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Laboratory note

Synthesis and antifungal activity of novel aza-D-homosteroids, hydroisoquinolines, pyridines and dihydropyridines

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Summary — A series of novel aza-D-homosteroids and their hydroisoquinoline precursors were synthesized and tested for antifungal activity against a variety of *Candida* strains and also *Aspergillus* species. A number of 4-substituted pyridines and tetrahydropyridines were also tested. Several compounds showed a broad spectrum of modest antifungal activity and three structures were investigated further for fungicidal and in vivo activity.

hydroisoquinoline / antifungal / *Candida* / aza-D-homosteroid

Introduction

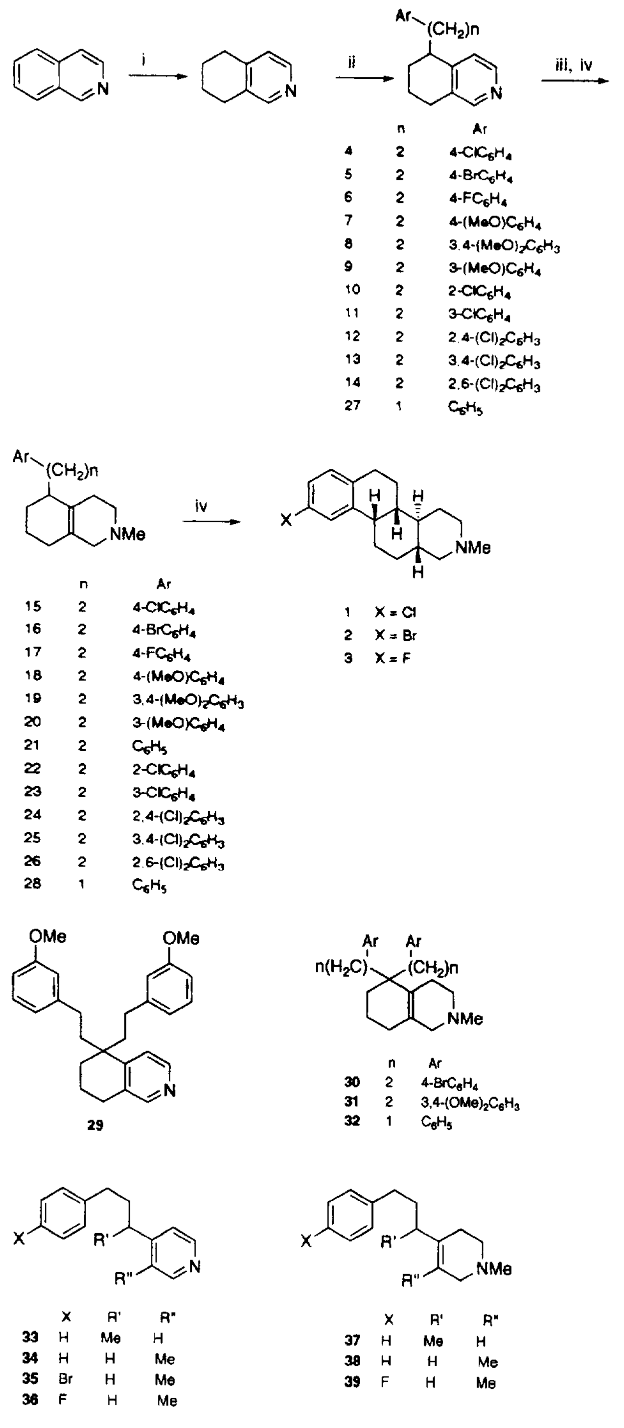
The problems associated with fungal infections have increased in recent years [1, 2]. For example, systemic fungal infections are becoming increasingly prevalent due to such factors as immune deficiencies in AIDS and cancer patients, the general aging process, and the side effects of other medications. Several mycoses such as chronic tinea pedis are refractory to existing therapy and there are still some untreatable mycoses such as those caused by *Scytalidium dimidiatum* and *S Hyalinum*, which are common infections in the tropics. Treatment of systemic *Candida* and *Aspergillus* infections in the neutropenic patient has also proved difficult.

