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Antifungal and cytotoxic activities of some *N*-substituted aniline derivatives bearing a hetaryl fragment

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Abstract—Diverse *N*-substituted anilines bearing hetaryl fragments were easily prepared from corresponding aldimines derived from commercially available aromatic aldehydes and anilines. 2-Furyl substituted anilines showed very good antifungal activities against dermatophytes, particularly against *Trichophyton rubrum* (MIC = 3.12–6.25 μg/mL). In addition, all active compounds, **45**–**47**, **73**, and **74**, were tested for cytotoxic activities against breast (MCF-7), lung (H-460), and central nervous system (SF-268) human cancer cell lines with the NCI-anticancer-drug screen. The activity of amines described in this paper, along with the low toxicity of most of them, shows promise for the future development of non-toxic new antimycotic agents.

1. Introduction

Secondary amines bearing a hetaryl ring are widely used throughout the chemical industry as basic intermediates to prepare fine chemicals, pharmaceuticals, and agrochemicals.[1] Because of their unique biological properties, they have also played an important role in chemotherapy of a variety of diseases.[2] As a consequence of their widespread use, the chemistry and biology of these compounds have received considerable attention from both theoretical and practical points of view, and organic and medicinal chemists still continue to be interested in exploring newer ways of synthesizing and testing them and studying their biological activities in different targets.

As part of our ongoing project devoted to the discovery of new structures with antifungal properties, we previously reported that *N*-aryl-*N*-[1-(hetaryl)but-3-enyl]-amines ('homoallylamines') (type **I**) and 2-hetaryl-4-methyl-1,2,3,4-tetrahydroquinolines (type **II**) (Fig. 1),

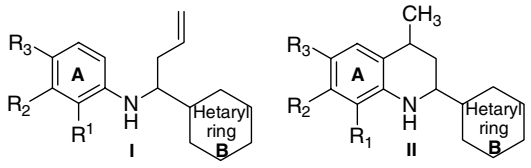

Figure 1. Structural types of the previously investigated amines with hetaryl moiety.

Keywords: *N*-substituted aniline derivatives; *N*-(Hetarylmethyl)anilines; *N*-Aryl-*N*-[1-(heteroyl)but-3-enyl]amines; Synthesis; Antifungal and cytotoxic properties; SAR.
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easily accessible from aldimines, displayed interesting activities mainly against opportunistic pathogenic dermatophytes.[3–5] In the last paper of this series,[5] it was possible to depict the main structural requirements of homoallylamines for displaying antifungal activity on the basis of computational studies: (a) presence of two aromatic rings (rings **A** and **B**); (b) presence of a heteroatom (with electronic lone pairs) or CH_3O groups on ring **B**; (c) the presence of a halogen atom (particularly Br or Cl) as R_3 on ring **A**. In addition, it was envisaged through the observation of a few examples that the elimination of the allyl moiety (giving place to secondary amines) resulted in a slight increase in antifungal activity.

Thus the antifungal evaluation of a more ample series of secondary amines, analogues of homoallylamines, seems appropriate in order to corroborate the importance of amines as antifungal compounds. In addition, the comparison of the cytotoxic activities and the antifungal properties will aid in determining the value of these structures as candidates for the development of new antifungal agents.

Herein, we report the preparation, physicochemical properties, antifungal and cytotoxic activities of a new series of amines: *N*-aryl-*N*-[1-(pyridyl, furyl, or thienyl)but-3-enyl]amines (homoallylamines), *N*-benzyl-, *N*-(furylmethyl)-, *N*-(thienylmethyl)-, and *N*-pyridylmethyl-anilines (*N*-substituted anilines), and 2-(*N*-arylmethylamino)-1-furyl(thienyl)acetonitriles (α-aminonitriles). All these compounds can be considered as *N*-hetarylmethylaniline derivatives, where a hydrogen atom of the CH_2 group is substituted by an allyl fragment or a nitrile group.

2. Results and discussion

2.1. Chemistry

The aldimines are valuable starting materials not only for different O- and/or N-containing heterocycles, but also for diverse secondary heteroaromatic amines,[6,7] which represent good candidates for bioscreening of diverse types of activities.[8,9] Thus, the *N*-hetaryl aldimines **1**–**40** (Table 1), the main starting materials in this investigation, were prepared from commercially available aromatic aldehydes (2-(3)-furancarboxyaldehydes or 2-(3)-thiophencarboxyaldehydes, *N*-methyl-2-pyrrolaldehyde, and 2-(3,4)-pyridinecarboxyaldehydes, benzaldehydes) and substituted anilines, according to published methods.[10–15] New series of these aldimines were converted into secondary amines bearing a hetaryl fragment: *N*-hetarylmethylanilines (type **A**), which comprise *N*-(furylmethyl)anilines **41**–**50**, *N*-(thienylmethyl)anilines **51**–**56**, *N*-[(1-methyl-1*H*-pyrrol-2-yl)methyl]anilines **57**–**59**, *N*-(pyridylmethyl)anilines **60**–**75**, and *N*-benzylanilines **76**–**80** or homoallylamines (type **B**), which include *N*-aryl-*N*-[1-(hetaryl)but-3-enyl]amines **81**–**92** (Scheme 1).

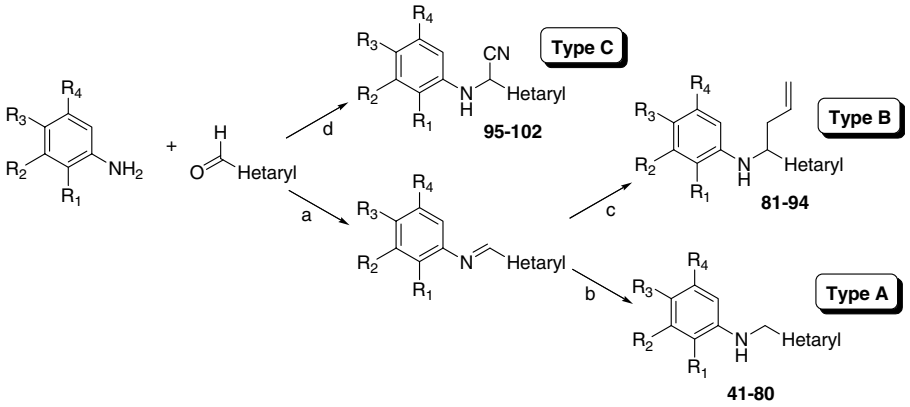
Since the reduction of aldimines with an excess of $NaBH_4$ in methanol is still the reaction of choice to produce the secondary amines in reasonably good yield, we employed this method in our work. Thus, the type **A**, *N*-(hetarylmethyl)anilines **41**–**80**, was prepared as colored solids in 80–100% yields after purification using SiO_2 chromatography column.

Table 1. Starting *N*-hetaryl aldimines **1**–**40** prepared from commercial anilines and heteroaromatic aldehydes

Aldimines	Hetaryl	R_1	R_2	R_3	R_4
1	2-Fu	H	H	H	H
2	2-Fu	H	H	Me	H
3	2-Fu	H	H	MeO	H
4	2-Fu	H	H	F	H
5	2-Fu	H	H	Cl	H
6	2-Fu	H	H	Br	H
7	2-Fu	H	Cl	Cl	H
8	3-Fu	H	H	H	H
9	3-Fu	H	H	Me	H
10	3-Fu	H	H	Cl	H
11	2-Thie	H	H	H	H
12	2-Thie	H	H	Me	H
13	2-Thie	H	H	Cl	H
14	3-Thie	H	H	H	H
15	3-Thie	H	H	Me	H
16	3-Thie	H	H	Cl	H
17	2-NMePyr	H	H	H	H
18	2-NMePyr	H	H	Me	H
19	2-NMePyr	H	H	Cl	H
20	2-Py	H	H	H	H
21	2-Py	H	H	Me	H
22	2-Py	H	H	I	H
23	2-Py	H	NO_2	H	H
24	2-Py	H	Me	H	Me
25	3-Py	H	H	H	H
26	3-Py	H	H	Me	H
27	3-Py	H	H	I	H
28	3-Py	H	NO_2	H	H
29	3-Py	H	Me	H	Me
30	4-Py	H	H	H	H
31	4-Py	H	H	Me	H
32	4-Py	H	H	Cl	H
33	4-Py	H	H	I	H
34	4-Py	H	NO_2	H	H
35	4-Py	H	Me	H	Me
36	Ar–NMe_2-*p*	H	H	H	H
37	Ar–OMe-*p*	H	H	H	H
38	Ar–OMe-*p*	H	H	H	NO_2
39	Ar–OH-*p*	H	H	H	H
40	Ar–NH_2-*m*	H	H	Me	H

The type **B**, (homoallylamines **81**–**94**), was obtained by nucleophilic addition of preformed allylmagnesium bromide to the C=N bond of respective aldimines[3–5] as well as of allyl indium reagent generated in situ by addition of allyl bromide to the suspension of indium powder in dry MeOH.[16] This series was easily prepared obtaining the secondary amines as colored solids or liquids in 75–98% yields after purification using SiO_2 chromatography column.

The preparation of the third type **C**, α-aminonitriles **95**–**102**, was realized via a one-pot three-component condensation of hetaryl aldehydes, anilines, and trimethylsilyl cyanide in the presence of a catalytic amount of molecular iodine at room temperature according to reported methodology[17] (Scheme 1).



Scheme 1. Reagents and conditions: (a) EtOH/reflux or rt; (b) $NaBH_4$/MeOH, rt; (c) $BrMgCH_2CH{=}CH_2$/dry diethyl ether, rt or $BrMgCH_2CH{=}CH_2$/In/dry methanol, rt; (d) Me_3SiCN/I_2, MeCN, rt.

2.2. Antifungal activity

The antifungal properties of compounds **41**–**102** were evaluated by the microbroth dilution method following the guidelines of the Clinical and Laboratory Standard Institute (CLSI), formerly National Committee for Clinical and Laboratory Standards (NCCLS), against a panel of 10 fungal species: four human opportunistic pathogenic yeasts, three hyalohyphomycetes and three dermatophytes. To carry out the antifungal evaluation, concentrations of compounds up to 250 μg/mL were incorporated to growth media according to published procedures.[18,19] Amphotericin B, terbinafine, and ketoconazole were used as positive controls.

The analysis of results was made considering the behaviour of amines against (a) yeasts and *Aspergillus* spp. and (b) dermatophytes (Table 2). When tested against (a), results showed that amines type **B** and **C** (**81**–**102**), and those type **A** that do not contain a hetaryl ring (**76**–**80**) were not active neither against yeasts nor *Aspergillus* spp. In contrast, most compounds type **A** containing heterocyclic **B** rings such as furan, thiophene, or pyridine (**41**–**80**) inhibit the growth of yeasts and *Aspergillus* spp. with moderate MICs ranging from 25 to 250 μg/mL.

Amines **47** and **73** showed interesting activities against *Cryptococcus neoformans.* Their MICs against this yeast were moderate but lower enough (=25 μg/mL) to be taken into account.[20–23] This yeast remains an important life-threatening complication for immunocompromised hosts, particularly for patients who have undergone transplantation of solid organs, and therefore, new compounds acting against this fungus are highly welcome.[24,25]

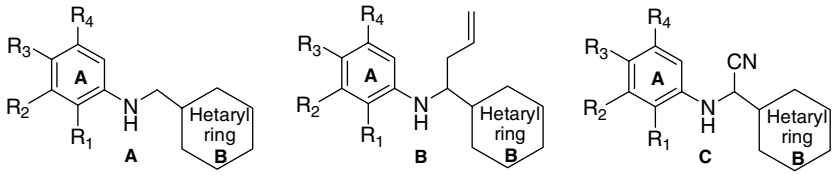
To evaluate the real importance of this activity, amines **47** and **73** were tested against 10 clinical isolates of *C. neoformans* provided by Malbrán Institute (Buenos Aires). Results are shown in Table 3. Unfortunately, the activity was similar to or lower (range of MIC values = 25–100 μg/mL) than those against the standard strain (ATCC 32264).

Results of the activity of amines against dermatophytes [point (b)] showed that with the exception of nitrile-substituted derivatives **95**–**102**, the rest of amines possessed varied and in most cases interesting activities.

Considering that a MIC <20 μg/mL could render a candidate for future research, compounds **45**–**47**, **73**, and **74** attracted our attention since they could represent leads for the development of new antifungals against *Microsporum gypseum*, *Trichphyton rubrum*, and *Trichphyton mentagrophytes*. The five compounds are amines with a non-substituted CH_2. Regarding the structure–activity relationships for these compounds against dermatophytes, the following observations are evident: (i) compounds containing a 2-furyl as R_5, were the most active of the series, showing very good antifungal activities against dermatophytes, particularly against *T. rubrum* (MIC = 3.12–6.25 μg/mL); (ii) electron-withdrawing substituents (4-Br, 4-Cl, or 3,4-diCl in *p*-position for furyl derivatives or in *m*- or *p*-positions for 4-pyridyl derivatives) on the benzene ring seem to play an important role in the activity showing MIC values between 3.12 and 12.5 μg/mL; (iii) compounds without substituent (**41**) or with donor substituents (**42** and **43**) show about 6–10 times lower activities against dermatophytes; (iv) when hetaryl fragment is a 2-, 3-, or 4-pyridyl ring, the activity seems to be not influenced by the substituents on ring **A**. Some other amines tested (**51**, **52**) showed interesting but lower activities than **45**–**47**.

