. MS *m/z* (EI) 255 (M^+, 15%). Found: C, 80.24; H, 8.11; N, 5.76; calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.49.

4-*N*-(4-Bromophenyl)amino-4-phenyl-2-butanol (88). Brownish solid. Yield 17%. IR (film) ν 3266 cm^{-1} (s, NH). ^1H NMR (400 MHz) *isomer A*: δ 1.14 (3H, d, $J=4.7$ Hz, 1-CH_3), 1.70–1.90 (2H, m, 3-H), 3.83–3.90 (1H, m, 2-H), 4.36 (1H, dd, $J=8.7$, 5.6 Hz, 4-H), 6.31 (2H, d, $J=8.8$ Hz, 2(6)-H_{Ar}), 7.04 (2H, d, $J=8.8$ Hz, 3(5)-H_{Ar}), 7.14–7.23 (5H, m, H_{Ph}). ^1H NMR (400 MHz) *isomer B*: δ 1.15 (3H, d, $J=6.1$ Hz, 1-CH_3), 1.70–1.90 (2H, m, 3-H), 4.36 (1H, dd, $J=8.7$, 5.6 Hz, 4-H), 4.50 (1H, dd, $J=8.0$, 4.1 Hz, 2-H), 6.29 (2H, d, $J=8.8$ Hz, 2(6)-H_{Ar}), 7.00 (2H, d, $J=8.8$ Hz, 3(5)-H_{Ar}), 7.14–7.23 (5H, m, H_{Ph}); ^{13}C NMR (100 MHz) δ 24.0/24.5, 46.4/47.1, 55.4/58.1, 67.2/67.4, 108.6/109.4, 115.0, 116.0, 126.1, 127.2 (2C), 129.0 (2C), 131.7 (2C), 143.0/143.4, 146.3; GC: $t_R=31.67$ min. MS *m/z* (EI) 319 (M^+ for ^{79}Br, 15%). Found: C, 59.87; H, 5.78; N, 4.66; calcd for $C_{16}H_{18}BrNO$: C, 60.00; H, 5.63; N, 4.37.

4-Phenyl-4-N-(2-isopropylphenyl)amino-2-butanol (89). Yellowish oil. Yield 41%. IR (film) ν 3398 cm^{-1} (s, NH, OH), ν 1131 cm^{-1} (s, C–O–C). ^1H NMR (400 MHz) *isomer A*: δ 1.20 (3H, d, $J=8.0$ Hz, 1-CH_3), 1.28 (3H, d, $J=6.6$ Hz, CH_3-*i*-Pr), 1.30 (3H, d, $J=6.6$ Hz, CH'_3-*i*-Pr), 1.87–2.02 (2H, m, 3-H), 2.99 (1H, quin., $J=6.6$ Hz, H-C-*i*-Pr), 4.01–4.03 (1H, m, 2-H), 4.54 (1H, dd, $J=8.0$, 4.8 Hz, 4-H), 6.45 (1H, d, $J=8.0$ Hz, 6-H_{Ar}), 6.69 (1H, t, $J=7.5$ Hz, 4-H_{Ar}), 6.91 (1H, dd, $J=8.0$, 7.5 Hz, 5-H_{Ar}), 7.13 (1H, d, $J=7.5$ Hz, 3-H_{Ar}), 7.26–7.33 (5H, m, H_{Ph}). ^1H NMR (400 MHz) *isomer B*: δ 1.20 (3H, d, $J=8.0$ Hz, 1-CH_3), 1.28 (3H, d, $J=6.6$ Hz, CH_3-*i*-Pr), 1.30 (3H, d, $J=6.6$ Hz, CH'_3-*i*-Pr), 1.87–2.02 (2H, m, 3-H), 2.99 (1H, quin., $J=6.6$ Hz, H-C-*i*-Pr), 3.96–4.01 (1H, m, 2-H), 4.68 (1H, dd, $J=8.7$, 4.8 Hz, 4-H), 6.33 (1H, d, $J=8.1$ Hz, 6-H_{Ar}), 6.64 (1H, t, $J=7.6$ Hz, 4-H_{Ar}), 6.91 (1H, dd, $J=8.0$, 7.5 Hz, 5-H_{Ar}), 7.13 (1H, d, $J=7.5$ Hz, 3-H_{Ar}), 7.26–7.33 (5H, m, H_{Ph}); ^{13}C NMR (100 MHz) δ 22.4, 22.5, 24.1/24.5, 27.2/27.4, 46.4/47.4, 55.4/58.4, 65.3/67.8, 111.3/112.8, 116.8/117.9, 124.8, 126.4, 126.7, 127.0 (2C), 128.7 (2C), 133.1/133.9, 143.6/143.8, 144.1; GC: two isomers (t_R A = 26.71, t_R B = 26.95 min). MS *m/z* (EI) for isomer A: 283 (M^+, 26%); for isomer B: 283 (M^+, 24%). Found: C,80.89; H, 8.54; N, 4.88; calcd for $C_{19}H_{25}NO$: C, 80.57; H, 8.83; N, 4.95.

Tetrahydroquinolines **90** and **91** have been reported previously in ref 7.

4-Methyl-2-(*n*-propyl)-1,2,3,4-tetrahydroquinoline (92). Yellowish oil. Yield 73%. IR (film) ν 3392 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 0.86 (3H, t, $J=8.0$ Hz, H_3C-Pr), 1.15 (1H, d, $J=7.1$ Hz, 3-Ha), 1.21 (3H, d, $J=6.7$ Hz, 4-CH_3), 1.30–1.34 (4H, m, $(CH_2)_2$–Pr), 1.82 (2H, ddd, $J=11.4$, 5.3, 2.6 Hz, 3-He), 2.80–2.84 (1H, m, 4-H), 3.17–3.20 (1H, m, 2-H), 3.47 (1H, br. s., H-N), 6.31 (1H, dd, $J=7.8$, 1.2 Hz, 8-H), 6.55 (1H, td, $J=8.0$, 1.2 Hz, 6-H), 6.82 (1H, td $J=7.8$, 1.2 Hz, 7-H), 7.01 (1H, d, $J=7.6$ Hz, 5-H); ^{13}C NMR (100 MHz) δ 14.2, 18.8, 20.2, 30.7, 38.5, 39.1, 51.4, 113.9, 116.9, 126.3, 126.8, 128.8, 144.6; GC: two isomers (t_R A = 17.47, t_R B = 18.05 min). MS *m/z* (EI) for isomer A: 189 (M^+, 100%); for isomer B: 189 (M^+, 100%). Found: C, 82.33; H, 10.34; N, 7.37; calcd for $C_{13}H_{19}N$: C, 82.54; H, 10.05; N, 7.41.

4,8-Dimethyl-2-(*n*-propyl)-1,2,3,4-tetrahydroquinoline (93). Yellowish oil. Yield 58%. IR (film) ν 3430 cm^{-1} (s, NH). ^1H NMR (200 MHz) δ 0.85 (3H, t, $J=8.1$ Hz, CH_3-Pr), 1.20 (3H, d, $J=6.2$ Hz, 4-$CH_{3Isomer\ A}$), 1.22 (3H, d, $J=6.2$ Hz, 4-$CH_{3Isomer\ B}$), 1.26–1.85 (6H, m, 3-H and $(CH_2)_2$), 2.15 (3H, s, 8-CH_3), 3.56–3.79 (1H, m, 4-H), 3.96–4.13 (1H, m, 2-H), 6.58–7.16 (3H, m, H_{Ar}); GC: two isomers (t_R A = 18.64, t_R B = 19.17 min). MS *m/z* (EI) for isomer A: 203 (M^+, 15%); for isomer B: 203 (M^+, 15%). Found: C, 82.89; H, 10.21; N, 6.99; calcd for $C_{14}H_{21}N$: C, 82.76; H, 10.34; N, 6.90.