Compared with the large number of antibacterial drugs which are available in medicine, there are far fewer antifungal agents, and despite recent developments over the last twenty years there is still a need for a genuinely broad-spectrum fungicidal agent. Currently used antifungal agents include: the polyenes [3–5] (eg, amphotericin B, nystatin and natamycin) which bind to and inhibit the formation of the fungal cell membrane; the imidazoles [6] (eg, miconazole, ketoconazole and clotrimazole) and triazoles [7–11] (eg, fluconazole, itraconazole and terconazole) which inhibit cytochrome P 450-dependent C-14 demethylation in the formation of ergosterol in the fungal cell membrane [12, 13]; and the allylamines [14, 15] (naftifine and terbinafine) which act against squalene epoxidase [16, 17]. More recently, the morpholine group of antifungal drugs (eg, amorolfine) have been developed and are found to inhibit Δ^8–Δ^7 isomerase and Δ^{14} reductase in sterol biosynthesis [18]. Other miscellaneous antifungal agents [1, 2] include tolnaftate, cyclopiroxolamine, haloprogin, griseofulvin, flucytosine, the echinocandins (eg, cilofungin) and the nikkomycins.

The antifungal activity of many of these agents results from inhibition of the biosynthesis of fungal steroids [12, 13, 19]. Therefore the recent synthesis [20] of the novel aza-D-homosteroids **1–3** is of particular interest since the azasteroid field in general has provided a rich source of compounds with diverse pharmaceutical properties [21–23], some of which have shown antifungal activity [24–26].

Chemistry

The synthesis of the novel aza-D-homosteroids **1–3** has been described previously [20] and is summarized in scheme 1. Treatment of 5,6,7,8-tetrahydroisoquinoline with potassium amide and a series of 2-iodoethyl benzenes gave the 5-substituted tetrahydroisoquinolines **4–14** and in most cases also gave a small yield of the 5,5-disubstituted product. Purification of the 5-substituted tetrahydroisoquinolines was conveniently carried out by distillation under reduced pressure while the disubstituted products were purified from the distillation residues by column chromatography. Treatment of compounds **4–14** with iodomethane in anhydrous diethyl ether gave the methiodide salts as precipitates which were treated immediately with sodium borohydride to give the octahydroisoquinolines **15–26**. The disubstituted octahydroisoquinolines **30–32** were similarly obtained from their respective tetrahydroisoquinolines.



Scheme 1.

The octahydroisoquinolines **15–17** on heating with 48% HBr for 16 h underwent double bond isomerization followed by cyclization [20] to give the azasteroids **1–3**, whereas the disubstituted octahydroisoquinolines failed to react under these conditions [20]. The pyridine structures **33–36** and the tetrahydropyridine structures **37–39** were synthesized in the same manner from the relevant substituted pyridines.

Pharmacology

All compounds were tested for in vitro antifungal activity against *Candida albicans* C316. The most active compounds resulting from these tests were tested for in vitro antifungal activity against a range of *Candida* strains as well as two *Aspergillus* strains. In vivo efficacy was measured on mice infected with acute systemic *C albicans*.

Results

The aza-D-homosteroids **1–3** and the synthetic intermediates **4–6** and **15–17** were tested for in vitro antifungal activity against *Candida albicans* C316 (table I). The aza-D-homosteroids were found to have low antifungal activity. However, the antifungal activities of the tetrahydroisoquinoline and octahydroisoquinoline intermediates were found to have a modest activity and consequently a further range of tetrahydroisoquinolines **7–14** and **27**, and octahydroquinolines **18–26** and **28** were synthesized and tested (table I). In general, it was found that the octahydroisoquinoline structures had better activity than the corresponding tetrahydroisoquinoline structures. However none of the structures tested were as active as amphotericin B (MIC = 0.008 μg/mL) or ketoconazole (MIC = 0.06 μg/mL).