It is worthwhile to emphasize that *T. rubrum* was the most sensitive fungus. This fungal sp. is responsible for approximately 80–93% of chronic and recurrent dermatophyte infections in human beings. It is the etiological agent of *Tinea unguium* (producer of invasive nail infections), *Tinea manuum* (palmar and interdigital areas of the hand infections), and *Tinea pedis* (Athlete's foot), the last one being the most prevalent fungal infection in developed countries and the first one accounting for 50% and 90% of all fingernail and toenail infections, respectively.[26] Regarding homoallylamines (type **B**), only compound **86** showed interesting activity against *T. mentagrophytes* adding a new datum to the previously reported SAR-studies of homoallylamines.[5]

Table 2. Antifungal activity of secondary amines **41**–**102**



Compound	Antifungal activity* MIC (μg/mL)															
	Hetaryl ring **B**	R_1	R_2	R_3	R_4	Type	*C.a.*	*C.t.*	*S.c.*	*C.n.*	*A.fu.*	*A.fl.*	*A.n.*	*M.g.*	*T.r.*	*T.m.*
41	2-Fu	H	H	H	H	A	250	250	>250	250	62.5	100	100	100	100	100
42	2-Fu	H	H	Me	H	**A**	>250	250	>250	100	125	250	250	100	25	50
43	2-Fu	H	H	MeO	H	**A**	>250	>250	>250	>250	250	250	250	100	100	50
44	2-Fu	H	H	F	H	**A**	100	125	125	100	100	250	250	100	25	62.5
45	2-Fu	H	H	Cl	H	**A**	62.5	75	50	50	50	50	62.5	12.5	6.25	12.5
46	2-Fu	H	H	Br	H	**A**	62.5	75	50	50	50	50	62.5	6.25	3.12	12.5
47	2-Fu	H	Cl	Cl	H	**A**	62.5	62.5	50	25	50	50	62.5	6.25	3.12	6.25
48	3-Fu	H	H	H	H	**A**	250	250	250	125	250	250	250	250	125	125
49	3-Fu	H	H	Me	H	**A**	250	250	250	125	250	250	250	125	250	250
50	3-Fu	H	H	Cl	H	**A**	125	125	125	62.5	62.5	62.5	62.5	125	62.5	62.5
51	2-Thie	H	H	H	H	**A**	>250	>250	>250	>250	>250	>250	>250	25	12.5	25
52	2-Thie	H	H	Me	H	**A**	>250	>250	>250	>250	>250	>250	>250	12.5	25	50
53	2-Thie	H	H	Cl	H	**A**	62.5	62.5	250	62.5	125	250	250	62.5	62.5	62.5
54	3-Thie	H	H	H	H	**A**	250	250	250	250	250	250	250	250	125	125
55	3-Thie	H	H	Me	H	**A**	>250	>250	>250	250	250	250	250	250	125	125
56	3-Thie	H	H	Cl	H	**A**	62.5	62.5	250	62.5	125	250	250	62.5	62.5	62.5
57	2-N–MePyr	H	H	H	H	**A**	>250	>250	>250	>250	>250	>250	>250	>250	250	250
58	2-N–MePyr	H	H	Me	H	**A**	>250	>250	>250	>250	>250	>250	>250	>250	>250	>250
59	2-N–MePyr	H	H	Cl	H	**A**	>250	>250	>250	125	>250	>250	>250	>250	250	250
60	2-Py	H	H	H	H	**A**	250	250	>250	>250	250	>250	250	125	25	25
61	2-Py	H	H	Me	H	**A**	>250	>250	>250	>250	>250	>250	>250	50	50	50
62	2-Py	H	H	I	H	**A**	>250	>250	200	100	200	100	100	25	25	25
63	2-Py	H	NO_2	H	H	**A**	100	100	100	50	200	100	200	50	50	50
64	2-Py	H	Me	H	Me	**A**	>250	200	>250	50	100	100	100	50	50	50
65	3-Py	H	H	H	H	**A**	250	250	>250	>250	250	250	250	125	25	25
66	3-Py	H	H	Me	H	**A**	>250	>250	>250	>250	>250	>250	>250	250	250	250
67	3-Py	H	H	I	H	**A**	>250	200	200	50	50	50	100	50	25	25
68	3-Py	H	NO_2	H	H	**A**	>250	>250	>250	>250	>250	>250	>250	25	25	25
69	3-Py	H	Me	H	Me	**A**	>250	>250	200	100	100	200	200	25	25	25
70	4-Py	H	H	H	H	**A**	>250	250	>250	>250	250	250	250	125	25	25
71	4-Py	H	H	Me	H	**A**	100	50	100	50	100	200	100	50	25	25
72	4-Py	H	H	Cl	H	**A**	31.2	31.2	62.5	62.5	125	125	125	62.5	62.5	62.5
73	4-Py	H	H	I	H	**A**	50	50	50	25	50	100	50	12.5	6.25	12.5
74	4-Py	H	NO_2	H	H	**A**	100	100	50	50	100	200	100	12.5	6.25	12.5
75	4-Py	H	Me	H	Me	**A**	250	250	250	50	100	200	100	25	25	25
76	Ar–NMe_2-*p*	H	H	H	H	**A**	>250	>250	>250	>250	200	>250	>250	>250	>250	>250
77	Ar–OMe-*p*	H	H	H	H	**A**	>250	>250	>250	>250	>250	>250	>250	25	25	25
78	Ar–OMe-*p*	H	H	H	NO_2	**A**	>250	>250	>250	>250	>250	>250	>250	>250	>250	>250
79	Ar–OH-*p*	H	H	H	H	**A**	>250	250	250	>250	>250	>250	>250	50	25	25
80	Ar–NH_2-*m*	H	H	Me	H	**A**	50	50	100	100	25	25	12.5	100	100	100
81	2-Fu	H	H	Me	H	**B**	>250	>250	>250	>250	>250	>250	>250	>250	>250	>250
82	2-Fu	H	Cl	Cl	H	**B**	>250	>250	>250	>250	>250	>250	>250	>250	>250	>250
83	3-Fu	H	H	H	H	**B**	>250	>250	>250	250	>250	>250	>250	125	62.5	62.5
84	3-Fu	H	H	Cl	H	**B**	>250	>250	>250	125	>250	>250	>250	62.5	62.5	62.5
85	2-Thie	H	H	H	H	**B**	>250	>250	>250	>250	>250	>250	>250	125	125	125
86	2-Thie	H	H	Me	H	**B**	>250	>250	>250	>250	>250	>250	>250	50	12.5	6.25
87	3-Thie	H	H	H	H	**B**	>250	>250	>250	250	>250	>250	>250	125	250	250
88	3-Thie	H	H	Me	H	**B**	>250	>250	>250	>250	>250	>250	>250	>250	>250	>250
89	3-Thie	H	H	Cl	H	**B**	>250	>250	>250	250	>250	>250	>250	>250	>250	>250
90	2-N–MePyr	H	H	Cl	H	**B**	>250	>250	>250	>250	>250	>250	>250	>250	250	250
91	4-Py	H	H	H	H	**B**	250	250	125	250	250	250	250	125	250	62.5
92	4-Py	H	H	MeO	H	**B**	>250	>250	>250	250	>250	>250	>250	62.5	125	125
93	4-Py	H	H	Br	H	**B**	>250	>250	250	>250	>250	>250	>250	16	16	31.2
94	4-Py	H	Me	H	Me	**B**	250	250	250	>250	>250	>250	>250	125	250	125
95	2-Fu	H	H	H	H	**C**	>250	>250	>250	>250	>250	>250	>250	>250	250	250
96	3-Fu	H	H	H	H	**C**	>250	>250	>250	>250	>250	>250	>250	>250	250	250

(*continued on next page*)

Table 2 (*continued*)

Compound	Antifungal activity* MIC (μg/mL)														
	Hetaryl ring **B**	R_1	R_2	R_3	R_4	Type	*C.a.*	*C.t.*	*S.c.*	*C.n.*	*A.fu.*	*A.fl.*	*A.n.*	*M.g.*	*T.r.*	*T.m.*
97	2-Thie	H	H	H	H	**C**	>250	>250	>250	>250	>250	>250	>250	>250	250	250
98	3-Thie	H	H	H	H	**C**	>250	>250	>250	>250	>250	>250	>250	>250	250	250
99	3-Thie	H	H	Me	H	**C**	>250	>250	>250	125	>250	>250	>250	250	125	125
100	3-Thie	H	H	Cl	H	**C**	>250	>250	>250	>250	>250	>250	>250	250	125	125
101	2-N–MePyr	H	H	H	H	**C**	>250	>250	>250	>250	>250	>250	>250	250	250	250
102	4-Py	H	H	H	H	**C**	>250	>250	>250	250	250	250	250	250	125	125
	Amp.						1	0.5	0.5	0.25	0.5	0.5	0.5	—	—	—
	Ket.						0.5	0.125	0.5	0.25	0.125	0.5	0.25	0.05	0.025	0.025
	Terb.													0.04	0.01	0.04

*Antifungal activity was determined with the microbroth dilution assay following the NCCLS guidelines. Fungi used: *C.a.*, *Candida albicans* ATCC10231; *C.t.*, *Candida tropicalis* C131; *C.n.*, *Cryptococcus neoformans* ATCC32264; *S.c.*, *Saccharomyces cerevisiae* ATCC9763; *A.n.*, *Aspergillus niger* ATCC9029; *A.fl.*, *Aspergillus flavus* ATCC 9170; *A.fu.*, *Aspergillus fumigatus* ATCC 26934; *M.g.*, *Microsporum gypseum* C 115; *T.r.*, *Trichophyton rubrum* C113; *T.m.*, *Trichophyton mentagrophytes* ATCC 9972. Amp., Amphotericin B; Ket., Ketoconazole; Terb., Terbinafine; n.t., not tested.

Table 3. Minimum inhibitory concentration (MIC, μg/mL) of amines **47** and **73** against clinical isolates of *C. neoformans*

	C.n.[a]	*C.n.*[b]	*C.n.*[c]	*C.n.*[d]	*C.n.*[e]	*C.n.*[f]	*C.n.*[g]	*C.n.*[h]	*C.n.*[i]	*C.n.*[j]	Median
47	25	100	25	25	25	100	100	100	100	100	70
73	25	100	25	50	50	50	50	50	100	100	60
Anfotericina B	0.25	0.13	0.06	0.25	0.25	0.25	0.13	0.25	0.06	0.50	
Fluconazol	—	7.8	3.9	3.9	15.6	1.9	31.2	31.2	3.9	7.8	
Itraconazol	—	<0.015	0.25	<0.015	<0.015	<0.015	0.25	0.50	<0.015	<0.015	
5-Fluocitosina	—	7.8	3.9	3.9	n.t.	15.6	7.8	7.8	3.9	7.8	
Voriconazol	—	<0.015	<0.015	<0.015	<0.015	0.030	0.25	0.50	0.015	0.030	

[a] *Cryptococcus neoformans* ATCC 32264.
[b] *C. neoformans* IM 983040.
[c] *C. neoformans* IM 972724.
[d] *C. neoformans* IM 042074.
[e] *C. neoformans* IM 983036.
[f] *C. neoformans* IM 00319.
[g] *C. neoformans* IM 972751.
[h] *C. neoformans* IM 031631.
[i] *C. neoformans* IM 031706.
[j] *C. neoformans* IM 961951.

2.3. Cytotoxic activity

In addition to the antifungal evaluation, the most active compounds, **47**, **73**, and **74**, were tested for cytotoxic activities against breast (MCF-7), lung (H-460), and central nervous system (SF-268) human cancer cell lines,[27] in order to determine the selectivity of amines towards the most sensitive fungi. Results showed (Table 4) that the cytotoxic activities were >10 μg/mL for amines **73** and **74** and were equal to 8 μg/mL for compound **47**, all cytotoxic MIC values higher than antifungal ones (MICs 3.12–6.25 μg/mL).

Table 4. Cytotoxic activities of secondary amines **47**, **73**, and **74**

Amines	Cytotoxicity IC_{50} (μg/mL)[a]		
	MCF- 7	H-460	SF-268
47	8 ± 0.2	8.7 ± 0.5	8.2 ± 0.5
73	>10	>10	>10
74	>10	>10	>10
Adri.	0.16 ± 0.1	0.18 ± 0.2	0.14 ± 0.1

[a] Cytotoxic analysis was made in 96-well microtiter plates using the SRB assay. Cell lines used: breast MCF-7, lung H-460 and central nervous system SF-268 human cancer cell lines. Adri., Adriamycin; n.t., not tested.

2.4. Computational studies

According to our experimental results, it appears that a more flexible connecting chain of an amine (type **A**) renders a more active compound. To give support to this presumption, we performed a comparative conformational study of compounds **41**, **83**, and **95** (all of them containing the same hetaryl ring, 2-furyl), which might be regarded as representative molecules of their respective types **A**, **B**, and **C.**

The conformational potential energy surfaces (PESs) of compounds **41**, **83**, and **95**, which were obtained varying the torsional angles $\Phi 1$ versus $\Phi 2$ each 15°, are shown in Figure 2. The surface for compound **41** (Fig. 2a) shows

that all possible interconversions among the conformers may follow very low-energy paths (note the extensive red zones in this PES). The surface for compound **83** (Fig. 2b) is quite different. Substantially high-energy barriers characterize the overall process. The surface of compound **95** (Fig. 2c) has some similarities with that of the compound **83**, but the picture is dominated by the height of the minimum corresponding to the conformation with Φ_1 and $\Phi_2 \approx -300°$; co-planar forms (Φ_1 and $\Phi_2 \approx 0°$ and 180°) appear to be forbidden.