6-Fluoro-4-methyl-2-(*n*-propyl)-1,2,3,4-tetrahydroquinoline (94). Yellowish oil. Yield 21%. IR (film) ν 3410 cm^{-1} (s, NH). ^1H NMR (400 MHz) δ 0.86 (3H, t, $J=8.3$ Hz, H_3C-Pr), 1.12 (1H, d, $J=12.0$ Hz, 3-Ha), 1.16 (3H, d, $J=6.0$ Hz, 4-CH_3), 1.31 (4H, br.s, $(CH_2)_2$–Pr), 1.81 (1H, ddd, $J=12.0$, 5.3, 2.5 Hz, 3-He), 2.77 (1H, sext., $J=8.1$ Hz, 4-H), 3.11 (1H, dt, $J=12.0$, 2.5 Hz, 2-H), 3.60 (1H, br. s., H–N), 6.25 (1H, dd, $J=8.0$, 4.0 Hz, 8-H), 6.54 (1H, t, $J=4.0$ Hz, 7-H), 6.72 (1H, d, $J=4.0$ Hz, 5-H); ^{13}C NMR (100 MHz) δ 14.1, 18.7, 20.1, 30.9, 38.1, 38.9, 51.6, 112.8, 113.2, 114.9, 127.9, 140.7, 155.6 ($J=233.0$ Hz, 6-C); GC: two isomers (t_R A = 17.75, t_R B = 18.20 min). MS *m/z* (EI) for isomer A: 207 (M^+, 13%); for isomer B: 207 (M^+, 11%). Found: C, 75.12; H, 8.99; N, 6.85; calcd for $C_{13}H_{18}FN$: C, 75.36; H, 8.70; N, 6.76.

4-[*N*-Acetyl-*N*-(4-methylphenyl)]amino-4-phenyl-2-butyl acetate (95). To a solution of **87** (2.7 mmol) in dry benzene (100 mL), an excess of acetic anhydride was added; after the addition was complete, the solution was heated under reflux 24 h. The reaction mixture was extracted with ethyl acetate (2×30 mL). The ethyl acetate layer was separated, dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography over silica (with heptane/ether) to give **95** as

reddish oil. Yield 86%. IR (film) ν 1738 and 1657 cm^{-1} (s, CO). ^1H NMR (200 MHz) δ 1.35 (3H, d, $J=6.0$ Hz, 1-CH_3), 1.74 (3H, s, CH_3CO), 2.04 (3H, s, CH_3COO), 2.32 (3H, s, CH_3), 1.83–1.97 (2H, m, 3-H), 4.95 (1H, q, $J=6.6$, 6.2 Hz, 2-H), 6.23 (1H, dd, $J=8.8$, 6.9 Hz, 4-H), 7.02–7.27 (9H, m, H_{Ar} and H_{Ph}). MS *m/z* (EI) 339 (M^+, 10%). Found: C, 74.21; H, 7.49; N, 4.33; calcd for $C_{21}H_{25}NO_3$: C, 74.34; H, 7.37; N, 4.13.

4-Methyl-2-(*n*-propyl)quinoline (96). To a solution of 1.0 mmol of tetrahydroquinoline 92 dissolved in 30 mL of benzene, 2.1 mmol of DDQ dissolved in benzene were added slowly. The reaction mixture was stirred at room temperature for 4 h, monitoring progress via TLC (heptane/ethylacetate (50:1), chromatoplates of Silufol UV_{254}). At the end of the reaction the mixture was filtered (solid product is DDHQ). The benzene was distilled; the residue was purified by column chromatography over silica (with heptane/ethylacetate, 50:1) to give 96 as reddish oil. Yield 58%. ^1H NMR (400 MHz) δ 0.85 (3H, t, $J=8.3$ Hz, H_3C–Pr), 1.22–1.30 (4H, br. s., $(CH_2)_2$–Pr), 1.25 (3H, s, 4-CH_3), 7.12 (1H, s, 3-H), 7.48 (1H, t, $J=7.0$ Hz, 6-H), 7.65 (1H, t, $J=8.3$ Hz, 7-H), 7.92 (1H, d, $J=8.3$ Hz, 8-H), 8.03 (1H, d, $J=8.6$ Hz, 5-H); ^{13}C NMR (100 MHz) δ 14.1, 18.7, 22.7, 41.2, 122.1, 123.5, 125.4, 127.0, 128.9, 129.3, 144.3, 147.5, 162.5. MS *m/z* (EI) 185 (M^+, 8%). Found: C, 84.55; H, 8.03; N, 7.46; calcd for $C_{13}H_{15}N$: C, 84.32; H, 8.11; N, 7.57.

General procedure for the synthesis of 2-pyridyl-tetrahydroquinolines (97–101, 103–107)

85% (v/v) Sulfuric acid (4 mL) was added dropwise at 0 °C to the homoallylamine (1.0 g) in chloroform; the resulting mixture was heated at 95–100 °C for 12–15 h while stirring vigorously. The reaction progress was monitored via TLC. At the end of the reaction the mixture was cooled down to 0 °C and concentrated sodium hydroxide solution was added to pH 12. Three 20-mL extractions with chloroform were performed. The organic layers were combined, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography over alumina with heptane and ethyl acetate. Tetrahydroquinoline **102** was obtained using polyphosphoric acid [relation 1:10 (p/p) of homoallylamine/acid].

4-Methyl-2-(3′-pyridyl)-1,2,3,4-tetrahydroquinoline (97). White crystals. Mp 125–127 °C. Yield 77%. IR (KBr) ν 3265 cm^{-1} (s, NH). ^1H NMR (400 MHz) *cis isomer*: δ 1.34 (3H, d, $J=6.8$ Hz, 4-CH_3), 1.75 (1H, q, $J=12.9$, 11.4 Hz, 3-Ha), 2.08 (1H, ddd, $J=12.9$, 5.2, 2.7 Hz, 3-He), 3.12 (1H, sept., $J=6.8$ Hz, 4-H), 4.03 (1H, br.s, H-N), 4.47 (1H, dd, $J=11.4$, 2.6 Hz, 2-H), 6.53 (1H, dd, $J=7.8$, 0.9 Hz, 8-H), 6.72 (1H, td, $J=7.6$ Hz, 6-H), 7.00 (1H, t, $J=7.6$ Hz, 7-H), 7.18 (1H, d, $J=7.6$ Hz, 5-H), 7.26 (1H, dd, $J=8.0$, 4.9 Hz, 5′-H_{Py}), 7.74 (1H, dt, $J=8.0$, 1.6 Hz, 4′-H_{Py}), 8.51 (1H, dt, $J=4.9$, 1.9 Hz, 6′-H_{Py}), 8.60 (1H, d, $J=2.0$ Hz, 2′-H_{Py}); ^{13}C NMR (100 MHz) δ 20.0, 31.0, 41.3, 54.5, 114.3, 117.9, 123.5, 125.8, 126.8, 126.9, 134.1, 139.6, 144.3, 148.5, 150.0; GC: two isomers (1 : 2.5) (t_R A = 29.98, t_R B = 30.62 min). MS *m/z* (EI) for isomer A: 224 (M^+, 100%); for isomer B: 224 (M^+, 100%). Found: C, 80.20; H, 7.38; N, 12.62; calcd for $C_{15}H_{16}N_2$: C, 80.36; H, 7.14; N, 12.50. Compound **98** have been previously reported in ref 16.