The most active octahydroisoquinolines **15–17** and **21–26** and the tetrahydroisoquinolines **4** and **27** were chosen for further testing against a range of *Candida* strains as well as two *Aspergillus* strains. Most of these compounds possessed a broad spectrum of antifungal activity including *Aspergillus* spp (table II), with the best compound being the tetrahydroisoquinoline structure **4**. Three compounds **4**, **21** and **27** were investigated for fungicidal activity and all three were found to be fungicidal. For example, after 3 h incubation compound **27** at 100 μg/mL reduced the count of *C albicans* from 5 x 10^6 cfu/mL to less than 10^2 cfu/mL and at 10 μg/mL reduced the count to 9 x

10^2 cfu/mL while no reduction from the control was seen at 1 μg/mL.

These three compounds were subsequently tested for in vivo efficacy on mice infected with acute systemic *C albicans* and were found to give some in vivo protection (table III). However, no good dose responses were achieved and no compound at any dose gave complete protection. The compounds were not overtly toxic, since uninfected mice treated with the same dosing regime showed no gross signs of toxicity and no deaths occurred.

The pyridine structures **33–36** and the tetrahydropyridine structures **37–39** were also tested in vitro (table I) and found to have a modest antifungal activity. However, the antifungal activities of the disubstituted tetrahydroisoquinoline **29** and the disubstituted octahydroisoquinolines **29–32** were low and of little interest.

Discussion

The compounds described in this paper represent a series of novel heterocyclic structures that possess broad spectrum antifungal activity in vitro. These compounds were not grossly toxic in uninfected mice but some toxicity in infected animals may account for the lack of dose response seen in vivo. Variation in bioavailability or metabolism may also account for the variable in vivo results but no further work was carried out to investigate these parameters.

Experimental protocols

Chemistry

Analyses indicated by the symbols of the elements or functions were within ±0.4% of theoretical values. Chromatography was carried out on silica gel (Merck 9385) at normal pressures. Mps (uncorrected) were obtained on a Kofler block. IR spectra were recorded as thin films or as KBr discs on a Perkin Elmer 298 infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 90 and 200 MHz on JEOL EX90 and JEOL FX200 spectrometers respectively, using $CDCl_3$ as solvent; chemical shifts are given in ppm values relative to the signal of Me_4Si (δ 0.00) for ^{1}H NMR spectra or $CDCl_3$ (δ 77.0) for ^{13}C NMR spectra. The number of hydrogens attached to each carbon in the ^{13}C NMR spectra were determined by DEPT techniques. *J*-Values are given in Hz to the nearest 0.5 Hz. Low resolution and high resolution mass spectra were recorded on a VG Masslab 7070F spectrometer, with only molecular ions (M^+) and major peaks being reported. The progress of all reactions was followed by TLC analysis using Kieselgel 60 F_{254} plates which were visualized by UV fluorescence (λ_{max} = 254 nm), and by staining with iodine vapour. R_f values are quoted to the nearest 0.05. All solvents were distilled before use. Anhydrous diethyl ether was obtained by distillation from sodium/benzophenone ketal under nitrogen. Anhydrous dichloromethane was obtained by distillation from phosphorus pentaoxide and stored over molecular sieves (4 Å). Anhydrous acetone was obtained by storage of redistilled acetone over molecular sieves (4 Å). Triethylamine was distilled from potassium hydroxide pellets. Organic solutions were dried over magnesium sulfate and concentrated under reduced pressure at not more than 40 °C. The alkyl iodides required for the alkylation experiments were prepared by the procedure described previously [20].

Table I. Anti-*Candida* activity of heterocyclic structures.

Compound	*MIC*[a] *(μg/mL)*
Aza-D-homosteroids	
1	100
2	>125
3	62
Tetrahydroisoquinolines	
4	8
5	31
6	31
7	125
8	>125
9	31
10	>125
11	31
12	>125
13	>125
14	>125
27	16
29	>125
Pyridines	
33	31
34	16
35	31
36	31
Octahydroisoquinolines	
15	8
16	8
17	16
18	62
19	>125
20	62
21	31
22	16
23	8
24	16
25	16
26	16
28	31
30	125
31	125
32	62
Tetrahydropyridines	
37	31
38	31
39	31

[a]Minimum inhibitory concentration in μg/mL against *Candida albicans* C316.