So, from Figure 2a–c it is clear that the molecular flexibility of compound **41** is significantly higher than that of compounds **81** and **95**. To better appreciate such results, the iso-energy curves included in an energy window of 5 Kcal/mol were denoted in red. Note the different sizes of the red zones in the contour diagrams and the different deeps and slopes of the valleys in the contour level diagrams shown in Figure 2a–c.

To confirm that the molecular flexibility and the relative stability of the various conformers are correct, the more accurate ab initio calculations (RHF/3-21G) were carried out. With this method, we evaluated the molecular flexibility of compounds **41** and **81** generating 1D cross-sections, i.e. potential energy curves, along Φ_1 and Φ_2. The two potential energy curves $E(\Phi_1)$ and $E(\Phi_2)$, as generated at the RHF/3-21G level of theory for compound **41**, are shown in Figure 3. The $E(\Phi_1)$ potential (Fig. 3a) shows 2-fold periodicity with two low-energy conformations at $\Phi_1 \approx 90°$ and $\Phi_1 \approx 270°$ displaying the co-planar forms ($\Phi_1 \approx 0$ and 180°) like disfavored conformations. The $E(\Phi_2)$ potential (Fig. 3b) shows 3-fold periodicity with a highly preferred minima at 180°. Figure 4a and b gives the $E(\Phi_1)$ and $E(\Phi_2)$ potential curves obtained for compound **81**. The general conformational behaviour of these PECs is comparable to those obtained for **41**. However, an important difference can be appreciated comparing Figures 3a and 4a. The

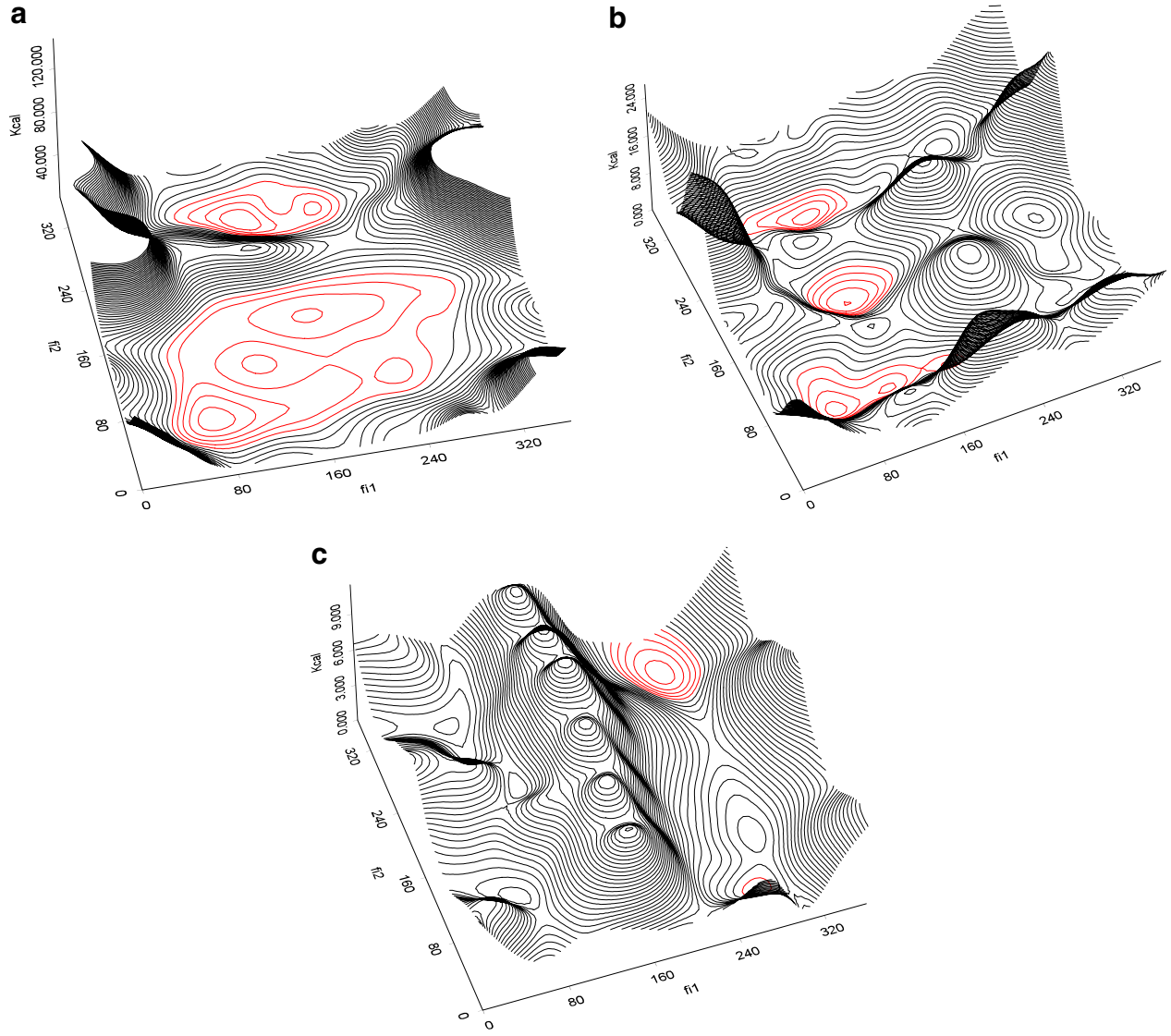


Figure 2. Conformational potential Energy Surface (PES) obtained for compounds **41** (**a**), **83** (**b**) and **95** (**c**) from AM1 calculations. Full cycle of rotation (from 0° to 360°) is shown for variables Φ_1 and Φ_2. The iso-energy curves included in an energy window of 5 Kcal/mol are denoted in red.

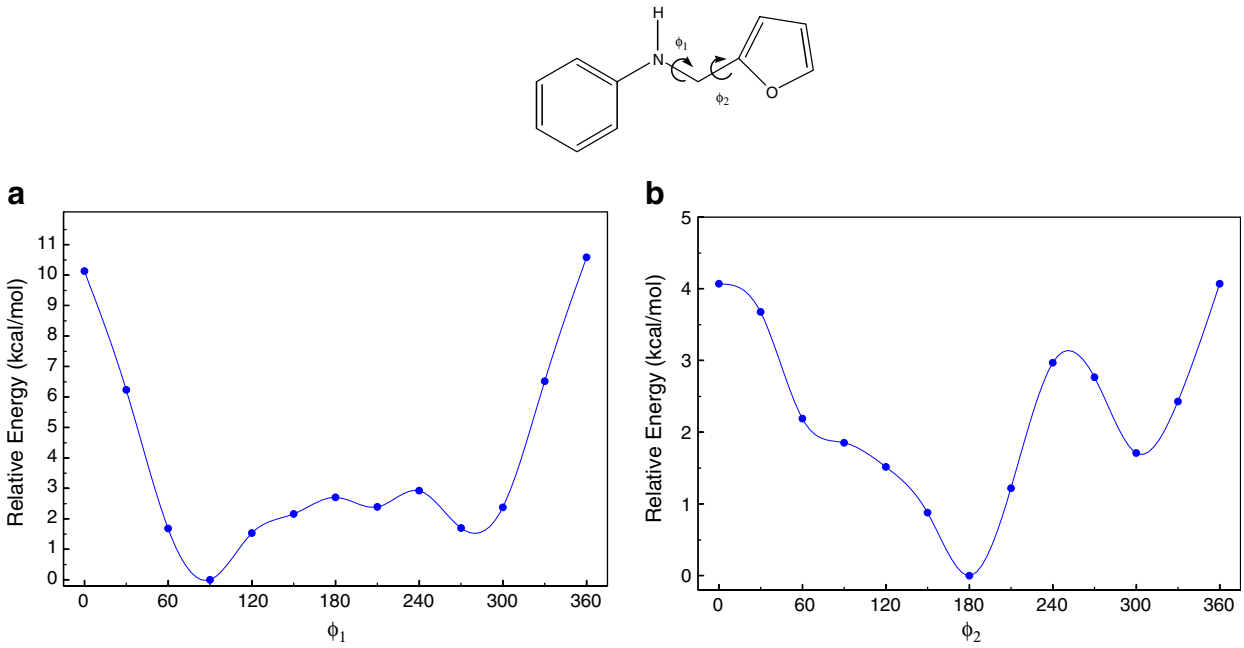


Figure 3. Potential Energy Curves (PECs) of torsional angles Φ_1(**a**) and Φ_2 (**b**) obtained for compound **41**. Each PEC was calculated at RHF/3-21G level of theory. Top: the structure of compound **41** showing the torsional angles Φ_1 and Φ_2.

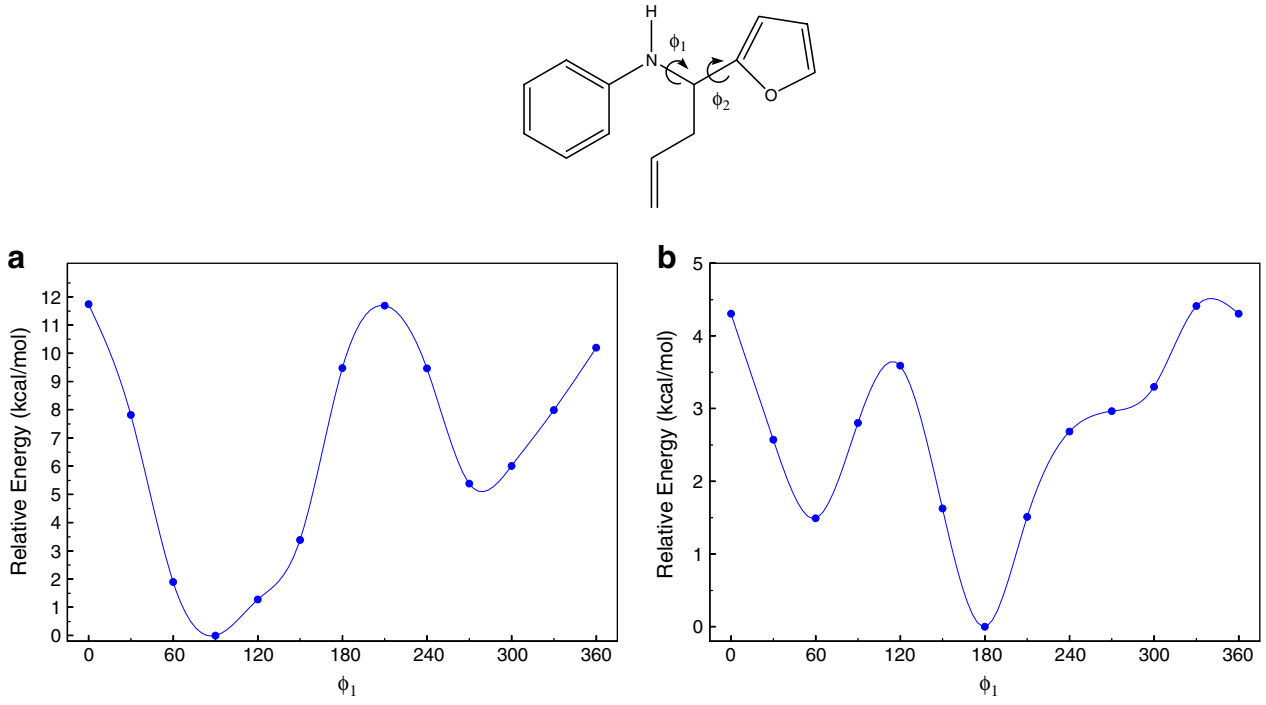


Figure 4. Potential Energy Curves (PECs) of torsional angles Φ_1(**a**) and Φ_2 (**b**) obtained for compound **83**. Each PEC was calculated at RHF/3-21G level of theory. Top: the structure of compound **83** showing the torsional angles Φ_1 and Φ_2.

energetic requirement to produce the conformational interconversion is markedly different. Whereas the barrier for Φ_1 in compound **41** is only 3.5 Kcal/mol (Fig. 3a), the same barrier is about 11.5 Kcal/mol for compound **81** (Fig. 4a). Compound **95** gives closely related results to those obtained for compound **81** (results not shown). These calculations confirm that the most active compounds type **A** possess a higher flexibility which should be an important feature for the antifungal behaviour. These results are in accordance with our preliminary observation that the presence of bulky substituents in the flexible connecting chain caused a dramatic decrease in the antifungal activity of homoallylamines.[4,5] The second observation based on experimental results (see above) was that the most active compounds contain a 2-furyl and not a 3-furyl as hetaryl ring (compare

MICs of **41**, **42**, and **47** with those of **48**, **49**, and **50**, respectively). This is not an unexpected result. Previously, we have postulated a short-range electrostatic interaction for ring **B**, which may result in Brönsted (H-bonded) complex formation.[5] Thus, these interactions might be markedly affected by the spatial position of heteroatoms possessing the electronic lone pairs. The present results are an additional support for such assumption.