4,6-Dimethyl-2-(2′-pyridyl)-1,2,3,4-tetrahydroquinoline (99). Yellow viscous oil. n_D^{20} 1.6052. Yield 79%. IR (film) ν 3356 cm^{-1} (s, NH). ^1H NMR (400 MHz) *cis isomer*: δ 1.30 (3H, d, $J=6.8$ Hz, 4-CH_3), 1.60 (1H, q, $J=12.4$, 11.5 Hz, 3-Ha), 2.03 (1H, ddd, $J=12.4$, 5.8, 2.6 Hz, 3-He), 2.25 (3H, s, 6-CH_3), 2.83–3.29 (1H, m, 4-H), 4.30 (1H, br. s, H–N), 4.58 (1H, dd, $J=11.5$, 2.6 Hz, 2-H), 6.53 (1H, d, $J=8.1$ Hz, 8-H), 6.94 (1H, d, $J=7.3$ Hz, 7-H), 7.14 (1H, dd, $J=7.7$ Hz, 3′-H_{Py}), 7.24 (1H, s, 5-H), 7.44 (1H, dd, $J=7.7$, 3.3 Hz, 5′-H_{Py}), 7.63–7.67 (1H, m, 4′-H_{Py}), 8.55–8.57 (1H, m, 6′-H_{Py}); GC: two isomers (1:2.5) (t_R A = 30.48, t_R B = 31.32 min). MS *m/z* (EI) for isomer A: 238 (M^+, 76%), 160 ($M-C_6H_6$, 100%); for isomer B: 238 (M^+, 63%), 160 ($M-C_6H_6$, 100%). Found: C, 80.80; H, 7.45; N, 11.76; calcd for $C_{16}H_{18}N_2$: C, 80.67; H, 7.56; N, 11.77.

4,6-Dimethyl-2-(4′-pyridyl)-1,2,3,4-tetrahydroquinoline (100). Yellow crystals. Mp 138–139 °C. Yield 72%. IR (KBr) ν 3300 cm^{-1} (s, NH). ^1H NMR (200 MHz) *cis isomer*: δ 1.34 (3H, d, $J=6.6$ Hz, 4-CH_3), 1.70 (1H, q, $J=12.8$, 11.3 Hz, 3-Ha), 2.11 (1H, ddd, $J=12.8$, 5.5, 2.6 Hz, 3-He), 2.26 (3H, s, 6-CH_3), 3.12 (1H, sept., $J=6.6$ Hz, 4-H), 3.86 (1H, br.s, H–N), 4.44 (1H, dd, $J=11.3$, 2.6 Hz, 2-H), 6.50 (1H, d, $J=8.0$ Hz, 8-H), 6.86 (1H, dd, $J=8.0$, 0.7 Hz, 7-H), 7.00 (1H, br.s, 5-H), 7.36 (2H, dd, $J=4.4$, 1.5 Hz, 3′(5′)-H_{Py}), 8.58 (2H, dd, $J=4.4$, 1.5 Hz, 2′(6′)-H_{Py}); GC: two isomers (1:2) (t_R A = 27.50, t_R B = 27.98 min). MS *m/z* (EI) for isomer A: 238 (M^+, 100%); for isomer B: 238 (M^+, 100%). Found: C, 80.46; H, 7.78; N, 11.86; calcd for $C_{16}H_{18}N_2$: C, 80.67; H, 7.56; N, 11.77.

4-Methyl-8-isopropyl-2-(3′-pyridyl)-1,2,3,4-tetrahydroquinoline (101). Yellow crystals. Mp 61–62 °C. Yield 79%. IR (KBr) ν 3385 cm^{-1} (s, NH). ^1H NMR (400 MHz) *cis isomer*: δ 1.25 (3H, d, $J=6.8$ Hz, $CH_{3i\text{-}Pr}$), 1.29 (3H, d, $J=6.8$ Hz, $CH'_{3i\text{-}Pr}$), 1.40 (3H, d, $J=6.6$ Hz, 4-CH_3), 1.69 (1H, q, $J=12.1$, 12.1 Hz, 3-Ha), 2.01 (1H, ddd, $J=12.1$, 6.0, 2.5 Hz, 3-He), 2.70 (1H, sept., $J=6.8$ Hz; H-$C_{i\text{-}Pr}$), 3.01 (1H, sept., $J=6.0$ Hz, 4-H), 3.88 (1H, s, H-N), 4.45 (1H, d, $J=11.3$ Hz, 2-H), 6.68 (1H, t, $J=7.6$ Hz, 6-H), 6.96 (1H, d, $J=7.3$ Hz, 7-H), 7.02 (1H, d, $J=7.6$ Hz, 5-H), 7.22 (1H, dd, $J=7.8$, 5.0 Hz, 5′-H_{Py}), 7.70 (1H, d, $J=7.8$ Hz, 4′-H_{Py}), 8.47 (1H, d, $J=5.0$ Hz, 6′-H_{Py}), 8.59 (1H, s, 2′-H_{Py}), *trans isomer*: δ 1.25 (3H, d, $J=6.8$ Hz, $CH_{3i\text{-}Pr}$), 1.29 (3H, d, $J=6.8$ Hz, $CH'_{3i\text{-}Pr}$), 1.56 (3H, d, $J=6.6$ Hz, 4-CH_3), 1.77 (1H, dt, $J=12.1$, 10.1 Hz, 3-Ha), 1.95 (1H, ddd, $J=12.1$, 5.5, 2.5 Hz, 3-He), 2.85 (1H, sept., $J=6.8$ Hz, H-$C_{i\text{-}Pr}$), 3.64 (1H, sept., $J=5.0$ Hz, 4-H), 4.01 (1H, s, H–N), 4.41 (1H, d, $J=2.5$ Hz, 2-H), 6.75 (1H, t, $J=7.6$ Hz, 6-H), 6.91 (2H, d, $J=7.6$ Hz, 5(7)-H), 7.12 (1H, dd, $J=7.6$, 5.0 Hz, 5′-H_{Py}), 7.58 (1H, d, $J=7.6$ Hz, 4′-H_{Py}), 8.34 (1H, d, $J=5.0$ Hz, 6′-H_{Py}), 8.56 (1H, s, 2′-H_{Py}); ^{13}C NMR (100 MHz) δ 20.3/20.0, 22.1/22.2, 22.5/22.6, 27.2/27.8, 31.5/31.8, 41.1/41.2, 54.6/54.8, 117.2/117.5, 122.9/123.0,

123.6/123.7, 124.3/124.4, 125.7/125.8, 131.4, 134.2/134.3, 140.2/140.4, 140.2/141.0, 148.1/148.2, 148.6/149.1; GC: two isomers (1.6:6.4) (t_R A = 32.75, t_R B = 33.52 min). MS *m/z* (EI) for isomer A: 266 (M^+, 100%); for isomer B: 266 (M^+, 100%); Found: C, 81.33; H, 8.45; N, 10.29; calcd for $C_{18}H_{22}N_2$: C, 81.20; H, 8.27; N, 10.53.

6-Methoxy-4-methyl-2-(3′-pyridyl)-1,2,3,4-tetrahydroquinoline (102). White crystals. Mp 135–137 °C. Yield 48%. IR (KBr) ν 3351 cm^{-1} (s, NH). ^1H NMR (400 MHz) *cis isomer*: δ 1.26 (3H, d, *J* = 6.6 Hz, 4-CH_3), 1.67 (1H, q, *J* = 13.1, 11.6 Hz, 3-Ha), 2.02 (1H, ddd, *J* = 13.1, 5.5, 2.5 Hz, 3-He), 3.06 (1H, sept., *J* = 6.6 Hz, 4-H), 3.68 (3H, s, CH_3O), 4.34 (1H, dd, *J* = 11.6, 2.5 Hz, 2-H), 6.43 (1H, d, *J* = 8.6 Hz, 8-H), 6.56 (1H, dd, *J* = 8.6, 2.5 Hz, 7-H), 6.71 (1H, d, *J* = 2.5 Hz, 5-H), 7.20 (1H, dd, *J* = 7.6, 4.5 Hz, 5′-H_{Py}), 7.69 (1H, dt, *J* = 7.6, 1.5 Hz, 4′-H_{Py}), 8.46 (1H, dd, *J* = 4.5, 1.5 Hz, 6′-H_{Py}), 8.55 (1H, d, *J* = 2.0 Hz, 2′-H_{Py}); ^{13}C NMR (100 MHz) δ 20.3; 31.4, 41.4, 54.8, 55.8, 112.5, 113.1, 115.3, 123.6, 127.8, 134.2, 138.5, 139.8, 148.6, 149.0, 152.4; GC: two isomers (1:20) (t_R A = 31.00, t_R B = 31.91 min). MS *m/z* (EI) for isomer A: 254 (M^+, 100%); for isomer B: 254 (M^+, 100%). Found: C, 75.45; H, 7.32; N, 11.30; calcd for $C_{16}H_{18}N_2O$: C, 75.59; H, 7.09; N, 11.02.