Table II. Antifungal spectrum of some hydroisoquinolines.

Organism		*Minimum inhibitory concentration (µg/mL) against compound*											
		4	***15***	***16***	***17***	***21***	***22***	***23***	***24***	***25***	***26***	***27***	***34***
Candida albicans	C316	8	8	8	16	31	16	8	16	16	16	16	16
Candida albicans	1208E	8	4	16	31	31	62	31	62	31	125	31	16
Candida albicans	2005E	8	8	2	8	31	62	8	8	8	16	16	8
Candida albicans	2402E	8	8	4	31	31	62	16	62	31	16	31	16
Candida albicans	2381E	8	4	16	16	31	16	16	31	31	16	31	16
Candida glabrata	2375E	4	8	16	31	62	16	16	31	16	16	4	16
Candida glabrata	2376E	4	8	16	31	62	16	16	31	16	16	16	16
Candida krusei	2374E	8	4	8	16	16	16	16	31	31	16	62	31
Candida parapsilosis	2372E	2	4	8	31	16	16	8	8	16	8	31	16
Candida pseudotropicalis	2371E	8	2	8	8	16	8	4	8	8	4	4	8
Aspergillus flavus	C1150	4	31	31	62	62	125	31	62	31	62	62	31
Aspergillus fumigatus	4186E	4	31	16	31	31	125	31	62	31	62	31	16

Syntheses

5,6,7,8-Tetrahydroisoquinoline. Isoquinoline was reduced with hydrogen over a 5% palladium charcoal catalyst using trifluoroacetic acid as solvent by the method of Vierhapper and Eliel [27].

The syntheses of the following compounds have been described elsewhere [20]: (±)-[4aα, 4bβ, 10bβ, 12aβ]-9-chloro-2-methyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydronaphtho-[2,1-f]isoquinoline **1**, (±)-[4aα, 4bβ, 10bβ, 12aβ]-9-bromo-2-methyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydronaphtho[2,1-f]isoquinoline **2**, (±)-[4aα, 4bβ, 10bβ, 12aβ]-9-fluoro-2-methyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydronaphtho[2,1-f]isoquinoline **3**, (±)-5-(4'-chlorophenethyl)-5,6,7,8-tetrahydroisoquinoline **4**, (±)-5-(4'-bromophenethyl)-5,6,7,8-tetrahydroisoquinoline **5**, (±)-5-(4'-fluorophenethyl)-5,6,7,8-tetrahydroisoquinoline **6**, (±)-5-(4'-chlorophenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **15**, (±)-5-(4'-bromophenethyl)-2-methyl-1,2,3,-4,5,6,7,8-octahydroisoquinoline **16**, (±)-5-(4'-fluorophenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **17**, (±)-2-methyl-5-phenethyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **21**, and 5,5-bis-(4'-bromophenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **30**. The synthesis of 5,5-dibenzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **24** will be described elsewhere (Gibson A, Gray A, Patrick GL, manuscript in preparation).