As a third structure–activity relationship, it was stated based on experimental data that electron-withdrawing

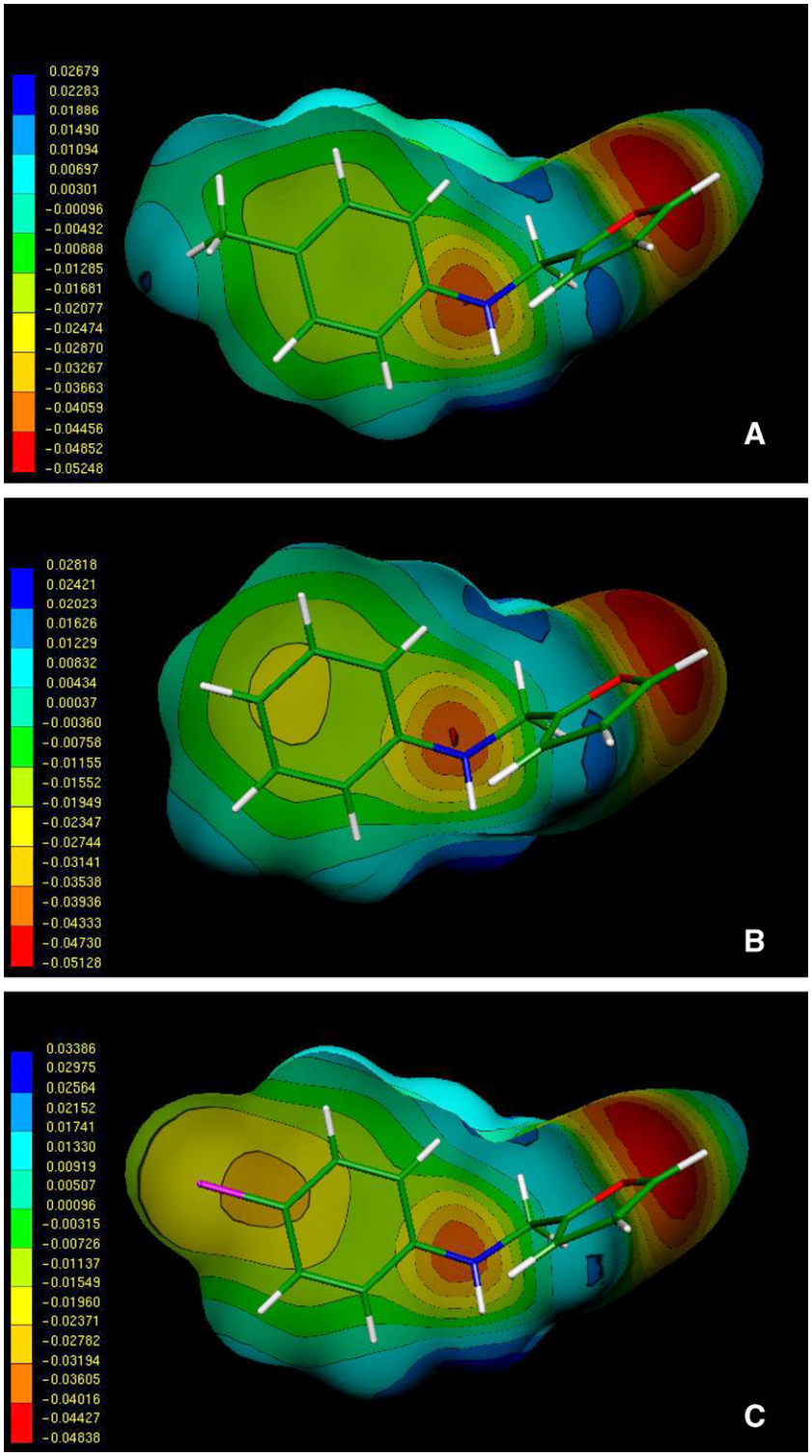


Figure 5. Electrostatic potential-encoded electron density surfaces of compounds **41** (**A**), **42** (**B**), and **45** (**C**). The surfaces were generated with Gaussian 03 after B3LYP/6-31G(d) calculations. The colours represent electrostatic potential with red indicating the strongest attraction to a positive point charge and blue indicating the strongest repulsion. The electrostatic potential is the energy of interaction of the positive point charge with the nuclei and electrons of a molecule. It provides a representative measure of overall molecular charge distribution.

substituents (4-Br, 4-Cl, or 3,4-diCl in *p*-position on the benzene ring for furyl derivatives or in *m*- or *p*-positions for 4-pyridyl derivatives) seem to play an important role in the activity. In an attempt to explain these results, we conducted a computer-assisted conformational and electronic study on compounds **41**, **42**, and **45**. The purpose was to obtain a more precise information about how these compounds resemble each other in terms of the spatial orientations of the essential components for receptor recognition. Figure 5 gives the Molecular Electrostatic Potentials (MEPs) obtained for compounds **41**, **42**, and **45**. The MEPs exhibited three regions with negative potentials. The minimum of lowest energy (deep red zone) is located in the in-plane lone pair region of oxygen. The $V(r)_{min} \approx -0.050$ el/au^3 values in the in-plane lone pair regions of oxygen are in accordance with previous findings[28] and indicate that this heteroatom is H-bond acceptor. The second minimum (light red and orange zone with $V(r)_{min} \approx -0.036$ el/au^3) corresponds to the zones located in the vicinity of the nitrogen atom in the connecting chain. In the benzene region (ring **A**), a much smaller minimum was found (yellow areas for compound **45** and light green areas for the other two compounds). This third minimum displays different $V(r)_{min}$ values for these compounds, varying from -0.031 el/au^3 for compound **45** to -0.0049 el/au^3 (almost a neutral potential) for compound **42**. The different electronic distribution observed on ring **A** is a direct consequence of the particular characteristic of the substituents (neutral, electron-donor, or electron-withdrawing). These effects might be well appreciated in Figure 5 and can explain the different antifungal activities obtained for these compounds. It becomes clear that replacing hydrogen with a chloride (or another halogen group) leads to a considerable perturbation of the electronic distribution of ring **A** in these compounds. This electrostatic effect could offer a complementary surface in the binding pocket rendering a more active compound. These results are in complete agreement with our previous results obtained for homoallylamine derivatives.[5]

3. Conclusion

We found that 2-furyl substituted anilines showed very good antifungal activities against dermatophytes, particularly against *Trichophyton rubrum* (MIC = 3.12–6.25 μg/mL) which is the fungus responsible for approximately 80–93% of chronic and recurrent dermatophyte infections in human beings. These infections, although not life-threatening, are recurrent in immunocompromised as well as immunocompetent patients and they are frequently very difficult to eradicate. In addition, all active compounds, **45**–**47**, **73**, and **74** were tested for cytotoxic activities against breast (MCF-7), lung (H-460), and central nervous system (SF-268) human cancer cell lines with the NCI-anticancer-drug screen. Results were analyzed from the point of view of the relationship between antifungal activity and toxicity. From the comparison of activities, it is clear that the antifungal activity of these compounds appears not to be due to their toxicity. Only compound **47** possesses both activities. The rest of compounds (**73** and **74**) which displayed good antifungal activities showed very low toxicities (IC_{50} >10 μg/mL). The activity of amines described in this paper, along with the low toxicity of most of them, shows promise for the future development of non-toxic new antimycotic agents. A conformational and electronic study performed on the most representative compounds of this series helped us to identify and understand the minimal structural requirements for the antifungal action of these molecules. On the basis of our results it appears that a significant molecular flexibility in the connecting chain could be necessary to produce the biological response.

4. Experimental

4.1. Chemistry

The melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. The IR spectra were recorded on a Nicolet Avatar 360-FT spectrophotometer in KBR. ^{1}H NMR spectra were recorded on Bruker AM-400 or AC-300 spectrometers. Chemical shifts are reported in ppm (δ) relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 ppm for protons). Signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; dd d, doublet of doublets of doublets; t, triplet; dt, doublet of triplets; td, triplet of doublets; q, quartet; quint., quintet; sext., sextet; m, multiplet; br, broad. On DEPT-135 spectra, the signals of CH_3, CH_2, and CH carbons are shown as positive (+) and negative (−), respectively. Quaternary carbons are not shown. A Hewlett Packard 5890a series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HP MS Chemstation Data system was used for MS identification at 70 eV using a 60 m capillary column coated with HP-5 [5%-phenyl-poly(dimethyl-siloxane)]. Elemental analyses were performed on a Perkin-Elmer 2400 Series II analyzer and were within ±0.4 of theoretical values. The reaction progress was monitored using thin layer chromatography on a silufol UV254 TLC aluminum sheet.

Synthesis of the aldimines **1**–**40** was performed according to the published literature.[11,15] Preparation and spectral data of the corresponding *N*-hetarylmethylaniline derivatives (**41**, **43**–**46**, **51**, **52**, **65**–**69**, and **76**–**80**) (series **A**) and homoallylamines (**85**, **86**) (series **B**) were described in our previous reports.[3–5,12–14]

4.1.1. Type A. The following amines are new and were prepared according to previous reports.[12–14]

4.1.1.1. *N*-(2-Furylmethyl)-*N*-(4-methylphenyl)amine (42). Yellow oil. Yield 96%. IR (film): ν 3409 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (1H, dd, J = 2.0, 1.0 Hz, 5-H_{Fu}), 7.03 (2H, dd, J = 8.0, 0.4 Hz, 3(5)-H_{Ar}), 6.63 (2H, dd, J = 8.0, 2.0 Hz, 2(6)-H_{Ar}), 6.34 (1H, dd, J = 3.0, 2.0 Hz, 4-H_{Fu}), 6.25 (1H, dd, J = 2.0, 1.0 Hz, 3-H_{Fu}), 4.31 (2H, s, H_2C–N), 3.98 (1H, br s, H–N), 2.27 (3H, s, 4-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.9, 145.9, 141.8 (+), 129.7 (+), 129.6 (+), 127.2,

113.3 (+), 113.2 (+), 110.3 (+), 106.8 (+), 41.8 (−), 20.4 (+). MS *m*/*z* (EI) 187 (M^+). Found: C, 76.85; H, 7.10; N, 7.25; calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48.

4.1.1.2. *N*-(2-Furylmethyl)-*N*-(3,4-dichlorophenyl)amine (47). Orange oil. Yield 98%. IR (film): *v* 3419 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.39 (1H, dd, *J* = 2.0, 1.0 Hz, 5-H_{Fu}), 7.19 (1H, d, *J* = 9.0 Hz, 5-H_{Ar}), 6.73 (1H, d, *J* = 3.0 Hz, 2-H_{Ar}), 6.48 (1H, dd, *J* = 9.0, 3.0 Hz, 6-H_{Ar}), 6.35 (1H, dd, *J* = 4.0, 2.0 Hz, 4-H_{Fu}), 6.25 (1H, dd, *J* = 4.0, 1.0 Hz, 3-H_{Fu}), 4.26 (2H, s, H_2C–N), 4.13 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 151.6, 146.9, 142.1 (+), 132.6, 130.8 (+), 120.2, 114.0 (+), 112.7 (+), 110.3 (+), 107.5 (+), 40.7 (−). MS *m*/*z* (EI) 241 (M^+ for ^{35}Cl). Found: C, 54.86; H, 3.90; N, 5.50; calcd for $C_{11}H_9Cl_2NO$: C, 54.57; H, 3.75; N, 5.79.

4.1.1.3. *N*-(3-Furylmethyl)-*N*-phenylamine (48). Yellow oil. Yield 98%. IR (film): *v* 3413, 1605 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.44 (2H, br d, *J* = 1.8 Hz, 2(5)-H_{Fu}), 7.28 (2H, t, *J* = 8.0 Hz, 3(5)-H_{Ph}), 6.84 (1H, t, *J* = 7.3 Hz, 4-H_{Ph}), 6.71 (2H, d, *J* = 8.5 Hz, 2(6)-H_{Ph}), 6.46 (1H, s, 4-H_{Fu}), 4.18 (2H, s, H_2C–N), 3.78 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 147.8, 143.0 (+), 139.7 (+), 129.0 (2C, +), 123.2, 117.5 (+), 112.8 (2C, +), 110.0 (+), 39.0 (−). MS *m*/*z* (EI) 173 (M^+). Found: C, 76.55; H, 6.56; N, 8.00; calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09.

4.1.1.4. *N*-(3-Furylmethyl)-*N*-(4-methylphenyl)amine (49). Yellow oil. Yield 97%. IR (film): *v* 3410, 1620 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.44 (2H, s, 2(5)-H_{Fu}), 7.06 (2H, d, *J* = 8.3 Hz, 3(5)-H_{Ar}), 6.64 (2H, d, *J* = 8.3 Hz, 2(6)-H_{Ar}), 6.46 (1H, s, 4-H_{Fu}), 4.19 (2H, s, H_2C–N), 3.72 (1H, br s, H–N), 2.31 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 145.7, 143.1 (+), 139.8 (+), 129.7 (2C, +), 126.9, 123.5, 113.1 (2C, +), 110.1 (+), 39.6 (−), 20.3 (+). MS *m*/*z* (EI) 187 (M^+). Found: C, 76.86; H, 6.92; N, 7.55; calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48.