6-Bromo-4-methyl-2-(3′-pyridyl)-1,2,3,4-tetrahydroquinoline (103). Yellow crystals. Mp 135–137 °C. Yield 34%. IR (KBr) ν 3261 cm^{-1} (s, NH). ^1H NMR (400 MHz) *cis isomer*: δ 1.31 (3H, d, *J* = 6.6 Hz, 4-CH_3), 2.06 (1H, br.d, *J* = 12.1 Hz, 3-He), 1.69 (1H, q, *J* = 12.1, 11.6 Hz, 3-Ha), 3.07 (1H, quin., *J* = 5.5 Hz, 4-H), 4.06 (1H, br.s, H–N), 4.44 (1H, d, *J* = 10.6 Hz, 2-H), 6.33 (1H, d, *J* = 8.1 Hz, 8-H), 7.07 (1H, d, *J* = 8.1 Hz, 7-H), 7.16–7.27 (2H, m, 5-H and 5′-H_{Py}), 7.72 (1H, d, *J* = 7.6 Hz, 4′-H_{Py}), 8.51 (1H, s, 6′-H_{Py}), 8.58 (1H, d, *J* = 2.0 Hz, 2′-H_{Py}); *trans isomer* δ: 1.41 (3H, d, *J* = 6.5 Hz, 4-CH_3), 1.76 (1H, d, *J* = 12.6 Hz, 3-Ha), 1.89–1.93 (1H, m, 3-He), 2.79 (1H, br.s, 4-H), 4.15 (1H, br.s, H–N), 4.23 (1H, s, 2-H), 6.54 (1H, d, *J* = 8.6 Hz, 8-H), 6.95 (1H, dd, *J* = 8.6, 2.5 Hz, 7-H), 7.04 (1H, s, 5-H), 7.13 (1H, dd, *J* = 8.1, 5.0 Hz, 5′-H_{Py}), 6.46 (1H, d, *J* = 8.1 Hz, 4′-H_{Py}), 8.38 (1H, s, 6′-H_{Py}), 8.61 (1H, s, 2-H_{Py}); ^{13}C NMR (100 MHz) δ 19.8/23.5, 29.4/31.1, 37.5/40.7, 49.8/54.4, 115.7/115.8, 116.6, 123.5/123.6, 129.5/129.6, 131.8/131.9, 134.1/134.2, 139.6, 139.2, 142.5/143.3, 148.4/148.5, 148.9/149.2; GC: two isomers (1:4.1) (t_R A = 34.84, t_R B = 35.90 min). MS *m/z* (EI) for isomer A: 302 (M^+ for ^{79}Br, 100%); for isomer B: 304 (M^+ for ^{81}Br, 100%). Found: C, 59.54; H, 5.11; N, 9.12; calcd for $C_{15}H_{15}BrN_2$: C, 59.41; H, 4.95; N, 9.24.

6-Chloro-4-methyl-2-(3′-pyridyl)-1,2,3,4-tetrahydroquinoline (104). Yellow crystals. Mp 140–142 °C. Yield 56%. IR (KBr) ν 3268 cm^{-1} (s, NH). ^1H NMR (400 MHz) *cis isomer*: δ 1.24 (3H, d, *J* = 7.1 Hz, 4-CH_3), 1.63 (1H, q, *J* = 12.9, 11.1 Hz, 3-Ha), 2.00 (1H, ddd, *J* = 12.9, 5.0, 2.5 Hz, 3-He), 3.01 (1H, sept., *J* = 5.0 Hz, 4-H), 4.00 (1H, br.s, H–N), 4.38 (1H, dd, *J* = 11.1, 2.5 Hz, 2-H), 6.38 (1H, d, *J* = 8.6 Hz, 8-H), 6.87 (1H, dd, *J* = 8.6, 2.0 Hz, 7-H), 7.03 (1H, d, *J* = 2.0 Hz, 5-H), 7.21 (1H, dd, *J* = 7.6, 5.0 Hz, 5′-H_{Py}), 7.66 (1H, dt, *J* = 7.6, 2.0 Hz, 4′-H_{Py}), 8.52 (1H, s, 6′-H_{Py}), 8.59 (1H, d, *J* = 1.5 Hz, 2′-H_{Py}); *trans isomer*: δ 1.39 (3H, d, *J* = 7.0 Hz, 4-CH_3), 1.75 (1H, dt, *J* = 12.9, 5.5 Hz, 3-Ha), 1.91 (1H, sept., *J* = 3.3 Hz, 3-He), 3.38 (1H, br.s, H-N), 3.54 (1H, sext., *J* = 3.3 Hz; 4-H), 4.38 (1H, t, *J* = 3.3 Hz, 2-H), 6.54 (1H, d, *J* = 8.6 Hz, 8-H), 6.95 (1H, dd, *J* = 8.6, 2.5 Hz, 7-H), 7.04 (1H, s, 5-H), 7.13 (1H, dd, *J* = 8.1, 5.0 Hz, 5′-H_{Py}), 7.57 (1H, dt, *J* = 8.1, 2.0 Hz, 4′-H_{Py}), 8.34 (1H, d, *J* = 2.0 Hz, 6′-H_{Py}), 8.52 (1H, s, 2′-H_{Py}); ^{13}C NMR (100 MHz) δ 19.0/19.8, 31.1/31.8, 40.7, 54.5, 117.3, 123.3/123.6, 126.9/127.1, 130.0, 132.5/132.6, 134.2, 135.4, 139.3, 142.7/142.8, 148.0/148.3, 148.4/149.1; GC: two isomers (1:1.7) (t_R A = 35.84, t_R B = 36.72). MS *m/z* (EI) for isomer A: 258 (M^+ for ^{35}Cl, 100%); for isomer B: 258 (M^+ for ^{35}Cl, 100%). Found: C, 69.53; H, 5.89; N, 10.76; calcd for $C_{15}H_{15}ClN_2$: C, 69.63; H, 5.80; N, 10.83.

6-Fluoro-4-methyl-2-(3′-pyridyl)-1,2,3,4-tetrahydroquinoline (105). Yellow crystals. Mp 114–115 °C. Yield 52%. IR (KBr) ν 3269 cm^{-1} (s, NH). ^1H NMR (400 MHz) *cis isomer*: δ 1.26 (3H, d, *J* = 6.6 Hz, 4-CH_3), 1.67 (1H, q, *J* = 13.1, 11.6 Hz, 3-Ha), 2.03 (1H, ddd, *J* = 13.1, 6.0, 2.5 Hz, 3-He), 3.06 (1H, sept., *J* = 6.0 Hz, 4-H), 3.81 (1H, br.s, H–N), 4.38 (1H, dd, *J* = 11.6, 2.5 Hz, 2-H), 6.41 (1H, dd, *J* = 8.6, 5.6 Hz, 8-H), 6.67 (1H, td, *J* = 8.1 Hz, 7-H), 6.83 (1H, dd, *J* = 10.1, 2.0 Hz, 5-H), 7.23 (1H, dd, *J* = 7.6, 5.0 Hz, 5′-H_{Py}), 7.64 (1H, dt, *J* = 7.6, 1.5 Hz, 4′-H_{Py}), 8.48 (1H, dd, *J* = 5.0, 1.5 Hz, 6′-H_{Py}), 8.55 (1H, s, 2′-H_{Py}); *trans isomer*: δ 1.42 (3H, d, *J* = 6.6 Hz, 4-CH_3), 1.77 (1H, dt, *J* = 13.1, 10.1 Hz, 3-Ha), 1.96 (1H, sept., *J* = 6.6 Hz, 3-He), 2.82 (1H, sext., *J* = 7.1 Hz, 4-H), 3.84 (1H, br.s, H–N), 4.42 (1H, d, *J* = 3.5 Hz, 2-H), 6.41 (1H, dd, *J* = 8.6, 5.6 Hz, 8-H), 6.67 (1H, td, *J* = 8.1 Hz, 7-H), 6.83 (1H, dd, *J* = 10.1, 2.0 Hz, 5-H), 7.23 (1H, dd, *J* = 7.6, 5.0 Hz, 5′-H_{Py}), 7.64 (1H, dt, *J* = 7.6, 1.5 Hz, 4′-H_{Py}), 8.48 (1H, dd, *J* = 5.0, 1.5 Hz, 6′-H_{Py}), 8.55 (1H, s, 2′-H_{Py}); ^{13}C NMR (100 MHz) δ 20.1/23.9, 31.3/36.5, 37.8/41.0, 50.1/54.7, 113.4 (d, *J* = 22.3 Hz), 113.5 (d, *J* = 23.0 Hz), 115.1 (d, *J* = 7.4 Hz), 123.6, 127.5 (d, *J* = 6.1 Hz), 134.2, 139.5, 140.5 (d, *J* = 2.0 Hz), 148.6, 149.2, 156.2 (d, *J* = −235.0 Hz); GC: two isomers (1:6.8) (t_R A = 26.30, t_RB = 26.78 min). MS *m/z* (EI) for isomer A: 242 (M^+, 100%); for isomer B: 242 (M^+, 100%). Found: C, 74.03; H, 6.52; N, 11.33; calcd for $C_{15}H_{15}FN_2$: C, 74.38; H, 6.20; N, 11.57.