*(±)-5-(4'-Methoxyphenethyl)-5,6,7,8-tetrahydroisoquinoline **7** and 5,5-bis-(4'-methoxyphenethyl)-5,6,7,8-tetrahydroisoquinoline **40**.* Potassium (2.47 g, 63.2 mmol) was added in portions to a solution of ammonia (400 mL) containing $Fe(NO_3)_3{\cdot}9H_2O$ (63 mg) to produce a blue solution. The solution was kept and occasionally swirled for 30 min, by which time the blue colour had dissipated. Freshly distilled 5,6,7,8-tetrahydroisoquinoline (8.40 g, 63.2 mmol) was added dropwise over a period of 10 min and the reaction mixture was kept for a further 10 min and occasionally swirled to give a red solution. 1-(2-iodoethyl)-4-methoxybenzene (16.6 g, 63.2 mmol) was added over a period of 25 min, with swirling of the mixture to give an orange solution, which was kept overnight to give a grey residue. The residue was taken up in ice-water and diethyl ether. The aqueous solution was extracted twice with diethyl ether then the organic extracts were combined and extracted twice with 5 M hydrochloric acid. The acidic extracts were washed with diethyl ether, neutralized to litmus paper with sodium hydrogen carbonate, then the mixture was basified with 10 M sodium hydroxide before extraction twice with diethyl ether. The organic extracts were dried, filtered, and concentrated to give an oil, which was distilled under reduced pressure to give 5,6,7,8-tetrahydroisoquinoline, and a higher boiling fraction identified as **7** which was obtained as an oil (8.66 g, 51%), bp: 158–160 °C/0.05 mmHg; *m/z*: 267, 266, 238, 237, 146, 135, 133, 132, 121, 108, 91 and 77; ^{1}H-NMR δ: 8.26 (2H, m, 1-H, 3-H), 7.09 (2H, d, *J* = 8.5 Hz, 2'-H), 6.98 (1H, d, *J* = 3.5 Hz, 4-H), 6.81 (2H, d, *J* = 8.5 Hz, 3'-H), 3.72 (3H, s, OMe), 2.90–2.45 (5H, m) and 2.10–1.60 (6H, m); ^{13}C-NMR δ: 157.6 (C, C-4'), 150.1 (CH, C-1), 149.5 (C, C-4a), 146.4 (CH, C-3), 133.7 (C, C-1'), 132.5 (C, C-8a), 128.9 (CH, C-2' and -5'), 122.7 (CH, C-4), 113.6 (CH, C-3' and -5'), 54.9 (CH_3, OMe), 37.7 (CH_2, CH_2Ar), 36.2 (CH, C-5), 32.1 (CH_2, C-8), 26.7 (CH_2), 26.3 (CH_2) and 19.5 (CH_2, C-7). Anal $C_{18}H_{21}NO$ (C, H, N).

The distillation residue was passed down a column of silica using ethyl acetate as eluent to give **40** as a gum (3.00 g, 12%);

m/z: 401, 400, 372, 280, 266, 146, 135, 121, 105, 91, 77 and 65; (found: M$^+$, 401.2357. $C_{27}H_{21}NO_2$ requires M, 401.2355); ^{1}H-NMR δ: 8.41 (1H, d, *J* = 5.5 Hz, 3-H), 8.38 (1H, s, 1-H), 7.21 (1H, d, *J* = 5.5 Hz, 4-H), 7.05 (4H, d, *J* = 8.5 Hz, 2'-H, 6'-H), 6.83 (4H, d, *J* = 8.5 Hz, 3'-H, 5'-H), 3.77 (6H, s, OMe), 2.76 (2H, m), 2.53 (2H, dt, *J* = 6.0 and 12.5 Hz, C*H*H'CH$_2$Ar), 2.33 (2H, dt, *J* = 5.0 and 13.0 Hz, CH*H'*CH$_2$Ar) and 2.10–1.80 (8H, m); ^{13}C-NMR δ: 157.8 (C, C-4'), 151.7 (C, C-4a), 150.6 (CH, C-1), 146.9 (CH, C-3), 134.3 (C, C-1'), 133.2 (C, C-8a), 128.9 (CH, C-2' and 6'), 121.2 (CH, C-4), 113.8 (CH, C-3' and -5'), 55.1 (CH_3, OMe), 44.4 (CH_2, CH_2Ar), 40.1 (C, C-5), 31.4 (CH_2, C-8), 29.8 (CH_2, CH_2CH_2Ar), 27.2 (CH_2, C-6) and 19.3 (CH_2, C-7). Anal $C_{27}H_{31}NO_2$ (C, H).