4.1.1.5. *N*-(3-Furylmethyl)-*N*-(4-chlorophenyl)amine (50). Yellow oil. Yield 95%. IR (film): *v* 3417, 1601 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.40 (2H, br d, *J* = 1.7 Hz, 2(5)-H_{Fu}), 7.14 (2H, d, *J* = 8.9 Hz, 3(5)-H_{Ar}), 6.56 (2H, d, *J* = 8.8 Hz, 2(6)-H_{Ar}), 6.40 (1H, s, 4-H_{Fu}), 4.14 (2H, s, H_2C–N), 3.67 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 146.5, 143.4 (+), 140.0 (+), 129.0 (2C, +), 122.9, 122.3, 114.0 (2C, +), 110.0 (+), 39.4 (−). MS *m*/*z* (EI) 207 (M^+ for ^{35}Cl). Found: C, 63.56; H, 4.90; N, 6.58; calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75.

4.1.1.6. *N*-(Thien-2-ylmethyl)-*N*-(4-chlorophenyl)amine (53). Yellow oil. Yield 96%. IR (film): *v* 3419 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.23 (1H, dd, *J* = 4.9, 1.0 Hz, 4-H_{Thie}), 7.14 (2H, d, *J* = 8.7 Hz, 3(5)-H_{Ar}), 7.02–6.96 (2H, m, 3,5-H_{Thie}), 6.61 (2H, d, *J* = 8.7 Hz, 2(6)-H_{Ar}), 4.49 (2H, s, H_2C–N), 4.05 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 145.9, 142.3, 129.1 (2C, +), 126.9 (+), 125.2 (+), 124.7 (+), 122.7, 114.3 (2C, +), 43.5 (−). MS *m*/*z* (EI) 223 (M^+ for ^{35}Cl). Found: C, 59.26; H, 4.66; N, 6.43; calcd for $C_{11}H_{10}ClNS$: C, 59.05; H, 4.51; N, 6.26.

4.1.1.7. *N*-(Thien-3-ylmethyl)-*N*-phenylamine (54). Yellow oil. Yield 98%. IR (film): *v* 3413, 1601 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.31 (1H, dd, *J* = 4.7, 3.0 Hz, 5-H_{Thie}), 7.24 (2H, t, *J* = 7.4 Hz, 3(5)-H_{Ph}), 7.19 (1H, br s, 2-H_{Thie}), 7.15 (1H, d, *J* = 4.9 Hz, 4-H_{Thie}), 6.80 (1H, t, *J* = 7.3 Hz, 4-H_{Ph}), 6.67 (2H, d, *J* = 8.4 Hz, 2(6)-H_{Ph}), 4.33 (2H, s, H_2C–N), 3.87 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 147.8, 143.0, 129.1 (2C, +), 127.0 (+), 125.9 (+), 121.5 (+), 117.5 (+), 112.8 (2C, +), 43.5 (−). MS *m*/*z* (EI) 189 (M^+). %. Found: C, 69.77; H, 5.99; N, 7.29; calcd for $C_{11}H_{11}NS$: C, 69.80; H, 5.86; N, 7.40.

4.1.1.8. *N*-(Thien-3-ylmethyl)-*N*-(4-methylphenyl)amine (55). Yellow oil. Yield 98%. IR (film): *v* 3410, 1616 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.28 (1H, dd, *J* = 4.8, 2.9 Hz, 5-H_{Thie}), 7.15 (1H, br s, 2-H_{Thie}), 7.06 (1H, d, *J* = 4.6 Hz, 4-H_{Thie}), 7.00 (2H, d, *J* = 8.1 Hz, 3(5)-H_{Ar}), 6.57 (1H, d, *J* = 8.3 Hz, 2(6)-H_{Ar}), 4.28 (2H, s, H_2C–N), 3.69 (1H, br s, H–N), 2.25 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 145.7, 140.6, 129.7 (2C, +), 127.1 (+), 125.9 (+), 121.5 (+), 113.0 (2C, +), 44.0 (−), 20.3 (+). MS *m*/*z* (EI) 203 (M^+). Found: C, 70.76; H, 6.77; N, 6.70; calcd for $C_{12}H_{13}NS$: C, 70.89; H, 6.45; N, 6.89.

4.1.1.9. *N*-(Thien-3-ylmethyl)-*N*-(4-chlorophenyl)amine (56). Yellow oil. Yield 97%. IR (film): *v* 3417, 1601 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.34 (1H, dd, *J* = 4.9, 3.0 Hz, 5-H_{Thie}), 7.20 (1H, br d, *J* = 1.9 Hz, 2-H_{Thie}), 7.17 (2H, d, *J* = 8.7 Hz, 3(5)-H_{Ar}), 7.10 (2H, d, *J* = 4.9 Hz, 4-H_{Thie}), 6.59 (2H, d, *J* = 8.8 Hz, 2(6)-H_{Ar}), 4.32 (2H, s, H_2C–N), 3.95 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 146.4, 139.9, 129.0 (2C, +), 126.9 (+), 126.2 (+), 122.0, 121.7 (+), 113.9 (2C, +), 43.7 (−). MS *m*/*z* (EI) 223 (M^+ for ^{35}Cl). Found: C, 59.22; H, 4.30; N, 6.16; calcd for $C_{11}H_{10}ClNS$: C, 59.05; H, 4.51; N, 6.26%.

4.1.1.10. *N*-[(1-Methyl-1*H*-pyrrol-2-yl)methyl]phenylamine (57). Yellow oil. Yield 90%. IR (film): *v* 3379, 1605 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.22 (2H, td, *J* = 7.4, 1.5 Hz, 3(5)-H_{Ph}), 6.76 (1H, t, *J* = 7.4 Hz, 5-H_{Pyr}), 6.68 (2H, d, *J* = 7.7 Hz, 2(6)-H_{Ph}), 6.63 (1H, br d, *J* = 1.8 Hz, 4-H_{Ph}), 6.14 (1H, br d, *J* = 1.4 Hz, 4-H_{Pyr}), 6.11 (1H, br t, *J* = 2.2 Hz, 3-H_{Pyr}), 4.21 (2H, s, H_2C–N), 4.15 (1H, br s, H–N), 3.61 (3H, s, CH_3–N); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 147.9, 129.2 (2C, +), 122.7 (+), 115.0, 117.7 (+), 112.8 (2C, +), 108.5 (+), 106.8 (+), 40.3 (−), 33.6 (+). MS *m*/*z* (EI) 186 (M^+). Found: C, 77.16; H, 7.67; N, 15.23; calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04.

4.1.1.11. *N*-[(1-Methyl-1*H*-pyrrol-2-yl)methyl]-*N*-(4-methylphenyl)amine (58). Yellow oil. Yield 89%. IR (film): *v* 3379, 1616 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.05 (2H, d, *J* = 8.0 Hz, 3(5)-H_{Ar}), 6.64 (1H, s, 5-H_{Pyr}), 6.63 (2H, d, *J* = 8.0 Hz, 2(6)-H_{Ar}), 6.13 (1H, br s, 4-H_{Pyr}), 6.10 (1H, br t, *J* = 2.6 Hz, 3-H_{Pyr}), 4.21 (2H, s, H_2C–N), 3.64 (3H, s, CH_3–N), 3.55 (1H, br

s, H–N), 2.28 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.6, 129.7 (2C, +), 127.2, 122.8 (+), 115.3, 113.2 (2C, +), 108.5 (+), 106.8 (+), 40.8 (−), 33.7 (+), 20.4 (+). MS *m*/*z* (EI) 200 (M^+). Found: C, 78.15; H, 7.96; N, 13.85; calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99.

4.1.1.12. *N*-[(1-Methyl-1*H*-pyrrol-2-yl)methyl]-*N*-(4-chlorophenyl)amine (59). Orange oil. Yield 88%. IR (film): *v* 3379, 1597 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.17 (2H, d, J = 8.8 Hz, 3(5)-H_{Ar}), 6.65 (1H, t, J = 2.3 Hz, 5-H_{Pyr}), 6.61 (2H, dd, J = 8.8, 2.4 Hz, 2(6)-H_{Ar}), 6.14 (1H, br dd, J = 3.4, 1.8 Hz, 4-H_{Pyr}), 6.11 (1H, t, J = 2.8 Hz, 3-H_{Pyr}), 4.85 (1H, br s, H–N), 4.20 (2H, s, H_2C–N), 3.63 (3H, s, CH_3–N); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.5, 129.0 (2C, +), 122.9 (+), 122.3, 116.2, 113.9 (2C, +), 108.6 (+), 106.9 (+), 40.4 (−), 33.7 (+). MS *m*/*z* (EI) 220 (M^+ for ^{35}Cl). Found: C, 65.22; H, 5.99; N, 12.54; calcd for $C_{12}H_{13}ClN_2$: C, 65.31; H, 5.94; N, 12.69.

4.1.1.13. *N*-(2-Pyridylmethyl)phenylamine (60). Colorless solid. Mp 48–50 °C. Yield 95%. IR (KBr): *v* 3312, 1615 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.73 (1H, br dd, J = 4.8, 1.1 Hz, 6-H_{Py}), 7.67 (1H, td, J = 7.8 Hz, 5-H_{Py}), 7.33 (1H, d, J = 7.7 Hz, 4-H_{Py}), 7.20 (1H, dd, J = 7.4, 4.8 Hz, 3-H_{Py}), 6.95 (2H, d, J = 8.3 Hz, 3(5)-H_{Ph}), 6.70 (1H, t, J = 8.0 Hz, 4-H_{Ph}), 6.48 (2H, d, J = 8.3 Hz, 2(6)-H_{Ph}), 4.45 (2H, s, H_2C–N), 4.12 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.9, 149.2 (+), 145.5, 136.9 (+), 129.6 (+), 129.9 (+), 126.7, 122.0 (+), 121.8 (+), 113.3 (+), 113.4 (+), 49.6 (−). MS *m*/*z* (EI) 184 (M^+). Found: C, 78.45; H, 6.80; N, 15.02; calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21.

4.1.1.14. *N*-(2-Pyridylmethyl)-*N*-(4-methyphenyl)amine (61). Colorless solid. Mp 42 °C. Yield 90%. IR (KBr): *v* 3314, 1616 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.71 (1H, br dd, J = 4.7, 1.0 Hz, 6-H_{Py}), 7.65 (1H, td, J = 7.8 Hz, 5-H_{Py}), 7.36 (1H, d, J = 7.8 Hz, 4-H_{Py}), 7.19 (1H, dd, J = 7.3, 4.9 Hz, 3-H_{Py}), 6.94 (2H, d, J = 8.3 Hz, 3(5)-H_{Ar}), 6.48 (2H, d, J = 8.2 Hz, 2(6)-H_{Ar}), 4.43 (2H, s, H_2C–N), 4.10 (1H, br s, H–N), 2.25 (3H, s, 4-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.8, 149.1 (+), 145.6, 136.7 (+), 129.8 (+), 129.7 (+), 126.8, 122.1 (+), 121.6 (+), 113.2 (+), 113.1 (+), 49.7 (−), 20.4 (+). MS *m*/*z* (EI) 198 (M^+). Found: C, 78.45; H, 7.20; N, 13.90; calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13.

4.1.1.15. *N*-(2-Pyridylmethyl)-*N*-(4-iodophenyl)amine (62). Colorless solid. Mp 73–74 °C. Yield 85%. IR (KBr): *v* 3263, 1588 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.58 (1H, br d, J = 4.4 Hz, 6-H_{Py}), 7.68 (1H, t, J = 7.6 Hz, 5-H_{Py}), 7.41 (2H, d, J = 8.8 Hz, 3(5)-H_{Ar}), 7.33 (1H, d, J = 7.9 Hz, 4-H_{Py}), 7.23 (1H, br d, J = 4.8 Hz, 3-H_{Py}), 6.45 (2H, d, J = 9.0 Hz, 2(6)-H_{Ar}), 4.81 (1H, br s, H–N), 4.44 (2H, s, H_2C–N); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.6, 148.7, 147.3 (+), 137.8 (+), 137.7 (+), 137.5 (+), 122.4 (+), 121.9 (+), 115.3 (+), 115.2 (+), 78.4, 48.6 (−). MS *m*/*z* (EI) 310 (M^+). Found: C, 46.77; H, 3.60; N, 8.89; calcd for $C_{12}H_{11}IN_2$: C, 46.47; H, 3.58; N, 9.03.

4.1.1.16. *N*-(2-Pyridylmethyl)-*N*-(3-nitrophenyl)amine (63). Yellow solid. Mp 79–80 °C. Yield 85%. IR (KBr): *v* 3382, 1618 (s, NH), *v* 1526, 1344 cm^{-1} (s, NO_2); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.63 (1H, br d, J = 4.8 Hz, 6-H_{Py}), 7.73 (1H, td, J = 7.6 Hz, 5-H_{Py}), 7.56 (1H, dd d, J = 8.1, 2.0, 0.8 Hz, 4-H_{Ar}), 7.50 (1H, t, J = 2.3 Hz, 2-H_{Ar}), 7.36 (1H, d, J = 7.8 Hz, 4-H_{Py}), 7.31 (1H, t, J = 8.1 Hz, 5-H_{Ar}), 7.26 (1H, br dd, J = 7.6, 5.1 Hz, 3-H_{Py}), 6.99 (1H, dd d, J = 8.1, 2.3, 0.8 Hz, 6-H_{Ar}), 5.43 (1H, br s, H–N), 4.53 (2H, s, H_2C–N). MS *m*/*z* (EI) 229 (M^+). Found: C, 62.45; H, 5.05; N, 18.00; calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33.