6,8-Difluoro-4-methyl-2-(3′-pyridyl)-1,2,3,4-tetrahydroquinoline (106). Red oil. Yield 26%. IR (film) ν 3356 cm^{-1} (s, NH). ^1H NMR (400 MHz) *cis isomer*: δ 1.40 (3H, d, *J* = 7.1 Hz, 4-CH_3), 1.75 (1H, q, *J* = 14.6, 14.1 Hz, 3-Ha), 1.89 (1H, ddd, *J* = 14.6, 5.5, 2.5 Hz, 3-He), 3.53 (1H, br.s, H–N), 3.64 (1H, quint., *J* = 7.1 Hz, 4-H), 4.46 (1H, t, *J* = 14.1 Hz, 2-H), 6.29 (1H, d, J_{HH} = 3.0 Hz, 7-H), 6.65 (1H, d, J_{HH} = 3.0 Hz, 5-H), 7.16 (1H, dd, *J* = 7.6, 4.5 Hz, 5′-H_{Py}), 7.59 (1H, d, *J* = 7.6 Hz, 4′-H_{Py}), 8.37 (1H, d, *J* = 4.5 Hz, 6′-H_{Py}), 8.47 (s, 1H, 2′-H_{Py}); ^{13}C NMR (100 MHz) δ 19.1, 37.2, 46.9, 56.0, 101.7 (dd, *J* = 24.3, 23.6 Hz); 108.9 (dd, *J* = 22.3, 3.4 Hz), 123.4, 128.6 (dd, *J* = 12.8, 3.4 Hz), 131.9 (dd, *J* = 7.4, 7.4 Hz), 134.9, 139.0, 148.0, 148.4, 151.5 (dd, *J* = −241.0, 12.8 Hz), 155.2 (dd, *J* = −239.0, 12.8 Hz); GC: one isomer (t_R = 29.45 min). MS *m/z* (EI) 260 (M^+, 100%). Found:

C, 69.02; H, 5.55; N, 10.42; calcd for $C_{15}H_{14}F_2N_2$: C, 69.23; H, 5.38; N, 10.77.

8-Iodo-4-methyl-2-(3′-pyridyl)-1,2,3,4-tetrahydroquinoline (107). Red crystals. Mp 98–100 °C. Yield 12%. IR (KBr) ν 3365 cm^{-1} (s, NH). ^1H NMR (400 MHz) *cis isomer*: δ 1.18 (3H, d, $J=6.6$ Hz, 4-CH_3), 1.70 (1H, q, $J=12.1$, 12.0 Hz, 3-Ha), 2.02 (1H, dt, $J=12.1$, 2.5 Hz, 3-He), 3.11 (1H, sept., $J=6.6$ Hz, 4-H), 3.88 (1H, s, H-N), 4.45 (1H, dd, $J=11.1$, 2.5 Hz, 2-H), 6.69 (1H, t, $J=7.6$ Hz, 6-H), 6.97 (1H, d, $J=7.6$ Hz, 5-H), 7.02 (1H, d, $J=7.6$ Hz, 7-H), 7.23 (1H, dd, $J=7.6$, 5.0 Hz, 5′-H_{Py}), 7.71 (1H, d, $J=8.1$ Hz, 4′-H_{Py}), 8.48 (1H, d, $J=5.0$ Hz, 6′-H_{Py}), 8.60 (1H, s, 2′-H_{Py}); ^{13}C NMR (100 MHz) δ20.3, 30.3, 37.9, 50.1, 90.1, 123.0, 123.4, 123.7, 134.2, 136.7, 140.2, 141.0, 148.6, 149.1, 156.0; GC: one isomer ($t_R=33.71$ min). MS *m/z* (EI) 350 (M^+, 100%). Found: C, 51.33; H, 4.45; N, 7.80; calcd for $C_{15}H_{15}IN_2$: C, 51.43; H, 4.29; N, 8.00.

General procedure for the synthesis of quinolines (108–116)

In a 50 mL flask a mixture of powdered sulphur (0.03 mol) and tetrahydroquinoline (97–101 and 103–106) (0.01 mol) is placed and the flask is then placed in a sand bath which is heated to 260–280 °C for 10–30 min, until evolution of hydrogen sulphide has ceased. The residue was purified by column chromatography over alumina with heptane/ethyl acetate, to yield quinolines (108–116).

4-Methyl-2-(3′-pyridyl)quinoline (108). White crystals. Mp 67–68 °C. Yield 76%. ^1H NMR (200 MHz) δ 2.79 (3H, d, $J=0.7$ Hz, 4-CH_3), 7.45 (1H, ddd, $J=8.0$, 4.8, 0.7 Hz, 5′-H_{Py}), 7.58 (1H, ddd, $J=8.4$, 7.7, 1.5 Hz; 6-H), 7.79–7.81 (2H, m, 3(7)-H), 8.02 (1H, dd, $J=8.4$, 1.5 Hz, 8-H), 8.18 (1H, ddd, $J=8.4$, 1.5, 0.7 Hz, 5-H), 8.50 (1H, dt, $J=8.0$, 2.2 Hz, 4′-H_{Py}), 8.70 (1H, dd, $J=4.8$, 1.5 Hz, 6′-H_{Py}), 9.34 (1H, dd, $J=2.2$, 0.7 Hz, 2′-H_{Py}). MS *m/z* (EI) 220 (M^+, 100%). Found: C, 81.87; H, 5.66; N, 12.50; calcd for $C_{15}H_{12}N_2$: C, 81.82; H, 5.45; N, 12.73.

Quinoline **109** has been reported previously in ref 16

4,6-Dimethyl-2-(2′-pyridyl)quinoline (110)

Yellow crystals. Mp 134–135 °C. Yield 84%. ^1H NMR (200 MHz) δ 2.58 (3H, s, 6-CH_3), 2.77 (3H, d, $J=0.7$ Hz, 4-CH_3), 7.38 (1H, ddd, $J=7.7$, 4.8, 1.5 Hz, 5′-H_{Py}), 7.56 (1H, dd, $J=8.4$, 1.8 Hz, 7-H), 7.78 (1H, s, 5-H), 7.86 (1H, td, $J=8.0$ Hz, 3′-H_{Py}), 8.07 (1H, d, $J=8.4$ Hz, 8-H), 8.36 (1H, d, $J=0.7$ Hz, 3-H), 8.62 (1H, dt, $J=8.0$, 1.8 Hz, 4′-H_{Py}), 8.73 (1H, ddd, $J=4.8$, 1.8, 1.1 Hz, 6′-H_{Py}). MS *m/z* (EI) 234 (M^+, 100%). Found: C, 81.98; H, 5.87; N, 12.14; calcd for $C_{16}H_{14}N_2$: C, 82.05; H, 5.98; N, 11.97.