(±)-5-(3',4'-Dimethoxyphenethyl)-5,6,7,8-tetrahydroisoquinoline **8** *and 5,5-bis-(3',4'-dimethoxyphenethyl)-5,6,7,8-tetrahydroisoquinoline* **41**. Freshly distilled 5,6,7,8-tetrahydroisoquinoline (7.78 g, 58.5 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (2.29 g, 58.5 mmol) in ammonia (400 mL) in the presence of $Fe(NO_3)_3 \cdot 9H_2O$ (58 mg)]. The resulting carbanion was treated as above with 1,2-dimethoxy-4-(2-iodoethyl)-benzene (17.2 g, 58.2 mmol) and worked up as previously described. Distillation under reduced pressure gave unreacted 5,6,7,8-tetrahydroisoquinoline and a higher boiling fraction which was redistilled to give **8** as a yellow oil (10.3 g, 59%), bp: 220 °C/0.05 mmHg; *m/z*: 297, 296, 282, 251, 165, 164, 152, 151, 146, 137, 133, 132, 121, 117, 107, 91 and 77; ^{1}H-NMR δ: 8.28 (2H, m, 1-H, 3-H), 7.02 (1H, d, *J* = 5.0 Hz, 4-H), 6.80–6.70 (3H, m, Ar-H), 3.90 (3H, s, OMe), 3.80 (3H, s, OMe), 2.70–2.60 (5H, m) and 2.10–1.70 (6H, m) ; ^{13}C-NMR δ: 150.1 (CH, C-1), 149.4 (C, C-4a), 148.6 (C, C-3'), 147.6 (C, C-4'), 146.3 (CH, C-3), 134.3 (C, C-1'), 132.5 (C, C-8a), 122.6 (CH, C-4), 120.2 (CH, C-6'), 111.5 (CH, C-5'), 111.1 (CH, C-2'), 55.6 (2 x CH_3, OMe), 36.2 (CH, C-5), 32.1 (CH_2, C-8), 26.7.(CH_2), 26.3 (CH_2) and 19.4 (CH_2, C-7). Anal $C_{19}H_{23}NO_2$ (C, H, N).

The distillation residue was passed down a column of silica using ethyl acetate as eluent to give **41** as a gum (1.16 g, 4%); *m/z*: 461, 446, 297, 165, 152, 151, 146, 137, 121, 107, 91, 84 and 77; (found: M$^+$, 461.2565; $C_{29}H_{35}NO_4$ requires M, 461.2566); ^{1}H-NMR δ: 8.40 (1H, d, *J* = 5.5 Hz, 3-H), 8.36 (1H, s, 1-H), 7.23 (1H, d, *J* = 5.5 Hz, 4-H), 6.80–6.60 (6H, m, Ar-H), 3.83 (3H, s, OMe), 3.82 (3H, s, OMe), 3.79 (3H, s, OMe), 3.78 (3H, s, OMe), 2.76 (2H, m), 2.50 (2H, m), 2.31 (2H, m) and 2.15–1.75 (8H, m); ^{13}C-NMR δ: 151.0 (C, C-3'), 150.1 (CH, C-1), 148.3 (C, C-4a), 146.6 (C, C-4'), 146.4 (CH, C-3), 134.4 (C, C-1'), 132.7 (C, C-8a), 120.6 (CH, C-4), 119.4 (CH, C-6'), 111.2 (CH, C-5'), 110.9 (CH, C-2'), 55.2 (2 x CH_3, OMe), 55.1 (2 x CH_3, OMe), 43.7 (CH_2, CH_2Ar), 39.5 (C, C-5), 30.7 (CH_2, C-8), 29.8 (CH_2, CH_2CH_2Ar), 26.6 (CH_2, C-5) and 18.8 (CH_2, C-7).