4.1.1.17. *N*-(2-Pyridylmethyl)-*N*-(3,5-dimethylphenyl)amine (64). Red oil. Yield 65%. IR (film): *v* 3399, 1605 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.61 (1H, br dd, J = 4.9, 1.0 Hz, 6-H_{Py}), 7.67 (1H, td, J = 7.8 Hz, 5-H_{Py}), 7.37 (1H, d, J = 7.8 Hz, 4-H_{Py}), 7.21 (1H, dd, J = 7.3, 4.9 Hz, 3-H_{Py}), 6.42 (1H, s, 4-H_{Ar}), 6.35 (2H, s, 2(6)-H_{Ar}), 4.48 (2H, s, H_2C–N), 3.78 (1H, br s, H–N), 2.26 (6H, s, 3(5)-CH_3). MS *m*/*z* (EI) 212 (M^+). Found: C, 79.05; H, 7.80; N, 13.32; calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20.

4.1.1.18. *N*-(4-Pyridylmethyl)phenylamine (70). Colorless solid. Mp 61–63 °C. Yield 94%. IR (KBr): *v* 3263, 1605 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.55 (2H, dd, J = 6.0, 1.6 Hz, 2(6)-H_{Py}), 7.29 (2H, d, J = 5.9 Hz, 3(5)-H_{Py}), 7.17 (2H, td, J = 7.4, 1.0 Hz, 3(5)-H_{Ph}), 6.74 (1H, t, J = 7.4 Hz, 4-H_{Ph}), 6.58 (2H, dd, J = 8.5, 0.8 Hz, 2(6)-H_{Ph}), 4.37 (2H, s, H_2C–N), 4.18 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.8 (2C, +), 149.0, 147.4, 129.3 (2C, +), 122.0 (2C, +), 118.0 (+), 112.8 (2C, +), 47.0 (−). MS *m*/*z* (EI) 184 (M^+). Found: C, 78.37; H, 6.46; N, 15.30; calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21.

4.1.1.19. *N*-(4-Pyridylmethyl)-*N*-(4-methylphenyl)amine (71). Colorless solid. Mp 70–71 °C. Yield 83%. IR (KBr): *v* 3292, 1602 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54 (2H, dd, J = 4.2, 1.5 Hz, 2(6)-H_{Py}), 7.31 (2H, d, J = 4.2 Hz, 3(5)-H_{Py}), 6.98 (2H, d, J = 8.3 Hz, 3(5)-H_{Ar}), 6.50 (2H, d, J = 8.4 Hz, 2(6)-H_{Ar}), 4.36 (2H, s, H_2C–N), 4.15 (1H, br s, H–N), 2.23 (3H, s, 4-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.5 (+), 149.4 (+), 145.1, 129.8 (+), 129.7 (+), 128.0, 123.4, 122.2 (+), 122.1 (+), 113.0 (+), 112.9 (+), 47.4 (−), 20.3 (+). MS *m*/*z* (EI) 198 (M^+). Found: C, 78.65; H, 7.20; N, 14.08; calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13.

4.1.1.20. *N*-(4-Pyridylmethyl)-*N*-(4-chlorophenyl)amine (72). White solid. Mp 106–107 °C. Yield 80%. IR (KBr): *v* 3271, 1601 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.55 (2H, d, J = 4.9 Hz, 2(6)-H_{Py}), 7.29 (2H, d, J = 5.2 Hz, 3(5)-H_{Py}), 7.12 (2H, d, J = 8.7 Hz, 3(5)-H_{Ar}), 6.51 (2H, d, J = 8.6 Hz, 2(6)-H_{Ar}), 4.36 (2H, s, H_2C–N), 4.15 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.6 (2C, +), 148.5, 145.9, 122.0, 128.9 (2C, +), 121.8 (2C, +), 113.7 (2C, +), 46.7 (−). MS *m*/*z* (EI) 218 (M^+ for ^{35}Cl). Found: C, 65.76; H, 5.24; N, 12.63; calcd for $C_{12}H_{11}ClN_2$: C, 65.91; H, 5.07; N, 12.81.

4.1.1.21. *N*-(4-Pyridylmethyl)-*N*-(4-iodophenyl)amine (73). White solid. Mp 106–107 °C. Yield 80%. IR (KBr): ν 3383, 1590 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.57 (2H, dd, J = 4.4, 1.5 Hz, 2(6)-H_{Py}), 7.43 (2H, dd, J = 6.8, 2.0 Hz, 3(5)-H_{Ar}), 7.28 (2H, dd, J = 4.4, 1.5 Hz, 3(5)-H_{Py}), 6.38 (2H, dd, J = 6.8, 2.5 Hz, 2(6)-H_{Ar}), 4.38 (2H, s, H_2C–N), 4.08 (1H, br s, H–N). MS *m*/*z* (EI) 310 (M^+). Found: C, 46.76; H, 3.84; N, 9.41; calcd for $C_{12}H_{11}IN_2$: C, 46.47; H, 3.58; N, 9.03.

4.1.1.22. *N*-(4-Pyridylmethyl)-*N*-(3-nitrophenyl)amine (74). Yellow solid. Mp 89–90 °C. Yield 72%. IR (KBr): ν 3250, 1602 (s, NH), 1523, 1341 cm^{-1} (s, NO_2); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.61 (2H, dd, J = 4.5, 1.8 Hz, 2(6)-H_{Py}), 7.59 (1H, dd d, J = 8.1, 2.3, 1.0 Hz, 4-H_{Ar}), 7.42 (1H, t, J = 2.3 Hz, 5-H_{Ar}), 7.33–7.28 (3H, m, 2-H_{Ar} and, 3(5)-H_{Py}), 6.87 (1H, dd d, J = 8.3, 2.5, 0.8 Hz, 6-H_{Ar}), 4.69 (1H, br s, H–N), 4.48 (2 H, d, J = 5.8 Hz, H_2C–N). MS *m*/*z* (EI) 229 (M^+). Found: C, 62.45; H, 4.53; N, 18.50; calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33.

4.1.1.23. *N*-(4-Pyridylmethyl)-*N*-(3,5-dimethylphenyl)amine (75). Yellow solid. Mp 93–94 °C. Yield 82%. IR (KBr): ν 3275, 1605 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.57 (2 H, dd, J = 4.4, 1.5 Hz, 2(6)-H_{Py}), 7.33 (2 H, br d, J = 4.4 Hz, 3(5)-H_{Py}), 6.43 (1 H, s, 4-H_{Ar}), 6.24 (2 H, s, 2(6)-H_{Ar}), 4.39 (2H, s, H_2C–N), 4.12 (1H, br s, H–N), 2.24 (6H, s, 3(5)-CH_3). MS *m*/*z* (EI) 212 (M^+). Found: C, 79.05; H, 7.88; N, 13.15; calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20.

4.1.2. Type B. New homoallylamines (**81**, **82**, **91**–**94**) and (**83**, **84**, **87**–**90**) were obtained following with the procedures described by our laboratories[3–5] and by Vilaivan et al.,[16], respectively.

4.1.2.1. *N*-(4-Methylphenyl)-*N*-[1-(furan-2-yl)but-3-enyl]amine (81). Yellow oil. Yield 78%. IR (film): ν 3373 (s, NH), 1504, 923 cm^{-1} (s, C=CH); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 (1H, dd, J = 1.7, 0.7 Hz, 5-H_{Fu}), 6.94 (2H, d, J = 8.1 Hz, 3(5)-H_{Ar}), 6.52 (2H, d, J = 8.4 Hz, 2(6)-H_{Ar}), 6.25 (1H, dd, J = 3.2, 1.9 Hz, 4-H_{Fu}), 6.14 (1H, d, J = 3.2 Hz, 3-H_{Fu}), 5.79–5.68 (1H, m, =CH), 5.16–5.09 (2H, m, $=CH_2$), 4.50 (1H, t, J = 6.3 Hz, 4-H), 3.84 (1H, br s, NH), 2.65–2.61 (2H, m, $–CH_2$), 2.20 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9, 144.7, 141.4 (+), 134.0 (+), 129.6 (2C, +), 127.0, 118.2 (−), 113.7 (2C, +), 110.1 (+), 106.0 (+), 51.6 (+), 39.2 (−), 20.3 (+). MS *m*/*z* (EI) 227 (M^+), 186 [$(M–C_3H_5)^+$]. Found: C, 79.05; H, 7.88; N, 6.35; calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16.

4.1.2.2. *N*-(3,4-Dichlorophenyl)-*N*-[1-(furan-2-yl)but-3-enyl]amine (82). Yellow oil. Yield 71%. IR (film): ν 3392 (s, NH), 1505, 920 cm^{-1} (s, C=CH); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34 (1H, dd, J = 1.9, 0.9 Hz, 5-H_{Fu}), 7.14 (1H, d, J = 8.5 Hz, 6-H_{Ar}), 6.66 (1H, d, J = 2.8 Hz, 2-H_{Ar}), 6.41(1H, dd, J = 8.7, 2.8 Hz, 5-H_{Ar}), 6.28 (1H, dd, J = 3.2, 1.7 Hz, 4-H_{Fu}), 6.14 (1H, d, J = 3.2 Hz, 3-H_{Fu}), 5.80–5.66 (1H, m, =CH), 5.19–5.13 (2H, m, CH_2=), 4.48 (1H, t, J = 6.3 Hz, 4-H), 4.05 (1H, br s, NH), 2.65–2.61 (2H, m, $–CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.6, 146.4, 141.8 (+), 133.4 (+), 132.7, 130.5 (+), 120.3, 118.8 (−), 114.7 (+), 113.0 (+), 110.2 (+), 106.4 (+), 51.1 (+), 39.0 (−). MS *m*/*z* (EI) 281 (M^+), 240 [$(M–C_3H_5)^+$ for ^{35}Cl]. Found: C, 59.34; H, 4.90; N, 4.71; calcd for $C_{14}H_{13}Cl_2NO$: C, 59.59; H, 4.64; N, 4.96.

4.1.2.3. *N*-[1-(Furan-3-yl)but-3-enyl]-*N*-phenylamine (83). Red oil. Yield 95%. IR (film): ν 3410, 1601 (s, NH), 1504, 922 cm^{-1} (s, C=CH); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43 (1H, t, J = 1.7 Hz, 5-H_{Fu}), 7.39 (1H, s, 2-H_{Fu}), 7.20 (2H, t, J = 7.5 Hz, 3(5)-H_{Ph}), 6.76 (1H, t, J = 7.3 Hz, 4-H_{Ph}), 6.66 (2H, d, J = 7.9 Hz, 2(6)-H_{Ph}), 6.42 (1H, br s, 4-H_{Fu}), 5.94–5.79 (1H, m, =CH), 5.26–5.17 (2H, m, CH_2=), 4.50 (1H, t, J = 6.3 Hz, 4-H), 3.75 (1H, br s, NH), 2.63 (2H, t, J = 6.8 Hz, $–CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.2, 143.1 (+), 139.5 (+), 134.3 (+), 129.1 (2C, +), 127.7, 118.3 (−), 117.6 (+), 113.5 (2C, +), 109.0 (+), 49.4 (+), 41.0 (−). MS *m*/*z* (EI) 213 (M^+), 172 [$(M–C_3H_5)^+$]. Found: C, 78.67; H, 7.21; N, 6.31; calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57.

4.1.2.4. *N*-(4-Chlorophenyl)-*N*-[1-(furan-3-yl)but-3-enyl]amine (84). Yellow oil. Yield 57%. IR (film): ν 3413, 1601 (s, NH), 1497, 922 cm^{-1} (s, C=CH); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38 (1H, t, J = 1.6 Hz, 5-H_{Fu}), 7.32 (1H, br d, J = 0.6 Hz, 2-H_{Fu}), 7.09 (2H, d, J = 8.8 Hz, 3(5)-H_{Ar}), 6.52 (2H, d, J = 8.8 Hz, 2(6)-H_{Ar}), 6.35 (1H, br t, J = 0.7 Hz, 4-H_{Fu}), 5.85–5.71 (1H, m, =CH), 5.21–5.14 (2H, m, CH_2=), 4.39 (1H, t, J = 6.2 Hz, 4-H), 3.80 (1H, br s, NH), 2.56 (2H, td, J = 6.9, 1.4 Hz, $–CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.8, 143.3 (+), 139.5 (+), 134.0 (+), 128.9 (2C, +), 127.3, 121.1, 118.5 (−), 114.6 (2C, +), 108.9 (+), 49.5 (+), 41.0 (−). MS *m*/*z* (EI) 247(M^+), 206 [$(M–C_3H_5)^+$ for ^{35}Cl]. %. Found: C, 67.75; H, 5.88; N, 5.39; calcd for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.65.