4,6-Dimethyl-2-(4′-pyridyl)quinoline (111). Yellow crystals. Mp 168–169 °C. Yield 75%. ^1H NMR (200 MHz) δ 2.59 (3H, s, 6-CH_3), 2.77 (3H, s, 4-CH_3), 7.59 (1H, dd, $J=8.8$, 1.8 Hz, 7-H), 7.71 (1H, s, 3-H), 7.78 (1H, s, 5-H), 8.01–8.12 (3H, m, 8-H and 3′(5′)-H_{Py}), 8.76 (2H, d, $J=5.8$ Hz, 2′(6′)-H_{Py}). MS *m/z* (EI) 234 (M^+, 100%). Found: C, 82.12; H, 5.87, N, 12.05; calcd for $C_{16}H_{14}N_2$: C, 82.05; H, 5.98; N, 11.97.

4-Methyl-8-isopropyl-2-(3′-pyridyl)quinoline (112). White solid. Mp 105–106 °C. Yield 59%. ^1H NMR (200 MHz) δ 1.44 (6H, d, $J=6.9$ Hz, CH_3 and CH'_3-*i*-Pr), 2.78 (3H, d, $J=0.7$ Hz, 4-CH_3), 4.50 (1H, quin., $J=6.9$, H-C-*i*-Pr), 7.45 (1H, ddd, $J=8.0$, 4.8, 0.7 Hz, 5′-H_{Py}), 7.55 (1H, d, $J=8.0$ Hz, 6-H), 7.64 (1H, dd, $J=7.3$, 1.8 Hz, 7-H), 7.75 (1H, d, $J=0.7$ Hz, 3-H), 7.87 (1H, dd, $J=8.0$, 1.8 Hz, 5-H), 8.56 (1H, dt, $J=8.0$, 2.2 Hz, 4′H_{Py}), 8.68 (1H, dd, $J=4.8$, 1.5 Hz, 6′-H_{Py}), 9.45 (1H, dd, $J=2.2$, 0.7 Hz, 2′-H_{Py}). MS *m/z* (EI) 262 (M^+, 50%). Found: C, 82.22; H, 6.95; N, 10.57; calcd for $C_{18}H_{18}N_2$: C, 82.44; H, 6.87; N, 10.69.

6-Bromo-4-methyl-(3′-pyridyl)quinoline (113). Yellow crystals. Mp 120–121 °C. Yield 25%. ^1H NMR (300 MHz) δ 2.74 (3H, d, $J=1.0$ Hz, 4-CH_3), 7.45 (1H, ddd, $J=7.7$, 4.9, 0.7 Hz, 5′-H_{Py}), 7.73 (1H, s, 3-H), 7.81 (1H, dd, $J=9.0$, 2.3 Hz, 7-H), 8.05 (1H, d, $J=9.0$ Hz, 8-H), 8.17 (1H, d, $J=2.3$ Hz, 5-H), 8.50 (1H, dt, $J=7.7$, 1.6 Hz, 4′-H_{Py}), 8.72 (1H, dd, $J=4.9$, 1.6 Hz, 6′-H_{Py}), 9.35 (1H, d, $J=1.3$ Hz, 2′-H_{Py})). MS *m/z* (EI) 300 (M^+ for ^{81}Br, 100%). Found: C, 59.92; H, 4.07; N, 9.51; calcd for $C_{15}H_{11}BrN_2$: C, 60.20; H, 3.68; N, 9.36.

6-Chloro-4-methyl-(3′-pyridyl)quinoline (114). Yellow crystals. Mp 127–128 °C. Yield 75%. ^1H NMR (400 MHz) δ 2.75 (3H, s, 4-CH_3), 7.45 (1H, dd, $J=8.0$, 4.8 Hz, 5′-H_{Py}), 7.67 (1H, dd, $J=8.9$, 2.3 Hz, 8-H), 7.97 (1H, d, $J=2.2$ Hz, 5-H), 7.73 (1H, s, 3-H), 8.09 (1H, d, $J=8.9$ Hz, 7-H), 8.47 (1H, dt, $J=8.0$, 1.8 Hz, 4′-H_{Py}), 8.70 (1H, dd, $J=4.8$, 1.8 Hz, 6′-H_{Py}), 9.33 (1H, d, $J=2.2$ Hz, 2′-H_{Py}). MS *m/z* (EI) 254 (M^+ for ^{35}Cl, 100%). Found: C, 70.47; H, 4.49, N, 11.33; calcd for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.32; N, 11.00.

6-Fluoro-4-methyl-2-(3′-pyridyl)quinoline (115). Yellow crystals. Mp 103–104 °C. Yield 83%. ^1H NMR (200 MHz) δ 2.70 (3H, s, 4-CH_3), 7.59–7.42 (3H, m, 5(8)-H and 5′-H_{Py}), 7.70 (1H, s, 3-H), 8.13 (1H, dd, $J=9.1$, $^4J_{H,F}=5.6$ Hz, 8-H), 8.52 (1H, d, $J=7.5$ Hz, 4′-H_{Py}), 8.67 (1H, d, $J=4.6$ Hz, 6′-H_{Py}), 9.32 (1H, s, 2′-H_{Py}). MS *m/z* (EI) 238 (M^+, 100%). Found: C, 75.45; H, 4.72; N, 11.66; calcd for $C_{15}H_{11}FN_2$: C, 75.63; H, 4.62; N, 11.77.

6,8-Difluoro-4-methyl-2-(3′-pyridyl)quinoline (116). Brown crystals. Mp 150–151 °C. Yield 41%. ^1H NMR (200 MHz) δ 2.72 (3H, s, 4-CH_3), 7.34–7.48 (3H, m, 5(7)-H and 5′-H_{Py}), 7.78 (1H, s, 3-H), 8.51 (1H, dt, $J=8.0$, 1.6 Hz, 4′-H_{Py}), 8.68 (1H, dd, $J=4.6$, 1.6 Hz, 6-H_{Py}), 9.30 (1H, d, $J=1.3$ Hz, 2′-H_{Py}); ^{13}C NMR (50 MHz) δ 19.4, 103.3 (dd, $J=21.4$, 4.6 Hz), 105.4 (dd, $J=29.0$, 22.9 Hz), 111.4 (dd, $J=21.4$, 3.1 Hz), 120.8, 123.8, 128.9 (dd, $J=10.7$, 3.1 Hz), 133.0, 135.0, 147.0, 148.6, 150.4, 153.8, 159.2 (dd, $J=-260.9$, 13.7 Hz), 159.6 (dd, $J=-247.2$, 12.2 Hz). MS *m/z* (EI) 256 (M^+, 100%). Found: C, 70.56; H, 3.58; N, 10.86; calcd for $C_{15}H_{10}F_2N_2$: C, 70.31; H, 3.91; N, 10.94.

General procedure for the synthesis of nitroquinolines (117 and 118)

Quinolines (**109** and **110**) (8.55 mmol) were dissolved, at −8 °C, in concentrated sulfuric acid (40 mL). A mixture of concentrated sulfuric acid (10 mL) and nitric acid (8.65 mmol) was added, slowly, at −8 °C. The reaction mixture was stirred and held at 0 °C for 0.5 h after all of the nitric acid has been added. The reaction mixture was poured on ice and the solution made alkaline with concentrated NH_4OH to precipitate the product. The product was extracted with $CHCl_3$ (4×50 mL). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The solid was purified by a short chromatography column over alumina (with heptane/ethyl acetate).