(±)-5-(3'-Methoxyphenethyl)-5,6,7,8-tetrahydroisoquinoline **9** *and 5,5-bis-(3'-methoxyphenethyl)-5,6,7,8-tetrahydroisoquinoline* **29**. Freshly distilled 5,6,7,8-tetrahydroisoquinoline (9.80 g, 73.7 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (2.88 g, 73.7 mmol) in ammonia (480 mL) in the presence of $Fe(NO_3)_3 \cdot 9H_2O$ (74 mg)]. The resulting carbanion was treated as above with 1-(2-iodoethyl)-3-methoxybenzene (19.3 g, 73.7 mmol) and worked up as previously described. Distillation under reduced pressure gave unreacted 5,6,7,8-tetrahydroisoquinoline and a higher boiling fraction identified as **9** which was obtained as an oil (9.67 g, 49%), bp: 175–177 °C/ 0.05 mmHg; R_f 0.45 (EtOAc); *m/z*: 267, 266, 238, 146, 132, 122, 91 and 77; ^{1}H-NMR δ: 8.27 (1H, s, 1-H), 8.26 (1H, d, *J* = 4.0 Hz, 3-H), 7.19 (1H, t, *J* = 8.0 Hz, 5'-H), 7.00 (1H, d, *J* = 4.0 Hz, 4-H), 6.74 (1H, s, 2'-H), 6.74 (2H, m, 4'-H, 6'-H), 3.76 (3H, s, OMe), 2.90–2.50 (5H, m) and 2.10–1.60 (6H, m); ^{13}C-NMR δ: 159.5 (C, C-3'), 150.2 (CH, C-1), 149.4 (C, C-4a), 146.4 (CH, C-3), 143.4 (C, C-1'), 132.6 (C, C-8a), 129.2 (CH, C-5'), 122.7 (CH, C-4), 120.5 (CH, C-6'), 116.0 (CH, C-2'), 110.8 (CH, C-4'), 54.8 (CH_3, OMe), 37.3 (CH, CH_2Ar), 36.3 (CH, C-5), 33.1 (CH_2, C-8), 26.7 (CH_2), 26.3 (CH_2) and 19.5 (CH_2, C-7). Anal $C_{18}H_{21}NO$ (C, H).

A sample of the free base of **9** was converted into the hydrochloride salt. Anal $C_{18}H_{22}ClNO$ (C, H, N, Cl).

The distillation residue was passed down a column of silica using ethyl acetate as eluent to give **29** as an oil (1.68 g, 6%); *m/z*: 401, 400, 372, 280, 266, 146, 135, 122, 121, 105, 91, 78, 77 and 65; ^{1}H-NMR δ: 8.41 (2H, m, 1-H, 3-H), 7.21 (2H, t, *J* = 8.0 Hz, 5'-H), 7.21 (1H, m, 4-H), 6.79–6.68 (6H, m, Ar-H), 3.76 (6H, s, OMe), 2.75 (2H, m), 2.54 (2H, dt, *J* = 5.5 and 12.0 Hz, C*H*H'CH$_2$Ar), 2.32 (2H, dt, *J* = 5.5 and 13.0 Hz, CH*H'*CH$_2$Ar) and 2.14–1.81 (8H, m); ^{13}C-NMR δ: 159.6 (C, C-3'), 151.5 (C, C-4a), 150.5 (CH, C-1), 146.9 (CH, C-3'), 143.8 (C, C-1'), 133.0 (C, C-8a), 129.2 (CH, C-5'), 121.1 (CH, C-4), 120.4 (CH, C-6'), 114.0 (CH, C-2'), 110.9 (CH, C-4'), 54.9 (CH_3, OMe), 43.9 (CH_2, CH_2Ar), 40.0 (C, C-5), 31.2 (CH_2, C8), 30.7 (CH_2, CH_2CH_2Ar), 27.1 (CH_2, C-6), and 19.2 (CH_2, C-7). Anal $C_{27}H_{31}NO_2$ (C, H).

Table III. Therapeutic effect of **4**, **21** and **28** in mice with systemic *C albicans* infections.

Compound	*Route of dosing*	*Dose (mg/kg)*	*No survivors/ total no tested*
4	po	100	4/10
		25	4/10
		6.2	0/10
		1.6	3/10
	sc	100	2/10
		25	1/10
		6.2	3/10
		1.6	1/10
	Control	–	0/5
21	po	100	2/5
		25	2/5
		6.2	0/5
		1.6	0/5
	sc	100	0/5
		25	2/5
		6.2	2/5
		1.6	1/5
	Control	–	0/5
27	po	100	2/5
		25	1/5
		6.2	1/5
		1.6	1/5
	sc	100	1/5
		25	0/5
		6.2	2/5
		1.6	4/5
	Control	–	0/5