4.1.2.5. *N*-[1-(Thien-3-yl)but-3-enyl]-*N*-phenylamine (87). Yellow oil. Yield 97%. IR (film): ν 3410, 1601 (s, NH), 1504, 918 cm^{-1} (s, C=CH); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34 (1H, dd, J = 4.9, 3.0 Hz, 5-H_{Thie}), 7.29–7.15 (3H, m, 3(5)-H_{Ph}, and 2-H_{Thie}), 7.11 (1H, dd, J = 5.0, 1.2 Hz, 4-H_{Thie}), 6.74 (1H, t, J = 7.3H, 4-H_{Ph}), 6.62 (2H, d, J = 7.7 Hz, 2(6)-H_{Ph}), 5.92–5.75 (1H, m, =CH), 5.26-5.18 (2H, m, CH_2=), 4.60 (1H, t, J = 6.5 Hz, 4-H), 4.16 (1H, br s, NH), 2.67 (2H, q, J = 6.7 Hz, $–CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.2, 144.7, 134.4 (+), 129.1 (2C, +), 127.7, 126.1 (+), 126.0 (+), 120.8 (+), 118.3 (−), 117.6 (+), 113.6 (+), 53.4 (+), 41.9 (−). MS *m*/*z* (EI) 229 (M^+), 188 [$(M–C_3H_5)^+$]. Found: C, 73.55; H, 6.47; N, 6.05; calcd for $C_{14}H_{15}NS$: C, 73.32; H, 6.59; N, 6.11.

4.1.2.6. *N*-[1-(Thien-3-yl)but-3-enyl]-*N*-(4-methylphenyl)-amine (88). Yellow oil. Yield 88%. IR (film): ν 3410, 1616 (s, NH), 1516, 914 cm^{-1} (s, C=CH); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.28 (1H, dd, J = 4.9, 3.0 Hz, 5-H_{Thie}), 7.15 (1H, d, J = 2.8 Hz, 2-H_{Thie}), 7.05 (1H, dd, J = 5.0, 1.0 Hz, 4-H_{Thie}), 6.95 (2H, d, J = 8.3 Hz, 3(5)-H_{Ar}), 6.50 (2H, d, J = 8.4 Hz, 2(6)-H_{Ar}), 5.97–5.68 (1H, m, =CH), 5.22–5.00 (2H, m, CH_2=), 4.52 (1H, t,

J = 6.4 Hz, 4-H), 4.15 (1H, br s, NH), 2.60 (2H, q, J = 6.9 Hz, –CH_2), 2.23 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.0, 134.5 (+), 129.6 (2C, +), 126.7, 126.1 (+), 125.9 (+), 120.7 (+), 118.2 (−), 117.6, 113.6 (2C, +), 53.6 (+), 41.9 (−), 20.3 (+). MS *m*/*z* (EI) 243 (M^+), 202 [$(M–C_3H_5)^+$]. Found: C, 74.34; H, 7.32; N, 5.43; calcd for $C_{15}H_{17}NS$: C, 74.03; H, 7.04; N, 5.76.

4.1.2.7. *N*-[1-(Thien-3-yl)but-3-enyl]-*N*-(4-chlorophenyl)-amine (89). Yellow oil. Yield 48%. IR (film): *v* 3413, 1597 (s, NH), 1497, 922 cm^{-1} (s, C=CH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (1H, dd, J = 4.9, 3.0 Hz, 5-H_{Thie}), 7.12 (1H, br d, J = 2.9 Hz, 2-H_{Thie}), 7.06 (2H, d, J = 8.8 Hz, 3(5)-H_{Ar}), 7.04 (1H, dd, J = 5.3, 1.0 Hz, 4-H_{Thie}), 6.48 (2H, d, J = 8.7 Hz, 2(6)-H_{Ar}), 5.84–5.65 (1H, m, =CH), 5.21–5.14 (2H, m, CH_2=), 4.50 (1H, t, J = 6.5 Hz, 4-H), 4.18 (1H, br s, NH), 2.69–2.52 (2H, m, –CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.7, 144.2, 134.1 (+), 128.9 (2C, +), 126.2 (+), 125.9 (+), 122.2, 120.9 (+), 118.5 (−), 114.6 (2C, +), 53.5 (+), 41.8 (−). MS *m*/*z* (EI) 263 (M^+), 222 [$(M–C_3H_5)^+$ for ^{35}Cl]. Found: C, 63.56; H, 5.07; N, 5.15; calcd for $C_{14}H_{14}ClNS$: C, 63.74; H, 5.35; N, 5.31.

4.1.2.8. *N*-[1-(1-Methyl-1*H*-pyrrol-2-yl)but-3-enyl]-*N*-(4-chlorophenyl)amine (90). Yellow oil. Yield 45%. IR (film): *v* 3413, 1601 (s, NH), 1500, 918 cm^{-1} (s, C=CH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.13 (1H, t, J = 2.7 Hz, 5-H_{Pyr}), 7.10 (2H, dd, J = 8.2, 2.5 Hz, 3(5)-H_{Ar}), 6.62 (1H, br s, 4-H_{Pyr}), 6.59 (1H, br s, 3-H_{Pyr}), 6.54 (2H, dd, J = 8.8, 2(6)-H_{Ar}), 6.01–5.75 (1H, m, =CH), 5.31–5.13 (2H, m, CH_2=), 4.05 (1H, br s, NH), 3.75 (1H, dt, J = 5.3, 1.6 Hz, 4-H), 3.57 (3H, s, CH_3–N), 2.66 (2H, t, J = 6.8 Hz, –CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.5, 134.9, 133.5 (+), 129.0 (2C, +), 116.4, 116.2 (−), 114.0 (2C, +), 113.5 (+), 106.7 (+), 106.6 (+), 52.9 (+), 46.6 (−), 33.9 (+). MS *m*/*z* (EI) 260 (M^+), 219 [$(M–C_3H_5)^+$ for ^{35}Cl]. Found: C, 69.34; H, 6.90; N, 10.66; calcd for $C_{15}H_{17}ClN_2$: C, 69.09; H, 6.57; N, 10.74.

4.1.2.9. *N*-(4-Phenyl)-*N*-[1-(pyridin-4-yl)but-3-enyl]-amine (91). Yellow oil. Yield 80%. IR (film): *v* 3406, 1601 (s, NH), 1504, 922 cm^{-1} (s, C=CH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.56 (2H, dd, J = 5.0, 1.6 Hz, 2(6)-H_{Py}), 7.31 (2H, dd, J = 4.4, 1.6 Hz, 3(5)-H_{Py}), 7.10 (2H, td, J = 7.7, 1.0 Hz, 3(5)-H_{Ph}), 6.69 (1H, tt, J = 7.3, 1.9 Hz, 4-H_{Ph}), 6.45 (2H, d, J = 8.5 Hz, 2(6)-H_{Ph}), 5.80–5.66 (1H, m, =CH), 5.24–5.18 (2H, m, CH_2=), 4.38 (1H, dd, J = 7.9, 5.0 Hz, 4-H), 4.19 (1H, br s, H–N), 2.66–2.57 (1H, m, –CH_A), 2.53–2.43 (1H, m, –CH_B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.8, 150.0 (2C, +), 146.6, 133.5 (+), 129.1 (2C, +), 121.6 (2C, +), 119.1 (−), 117.9 (+), 113.4 (2C, +), 56.2 (+), 42.4 (−). MS *m*/*z* (EI) 224 (M^+), 183 [$(M–C_3H_5)^+$]. Found: C, 80.54; H, 7.04; N, 12.40; calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49.

4.1.2.10. *N*-(4-Methoxylphenyl)-*N*-[1-(pyridin-4-yl)-but-3-enyl]amine (92). Yellow oil. Yield 85%, IR (film): *v* 3309, 1597 (s, NH), 1512, 922 cm^{-1} (s, C=CH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.53 (2H, dd, J = 4.5, 1.5 Hz, 2(6)-H_{Py}), 7.29 (2H, d, J = 6.0 Hz, 3(5)-H_{Py}), 6.68 (2H, d, J = 8.9 Hz, 3(5)-H_{Ar}), 6.40 (2H, d, J = 8.9 Hz, 2(6)-H_{Ar}), 5.77–5.67 (1H, m, =CH), 5.20 (1H, d, J = 6.0 Hz, CH_{2A}=), 5.16 (1H, s, CH_{2B}=), 4.29 (1H, dd, J = 8.0, 5.0 Hz, 4-H), 4.20 (1H, br s, NH), 3.68 (3H, s, OCH_3), 2.61–2.41 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.1, 152.2 149.8 (2C, +), 140.8, 133.6 (+), 121.6 (2C, +), 119.0 (−), 114.7 (2C, +), 114.5 (2C, +), 57.0 (+), 55.6 (+), 42.4 (−). MS *m*/*z* (EI) 254 (M^+), 213 [$(M–C_3H_5)^+$]. Found: C, 75.29; H, 7.32; N, 11.12; calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01.

4.1.2.11. *N*-(4-Bromophenyl)-*N*-[1-(pyridin-4-yl)but-3-enyl]amine (93). Yellow oil. Yield 75%. IR (film): *v* 3410, 1593 (s, NH), 1493, 922 cm^{-1} (s, C=CH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.55 (2H, dd, J = 4.4, 1.6 Hz, 2(6)-H_{Py}), 7.27 (2H, dd, J = 3.9, 1.7 Hz, 3(5)-H_{Py}), 7.16 (2H, dd, J = 8.8, 2.0 Hz, 3(5)-H_{Ar}), 6.31 (2H, dd, J = 8.8, 2.0 Hz, 2(6)-H_{Ar}), 5.78–5.63 (1H, m, =CH), 5.23–5.17 (2H, m, CH_2=), 4.34 (1H, quintet, J = 4.1 Hz, 4-H), 4.19 (1H, br s, H–N), 2.67–2.58 (1H, m, –CH_A), 2.52–2.42 (1H, m, –CH_B); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.1 (+), 150.0 (+), 145.5, 133.2 (+), 131.9 (2C, +), 128.1, 121.5 (2C, +), 119.5 (−), 115.0 (2C, +), 109.7, 56.2 (+), 42.3 (−). MS *m*/*z* (EI) 302 (M^+), 263 [$(M–C_3H_5)^+$ for ^{81}Br]. Found: C, 59.66; H, 5.16; N, 9.45; calcd for $C_{15}H_{15}BrN_2$: C, 59.42; H, 4.99; N, 9.24.

4.1.2.12. *N*-(3,5-Dimethylphenyl)-*N*-[1-(pyridin-4-yl)-but-3-enyl]amine (94). Yellow oil. Yield 85%. IR: *v* 3494, 1605 (s, NH), 1500, 914 cm^{-1} (s, C=CH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54 (2H, dd, J = 4.5, 1.5 Hz, 2(6)-H_{Py}), 7.29 (2H, dd, J = 4.7, 1.3 Hz, 3(5)-H_{Py}), 6.34 (1H, s, 4-H_{Ar}), 6.08 (2H, s, 2(6)-H_{Ar}), 5.76–5.65 (1H, m, =CH), 5.20–5.15 (2H, m, CH_2=), 4.35 (1H, dd, J = 7.7, 5.0 Hz, 4-H), 4.07 (1H, br s, H–N), 2.62–2.55 (1H, m, –CH_A), 2.48–2.41 (1H, m, –CH_B), 2.15 (6H, s, 3(5) –CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.9, 150.0 (2C, +), 146.8, 138.8 (2C), 133.6 (+), 121.5 (2C, +), 119.9 (+), 119.0 (−), 111.3 (2C, +), 56.2 (+), 42.4 (−), 21.4 (2C, +). MS *m*/*z* (EI) 252 (M^+), 211 [$(M–C_3H_5)^+$]. Found: C, 81.14; H, 7.70; N, 11.21; calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10.

4.1.3. Type C. New α-aminonitriles were obtained following the procedures described by De et al.[17]

4.1.3.1. 2-(2-Furyl)-2-(phenylamino)acetonitrile (95). Yellow oil. Yield 61%. IR (film): *v* 3359, 1605 (s, NH), 2241 cm^{-1} (s, CN); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41 (1H, t, J = 0.9 Hz, 5-H_{Fu}), 7.19 (2H, d, J = 7.5 Hz, 3(5)-H_{Ph}), 6.85 (1H, td, J = 7.4, 0.9 Hz, 4-H_{Ph}), 6.71 (2H, dd, J = 7.7, 0.8 Hz, 2(6)-H_{Ph}), 6.52 (1H, dd, J = 3.3, 0.7 Hz, 4-H_{Fu}), 6.36 (1H, dd, J = 3.1, 1.8 Hz, 3-H_{Fu}), 5.41 (1H, s, HC–CN), 4.11 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.0, 144.1, 144.0 (+), 129.6 (2C, +), 120.7 (+), 116.4, 114.5 (2C, +), 110.9 (+), 109.6 (+), 44.4 (+). MS *m*/*z* (EI) 198 (M^+). Found: C, 72.85; H, 5.23; N, 14.25; calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13.