4,6-Dimethyl-5-nitro-2-(3′-pyridyl)quinoline (117). Green crystals. Mp 160–161 °C. Yield 98%. IR (KBr) ν 1528, 1374 cm^{-1} (s, NO_2). ^1H NMR (300 MHz) δ 2.68 (3H, s, 6-CH_3), 2.49 (3H, s, 4-CH_3), 7.47 (1H, dd, J=8.0, 4.8 Hz, 5′-H_{Py}), 7.61 (1H, d, J=8.7 Hz, 8-H), 7.77 (1H, s, 3-H), 8.21 (1H, d, J=8.7 Hz, 7-H), 8.48 (1H, dt, J=8.0, 1.1 Hz, 4′-H_{Py}), 8.73 (1H, dd, J=4.8, 1.1 Hz, 6′-H_{Py}), 9.35 (1H, d, J=1.9 Hz, 2′-H_{Py}); ^{13}C NMR (75 MHz) δ 18.0, 19.6, 119.2, 123.3, 124.1, 129.2, 131.9, 133.1, 134.4, 135.2, 142.8, 146.9, 147.8, 149.2, 151.1, 155.0. MS m/z (EI) 279 (M^+, 100%). Found: C, 68.43; H, 4.57; N, 14.92; calcd for $C_{16}H_{13}N_3O_2$: C, 68.82; H, 4.66; N, 15.05.

4,6-Dimethyl-5-nitro-2-(2′-pyridyl)quinoline (118). Yellow crystals. Mp 134–136 °C. Yield 67%. IR (KBr) ν 1530, 1373 cm^{-1} (s, NO_2). ^1H NMR (200 MHz) δ 2.46 (3H, s, 6-CH_3), 2.67 (3H, d, J=0.7 Hz, 4-CH_3), 7.37 (1H, ddd, J=7.7, 4.8, 1.1 Hz, 5′-H_{Py}), 7.55 (1H, d, J=8.8 Hz, 7-H), 7.9 (1H, td, J=8.0 Hz, 3′-H_{Py}), 8.18 (1H, d, J=8.8 Hz, 8-H), 8.44 (1H, d, J=1.1 Hz, 3-H), 8.60 (1H, dt, J=8.0, 1.8 Hz, 4′-H_{Py}), 8.73 (1H, ddd, J=4.8, 1.8, 0.7 Hz, 6′-H_{Py}). MS m/z (EI) 279 (M^+, 100%). Found: C, 68.43; H, 4.57; N, 14.92; calcd for $C_{16}H_{13}N_3O_2$: C, 68.82; H, 4.66; N, 15.05.

5-Amino-4,6-dimethyl-2-(3′-pyridyl)quinoline (119). Under N_2 atmosphere, a solution of 5-nitroquinoline 117 (0.2 g, 0.72 mmol) in methanol (25 mL) was poured into a mixture of 10% palladium on charcoal (0.006 g) in methanol (5 mL). Sodium borohydride (0.068 g, 1.80 mmol) was added. The reaction mixture was stirred for 1.5 h. and then was acidified by 10% HCl (3 mL), neutralized by 1 M sodium hydroxide (5 mL) and concentrated under reduced pressure. The resulting mixture was extracted with $CHCl_3$ (4×10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Recrystallyzation in ethyl acetate gave 5-amino-4,6-dimethyl-2-(3′-pyridyl)quinoline **119** as orange brilliant crystals. Mp 155–157 °C. Yield 95%. IR (KBr) ν 3342, 3234 cm^{-1} (s, NH_2). ^1H NMR (400 MHz) δ 2.31 (3H, s, 6-CH_3), 3.06 (3H, s, 4-CH_3), 4.36 (2H, br.s, H_2N), 7.36–7.45 (3H, m, 3(7, 8)-H), 7.55 (1H, d, J=8.4 Hz, 5′-H_{Py}), 8.46 (1H, dt, J=8.4, 1.9 Hz, 4′-H_{Py}), 8.66 (1H, dd, J=4.8, 1.6 Hz, 6′-H_{Py}), 9.29 (1H, d, J=1.6 Hz, 2′-H_{Py}). MS m/z (EI) 249 (M^+, 100%). Found: C, 77.22; H, 6.15; N, 16.54; calcd for $C_{16}H_{15}N_3$: C, 77.11; H, 6.02; N, 16.87.

2-Pyridyl-tetrahydro-[2]benzazepines (120 and 121). Compounds **120** and **121** been obtained from 4-*N*-benzylamino-4-pyridyl-1-butenes and reported in ref 20.

***N*-(1-Allylcycloalkyl) arylamino derivatives (122–141).** Compounds **122–141** have been obtained from corresponding ketimines and allylmagnesium bromide following the general procedure.[21–23]

Biological Evaluation

Microorganisms and media

Dermatophytes. *M. canis* C 112, *Trichophyton rubrum* C 113, *E. floccosum* C 114, and *M. gypseum* C 115 as well as *Candida tropicalis* C 131 are clinical isolates and were kindly provided by CEREMIC (Centro de Referencia Micológica, Facultad ded Ciencias Bioquímicas y Farmacéuticas, Suipacha 531 (2000) Rosario, Argentina.

The strains were maintained on slopes of Sabouraud-dextrose agar[7] (SDA, Oxoid) and subcultured every 15 days to prevent pleomorphic transformations. Spore suspensions were obtained according to reported procedures[27] and adjusted to 10^6 spores with colony forming ability/mL.

Antifungal assays

The antifungal activity of homoallylamines, tetrahydroquinolines, quinolines and related compounds was evaluated with the agar dilution method by using Sabouraud-chloramphenicol agar for dermatophyte species as previously described.[24,28] Stock solutions of compounds (10 mg/mL in DMSO) were diluted to give serial 2-fold dilutions that were added to each medium resulting in concentrations ranging from 0.10 to 250 μg/mL. MIC for each compound was defined as the lowest concentration that produces no visible fungal growth after the incubation time.

Enzymatic assays

Strains and culture conditions. The *S. cerevisiae* strain used was MATa *trpI ura3 leu2 his3 pep4::HIS3 nuc1::LEU2*. Routine yeast growth (YEPD) was as described.[29]

Enzyme preparation. Cell extracts were obtained essentially as described previously.[30] Early logarithmic phase cells grown in 100 mL YEPD medium were collected, washed once with 50 mM Tris–HCl pH 7.5, suspended in 100 μL of the same buffer and broken with glass beads in a FastPrep FP120 apparatus (Savant, BIO 101, Inc.) (once a 15 s pulse at speed of 6.0). Broken material was collected and cell debris was removed by low speed centrifugation (5.000×g, 5 min at 4 °C). The supernatant was centrifuged at 18.000×g for 30 min at 4 °C

and the pellet was resuspended in 50 mM Tris–HCl pH 7.5 containing 33% glycerol (at a concentration of approximately 3 mg protein per mL) and stored at −80 °C. Protein was quantified by the Bradford dye-binding procedure[31] using the Bio-Rad Protein Assay Dye Reagent and bovine serum albumin as standard.

(1,3)-β-D-Glucan synthase assay. (1,3)-β-D-Glucan synthase assay was essentially as described previously.[30] The standard assay mixture contained 5 μL enzyme (15 μg protein), in a total volume of 40 μL. Two μL of methanol or the corresponding compounds (kept in stock solution, 10 mg/mL in methanol at −20 °C) were added to each reaction. The reaction was incubated for 30 min at 30 °C and stopped by addition of 1 mL 10% trichloroacetic acid. All reactions were carried out in duplicate. The drug Papulacandin B was a generous gifts from K. Scheibli and P. Traxler (Novartis, Basel, Switzerland). The antibiotic was kept in stock solution (10 mg/mL in methanol) at −20 °C.

Chitin synthase 1 assay. Chitin synthase-1 assay was performed as described previously.[32] The standard assay mixture contained 10 μL enzyme (30 μg protein) in a total volume of 50 μL. Two μL of methanol or the corresponding compounds (kept in stock solution, 10 mg/mL in methanol at −20 °C) were added to each reaction. Enzyme activation was performed by partial proteolysis of the reaction mixture with 2 μL trypsin (0.25 μg/μL) during 15 min at 30 °C and stopped by the addition of 2 μL trypsin inhibitor (0.375 μg/μL). The reaction was incubated for 90 min at 30 °C and stopped by addition of 1 μL 10% trichloroacetic acid. All reactions were carried out in duplicate.

Computational methods

The extensive search for low-energy conformations on the potential energy surface for homoallylamines reported here was carried out by first using the systematic routine GASCOS[33–35] in connection with the MM2 force field. Subsequently, ab-initio HF/3-21G calculations were used in the geometry optimization jobs, using the GAUSSIAN 98 program.[36] Molecular Electrostatic Potentials (MEPs)[37] were calculated using RHF/3-21G wave functions from the SPARTAN program.[38]

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References and Notes

1. Garber, G. In *Drugs*; Stevens, D. A., Ed.; Adis International: San Jose, 2001; Vol. 61, Suppl 1, p 1.
2. Meis, J. F; Verweij, P. E. In *Drugs*; Stevens, D. A., Ed.; Adis International: San Jose, 2001; Vol. 61, Supplement 1, pp 13.
3. Selitrennikoff, C. P. *Antifungal Drugs: (13)–β-Glucan-synthase Inhibitors*; Springer: Heidelberg, 1995, p. 1.
4. Barrett-Bee, K. J.; Ryder, N. S. In *Emerging Targets in Antibacterial and Antifungal Chemotherapy*; Sutcliffe, J., Georgopapadakou, N. H., Eds.; Chapman and Hall: New York, 1992; p 410.
5. White, T. C.; Marr, K. A.; Bowden, R. A. *Clin. Microbiol. Rev.* **1998**, *11*, 382.
6. Ablordeppey, S.; Fan, P.; Ablordeppey, J.; Mardenborough, L. *Curr. Med. Chem.* **1999**, *6*, 1151.
7. Urbina, J. M.; G-Cortés, J. C.; Palma, A.; López, S. N.; Zacchino, S. A.; Enriz, R. D.; Ribas, J. C.; Kouznetsov, V. V. *Bioorg. Med. Chem.* **2000**, *8*, 691.
8. López, S. N.; Castelli, M. V.; Zacchino, S. A.; Domínguez, J. N.; Lobo, G.; Charris-Charris, J.; G-Cortés, J. C.; Ribas, J. C.; Devia, C.; Rodríguez, A. M.; Enriz, R. D. *Bioorg. Med. Chem.* **2001**, *9*, 1999.
9. Zacchino, S. A.; Rodríguez, G. E.; Pezzenati, G.; Santecchia, C. B.; Giannini, F. A.; Enriz, R. D. *J. Ethnopharm.* **1998**, *62*, 35.
10. Layer, R. W. *Chem. Rev.* **1963**, *63*, 489.
11. Öcal, N.; Yolaçan, C.; Kaban, S.; Vargas, M.,L.Y.; Kouznetsov, V. V. *J. Heterocycl. Chem.* **2001**, *38*, 233.
12. Vargas Méndez, L. Y.; Kouznetsov, V.; Poveda, J. C.; Yolaçan, Ç; Öcal, N.; Aydodan, F. *Heterocycl. Commun.* **2001**, *7*, 129.
13. Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153.
14. Detailed report on spatial structure of diastereoisomeric tetrahydroquinolines will be published elsewhere.
15. Kuznetsov, V. V.; Aliev, A. E.; Prostakov, N. S. *Khimiya Geterotsiklicheskikh Soedinenii* **1994**, *1, 73; Chem. Abst.* **1994** *121*, 300.738.
16. Vargas Méndez, L. Y.; Kouznetsov, V.; Stashenko, E.; Bahsas, A.; Amaro-Luis, J. *Heterocycl. Commun.* **2001**, *7*, 323.
17. Haines, A. H., Ed. *Methods for the Oxidation of Organic Compounds*. Academic: New York, 1985 p. 16.
18. Lutun, S.; Guichard, E.; Hasiak, B.; Couturier, D. *Synth. Commun.* **1999**, *29*, 175.
19. Kouznetsov, V. V.; Palma, A.; Aliev, A. E. *Anales Química Int. Ed.* **1998**, *94*, 132.
20. Castro, J. R.; Ochoa, C. P.; Kouznetsov, V. V.; Stashenko, E. E.; Poveda, J. C.; Bahsas, A.; Amaro-Luis, J. *Heterocycl. Commun.* **2002**, *8*, 265.
21. Kouznetsov, V. V.; Palma, A. R.; Fernández, M.; Aliev, A. E.; Shevtsov, V. K.; Varlamov, A. V.; Prostakov, N. S. *Khim. Geterotsikl. Soedin* **1991**, *1, 350; Chem. Abst* **1992** *117* 48.300.
22. Palma, A. R.; Rozo, W.; Stashenko, E.; Molina, D.; Kouznetsov, V. V. *J. Heterocycl. Chem.* **1998**, *35*, 183.
23. Palma, A. R.; Vargas, L. Y.; Silva, J.; Kouznetsov, V. V. *Heterocycl. Commun.* **1998**, *4*, 455.
24. Zacchino, S. A.; Rodríguez, G. E.; Pezzenati, G.; Orellana, G.; Enriz, R. D.; Gonzalez Sierra, M. *J. Nat. Prod.* **1997**, *60*, 659.
25. Tkacz, J. In *Emerging Targets in Antibacterial and Antifungal Chemotherapy*; Sutcliffe J. M., Georgopapadakou, N. H., Eds.; Chapman and Hall: New York, 1992; p 495.

26. Cabib, E., Kang, M. S., Au-Young, J. In *Methods in Enzymology*; Abelson, J., Simmons, M., Eds.; Academic: San Diego, 1990; Vol. 138, p 643.
27. Wright, L.; Scott, E.; Gorman, S. *J. Antimicrob. Chemother*. **1983**, *12*, 317.
28. Zacchino, S. A.; López, S. N.; Pezzenati, G.; Furlán, R. L.; Santecchia, C. B.; Muñoz, L.; Giannini, F. A.; Rodríguez, A. M.; Enriz, R. D. *J. Nat. Prod*. **1999**, *63*, 1353.
29. Alfa, C., Fantes, P., Hyams, J., McLeod, M., Warbrick, E. In *Experiments with Fission Yeast: A Laboratory Course Manual*; Alfa, C., Fantes, P., Hyams, J., McLeod, M., Warbrick, E., Eds.; Cold Spring Harbor Laboratory: New York, 1993, p. 186.
30. Ishiguro, J.; Saitou, A.; Durán, A.; Ribas, J. C. *J. Bacteriol*. **1997**, *179*, 7653.
31. Bradford, M. M. *Anal. Biochem*. **1976**, *72*, 248.
32. Choi, W.; Cabib, E. *Anal. Biochem*. **1994**, *219*, 368.
33. Santagata, L. N.; Suvire, F. D.; Enriz, R. D.; Torday, V.; Csizmadia, I. G. *J. Mol. Struct. (TEOCHEM)* **1999**, *465*, 33.
34. Santagata, L. N.; Suvire, F. D.; Enriz, R. D. *J. Mol. Struct. (TEOCHEM)* **2000**, *536*, 173.
35. Santagata, L. N.; Suvire, F. D.; Enriz, R. D. *J. Mol. Struct. (TEOCHEM)* **2001**, *571*, 91.
36. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuresia, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Menucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ciolowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A.; *Gaussian 98*, Revision A 7, Gaussian Inc: Pittsburgh, PA, 1998.
37. Politzer, P.; Trulhar, D. G. In *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Truler, D. G., Eds.; Plenum: New York, 1981; p 1.
38. *PC Spartan Pro-User's Guide*, Wave function Inc.: Irvine, CA, 1999.
39. Gaughran, J. P.; Lai, M. H.; Kirsch, D. R.; Silverman, S. J. *J. Bacteriol*. **1994**, *176*, 5857.