4.1.3.2. 2-(3-Furyl)-2-(phenylamino)acetonitrile (96). Yellow oil. Yield 62%. IR (film): *v* 3356, 1605 (s, NH), 2237 cm^{-1} (s, CN); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.62 (1H, s, $J = 0.9$ Hz, 5-H_{Fu}), 7.41 (2H, br t, $J = 1.4$ Hz, 2-H_{Fu}), 7.21 (2H, t, $J = 7.6$ Hz, 3(5)-H_{Ph}), 6.84 (1H, t, $J = 7.4$ Hz, 4-H_{Ph}), 6.70 (2H, d, $J = 7.8$ Hz, 2(6)-H_{Ph}), 6.47 (1H, s, 4-H_{Fu}), 5.27 (1H, s, HC–CN), 3.92 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.5 (+), 144.3, 141.0 (+), 129.6 (2C, +), 120.5 (+), 120.1, 117.8, 114.3 (2C, +), 109.1 (+), 42.5 (+). MS *m/z* (EI) 198 (M^+). Found: C, 72.56; H, 5.21; N, 14.02; calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13.

4.1.3.3. 2-(2-Thienyl)-2-(phenylamino)acetonitrile (97). Yellow oil. Yield 80%. IR (film): *v* 3356, 1605 (s, NH), 2237 cm^{-1} (s, CN); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.26–7.23 (2H, m, 3,5-H_{Thie}), 7.16 (2H, t, $J = 7.7$ Hz, 3(5)-H_{Ph}), 6.92 (1H, t, $J = 4.1$ Hz, 4-H_{Thie}), 6.81 (1H, t, $J = 7.3$ Hz, 4-H_{Ph}), 6.67 (2H, d, $J = 8.4$ Hz, 2(6)-H_{Ph}), 5.50 (1H, d, $J = 8.1$ Hz, HC–CN), 4.12 (1H, br d, $J = 8.3$ Hz, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.0, 136.7, 129.5 (+), 127.1 (2C, +), 127.0 (2C, +), 120.6 (+), 117.5, 114.5 (2C, +), 46.0 (+). MS *m/z* (EI) 214 (M^+). Found: C, 67.55; H, 4.87; N, 13.21; calcd for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.07.

4.1.3.4. 2-(3-Thienyl)-2-(phenylamino)acetonitrile (98). Yellow oil. Yield 84%. IR (Film): *v* 3367, 1601 (s, NH), 2237 cm^{-1} (s, CN); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42 (1H, t, $J = 1.4$ Hz, 2-H_{Thie}), 7.26 (1H, dd, $J = 5.0$, 3.0 Hz, 5-H_{Thie}), 7.13 (2H, t, $J = 7.8$ Hz, 3(5)-H_{Ph}), 7.07 (1H, dd, $J = 5.0$, 1.0 Hz, 4-H_{Thie}), 6.76 (1H, t, $J = 7.4$ Hz, 4-H_{Ph}), 6.62 (2H, d, $J = 8.0$ Hz, 2(6)-H_{Ph}), 5.32 (1H, s, HC–CN), 3.90 (1H, br s, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.4, 134.5, 129.6 (2C, +), 127.8 (+), 126.1 (+), 124.3 (+), 120.4 (+), 118.2, 114.3 (2C, +), 46.0 (+). MS *m/z* (EI) 214 (M^+). Found: C, 67.43; H, 4.89; N, 12.97; calcd for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.07.

4.1.3.5. 2-(4-Methylphenylamino)-2-(3-thienyl)acetonitrile (99). Yellow oil. Yield 88%. IR (film): *v* 3356, 1616 (s, NH), 2233 cm^{-1} (s, CN); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42 (1H, dd, $J = 2.8$, 1.4 Hz, 2-H_{Thie}), 7.27 (1H, dd, $J = 5.0$, 3.0 Hz, 5-H_{Thie}), 7.07 (1H, dd, $J = 5.0$, 0.9 Hz, 4-H_{Thie}), 6.94 (2H, d, $J = 8.2$ Hz, 3(5)-H_{Ar}), 6.55 (2H, d, $J = 8.3$ Hz, 2(6)-H_{Ar}), 5.29 (1H, s, HC–CN), 3.80 (1H, br s, H–N), 2.13 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 142.1, 134.8, 130.1 (2C, +), 129.9, 127.7 (+), 126.2 (+), 124.1 (+), 118.3, 114.6 (2C, +), 46.6 (+), 20.5 (+). MS *m/z* (EI) 228 (M^+). Found: C, 68.15; H, 5.12; N, 12.43; calcd for $C_{13}H_{12}N_2S$: C, 68.39; H, 5.30; N, 12.27.

4.1.3.6. 2-(4-Chlorophenylamino)-2-(3-thienyl)acetonitrile (100). Yellow oil. Yield 88%. IR (film): *v* 3356, 1601 (s, NH), 2237 cm^{-1} (s, CN); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42 (1H, dd, $J = 2.8$, 1.6 Hz, 2-H_{Thie}), 7.28 (1H, dd, $J = 5.0$, 3.0 Hz, 5-H_{Thie}), 7.11–7.05 (3H, m, 4-H_{Thie}, and 3(5)-H_{Ar}), 6.56 (2H, d, $J = 8.8$ Hz, 2(6)-H_{Ar}), 5.28 (1H, d, $J = 8.8$ Hz, HC–CN), 3.98 (1H, d, $J = 8.8$ Hz, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.0, 134.1, 129.5 (2C, +), 129.1, 127.9 (+), 126.0 (+), 125.3, 124.4 (+), 115.5 (+), 46.1 (+). MS *m/z* (EI) 248 (M^+ for ^{35}Cl). Found: C, 57.77; H, 3.84; N, 11.03; calcd for $C_{12}H_9ClN_2S$: C, 57.95; H, 3.65; N, 11.26.

4.1.3.7. 2-(1-Methyl-1*H*-pyrrol-2-yl)-2-(phenylamino)acetonitrile (101). Yellow oil. Yield 60%. IR (film): *v* 3409 (s, NH), 2235 cm^{-1} (s, CN); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.31 (2H, td, $J = 7.5$, 0.9 Hz, 3(5)-H_{Ph}), 6.93 (1H, t, $J = 7.4$ Hz, 4-H_{Ph}), 6.80 (2H, d, $J = 7.7$ Hz, 2(6)-H_{Ar}), 6.71 (1H, br t, $J = 1.3$ Hz, 5-H_{Pyr}), 6.54 (1H, br dd, $J = 3.1$, 1.3 Hz, 4-H_{Pyr}), 6.15 (1H, br t, $J = 2.8$, 0.8 Hz, 2-H_{Pyr}), 5.40 (1H, d, $J = 8.9$ Hz, HC–CN), 4.05 (1H, s, H–N), 3.65 (3H, s, CH_3–N); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.3, 129.6 (2C, +), 129.2, 129.1, 125.0 (+), 120.5 (+), 114.3 (2C, +), 110.3 (+), 107.5 (+), 43.5 (+), 33.9 (+). MS *m/z* (EI) 211 (M^+). Found: C, 74.15; H, 6.09; N, 19.71; calcd for $C_{13}H_{13}N_3$: C, 73.91; H, 6.20; N, 19.89.

4.1.3.8. 2-(Phenylamino)-2-(pyridin-4-yl)acetonitrile (102). Yellow oil. Yield 69%. IR (film): *v* 3409, (s, NH), 2231 cm^{-1} (s, CN); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.68 (1H, d, $J = 2.1$, 2-H_{Py}), 8.52 (1H, dd, $J = 4.7$, 1.2, 6-H_{Py}), 7.79 (1H, d, $J = 8.0$ Hz, 3-H_{Py}), 7.24 (1H, dd, $J = 7.8$, 4.9 Hz, 5-H_{Py}), 7.14 (2H, td, $J = 8.2$, 1.8 Hz, 3(5)-H_{Ph}), 6.78 (1H, t, $J = 7.4$ Hz, 4-H_{Ph}), 6.65 (2H, d, $J = 7.8$ Hz, 2(6)-H_{Ph}), 5.35 (1H, d, $J = 8.5$ Hz, HC–CN), 4.20 (1H, d, $J = 8.5$ Hz, br s, H–N); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.6 (+), 148.6 (+), 144.2, 134.9 (+), 130.0, 129.6 (2C, +), 123.9 (+), 120.7 (+), 117.3, 114.4 (2C, +), 48.1 (+). MS *m/z* (EI) 209 (M^+). Found: C, 74.91; H, 5.45; N, 19.79; calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08.

4.2. Biological evaluation

4.2.1. Microorganisms and media. For the antifungal evaluation, strains from the American Type Culture Collection (ATCC), Rockville, MD, USA, and CEREMIC (C), Centro de Referencia en Micología, Facultad de Ciencias Bioquímicas y Farmacéuticas, Suipacha 531-(2000)-Rosario, Argentina, were used: *Microsporum canis* C 112, *Microsporum gypseum* C 115, *Trichophyton rubrum* C 110, *Trichophyton mentagrophytes* ATCC 9972, and *Epidermophyton floccosum* C 114. Strains were grown on Sabouraud-chloramphenicol agar slants for 48 h at 30 °C, maintained on slopes of Sabouraud-dextrose agar (SDA, Oxoid), and subcultured every 15 days to prevent pleomorphic transformations. Inocula of spore suspensions were obtained according to reported procedures[18,19] and adjusted to $1–5 \times 10^3$ spores with colony forming units (CFU)/mL.

4.2.2. Antifungal susceptibility testing. The Minimum Inhibitory Concentration (MIC) of each compound was determined by using broth microdilution techniques following the guidelines of the National Committee for Clinical Laboratory Standards for yeasts[18] and for filamentous fungi.[19] MIC values were determined in RPMI-1640 (Sigma, St. Louis, MO, USA) buffered to pH 7.0 with MOPS. Microtiter trays were incubated at

35 °C for yeasts and hyalohyphomycetes and at 28–30 °C for dermatophyte strains in a moist, dark chamber; MICs were recorded at 48 h for yeasts, and at a time according to the control fungus growth, for the rest of fungi. The susceptibilities of the standard drugs Ketoconazole, Terbinafine, and Amphotericin B were defined as the lowest concentration of drug which resulted in total inhibition of fungal growth.

For the assay, compound stock solutions were 2-fold diluted with RPMI-1640 from 250 to 0.98 μg/ml (final volume = 100 μl) and a final DMSO concentration ⩽1%. A volume of 100 μl of inoculum suspension was added to each well with the exception of the sterility control where sterile water was added to the well instead. The MIC was defined as the minimum inhibitory concentration of the compound, which resulted in total inhibition of the fungal growth.

4.2.3. Cytotoxic susceptibility testing. The cytotoxic activity was determined according to the method of Monks et al.[27] Briefly, the three human cells lines [breast (MCF-7), non-small cell lung (H-460), and central nervous system (SF-268)] obtained from U.S. National Cancer Institute (NCI) were counted, diluted with fresh medium, and added to 96-well microtiter plates (100 μL/well) containing test materials (1 mg in 100 μL in DMSO). Test plates were incubated for 2 days at 37 °C in a 5% CO_2 incubator. All treatments were performed in duplicate. After incubation periods, cells were fixed by addition of 50 μL of cold 50% aqueous TCA solution (4 °C for 60 min), washed 4–5 times with tap water, and air-dried. The fixed cells were stained with 100 μL sulforhodamine B (SRB) (0.4 % wt/vol in 1% acetic acid) for 15 min. Free SRB solution was then removed by rinsing with 1% acetic acid (5×). The plates were then air-dried, the bound dye was solubilized with 100 μL of 10 mM tris-base, and the absorbance was determined at 515 nm using an ELISA plate reader (Bio-Tek Instruments, Inc. Model ELX-800). Finally, the absorbance values obtained with each of the treatment procedures were averaged, and the averaged value obtained with the zero day control was substracted measuring in this way the relative cell growth or inviability in treated and untreated cells. From the curves, growth inhibition (or growth stimulation) and 50% inhibition of growth (GI_{50}) were calculated.[29] Adriamycin was used as the reference compound.

4.3. Computational methods

All calculations were carried out using the Gaussian 03 program.[30] The search for low-energy conformations on the potential energy surface for compounds **41**, **42**, and **45** was carried out by first using the systematic routine GASCOS[31–34] in connection with semiempirical AM1 calculations. Subsequently, ab initio (RHF/3-21G) and DFT (B3LYP/6-31G(d)) calculations were used in the geometry optimisation jobs. Minima were characterized through harmonic frequency analysis calculated at DFT level. Correlation effects were included using Density Functional Theory (DFT) with the Becke-3-Lee-Yang-parr (RB3LYP)[35] functional and 6-31G(d) basis set for the geometries obtained at the lower level of computation. Double scans were run at 15° intervals, from 0° to 360°, involving both Φ_1 and Φ_2 for each of the three compounds **41**, **81**, and **95** using AM1 computations. The graphical presentations of the PESs were generated using the program AXUN 5.0 plotting the total energy values as a dependent variable generated by the double scans over the independent variables Φ_1 and Φ_2. The optimum coordinates of Φ_1 and Φ_2 for all possible minima were then visually estimated from the level contours diagrams.

Potential energy curves (PEC) for Φ_1 and Φ_2 of compounds **41** and **83** have been obtained via one-dimensional (1D) scans using RHF/3-21G calculations. The energy has been calculated at 30° intervals of the dihedral angles. The electronic study of compounds **41**, **42**, and **45** was carried out using molecular electrostatic potentials (MEPs). MEPs have been shown to provide reliable information, both on the interaction sites of the molecules with point charges and on the comparative reactivities of these sites.[36–39] These MEPs were calculated using B3LYP/6-31G(d) wave functions from the MOLEKEL program.[40]

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