(±)-5-(2′-Chlorophenethyl)-5,6,7,8-tetrahydroisoquinoline ***10*** *and 5,5-bis-(2′-chlorophenethyl)-5,6,7,8-tetrahydroisoquinoline* ***42****.* Freshly distilled 5,6,7,8-tetrahydroisoquinoline (3.52 g, 26.5 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (1.04 g, 26.6 mmol) in ammonia (200 mL) in the presence of $Fe(NO_3)_3{\cdot}9H_2O$ (26 mg)]. The resulting carbanion was treated as above with 1-chloro-2-(2-iodoethyl)benzene (7.05 g, 26.5 mmol) and worked up as previously described. Distillation under reduced pressure gave unreacted 5,6,7,8-tetrahydroisoquinoline (1.48 g, 42% recovery), and a higher boiling fraction which was redistilled twice to give **10** as an oil (1.51 g, 5.57 mmol, 21%), bp: 148–152 °C/0.1 mmHg; R_f 0.4 (EtOAc); *m*/*z*: 273, 271, 236, 146, 133, 132, 131, 125, 117, 103, 91, 77 and 51; ^{1}H-NMR δ: 8.28 (1H, s, 1-H), 8.27 (1H, d, *J* = 5.5 Hz, 3-H), 7.33 (1H, dd, *J* = 8.0 and 1.5 Hz, 3'-H), 7.25–7.05 (3H, m, Ar-H), 7.04 (1H, d, *J* = 5.5 Hz, 4-H), 2.90–2.60 (5H, m) and 2.10–1.65 (6H, m); ^{13}C-NMR δ: 150.3 (CH, C-1), 149.3 (C, C-4a), 146.6 (CH, C-3), 139.5 (C, C-1'), 133.7 (C, C-2'), 132.7 (C, C-8a), 130.1 (CH, Ar), 129.4 (CH, Ar), 127.3 (CH, Ar), 126.7 (CH, Ar), 122.7 (CH, C-4), 36.8 (CH, C-5), 35.9 (CH_2, CH_2Ar), 31.2 (CH_2, C-8), 26.8 (CH_2), 26.5 (CH_2) and 19.7 (CH_2, C-7). Anal $C_{17}H_{18}ClN$ (C, H, Cl).

The distillation residue was passed down a column of silica using ethyl acetate as eluent to give **42** as an oil (0.47 g, 4%). Anal $C_{25}H_{25}Cl_2N$ (C, H).

(±)-5-(3′-Chlorophenethyl-5,6,7,8-tetrahydroisoquinoline ***11****.* Freshly distilled 5,6,7,8-tetrahydroisoquinoline (3.87 g, 29.1 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (1.14 g, 29.1 mmol) in ammonia (200 mL) in the presence of $Fe(NO_3)_3{\cdot}9H_2O$ (29 mg)]. The resulting carbanion was treated as above with 1-chloro-3-(2-iodoethyl)benzene (7.76 g, 29.1 mmol) and worked up as previously described. Distillation under reduced pressure gave unreacted 5,6,7,8-tetrahydroisoquinoline (1.34 g, 35% recovery), and a higher boiling fraction which was redistilled twice to give **11** as an oil (2.12 g, 27%), bp: 152–154 °C/0.1 mmHg; *m*/*z*: 273, 271, 146, 133, 132, 117, 103, 91, 77 and 57; (found: M^+, 271.1128; $C_{17}H_{18}$ ^{35}ClN requires M, 271.1128); ^{1}H-NMR δ: 8.27 (1H, s, 1-H), 8.27 (1H, d, *J* = 5.0 Hz, 3-H), 7.25–6.95 (4H, m, Ar-H), 6.98 (1H, d, *J* = 5.0 Hz, 4-H), 2.80–2.50 (5H, m) and 2.10–1.60 (6H, m); ^{13}C-NMR δ: 150.1 (CH, C-1), 148.9 (C, C-4a), 146.4 (CH, C-3), 143.7 (C, C-1'), 133.8 (C, C-3'), 133.5 (C, C-8a), 129.3 (CH, C-5'), 128.1 (CH, C-2'), 126.2 (CH, C-6'), 125.7 (CH, C-4'), 122.5 (CH, C-4), 37.1 (CH_2, CH_2Ar), 36.2 (CH, C-5), 32.6 (CH_2, C-8), 26.6 (CH_2), 26.2 (CH_2) and 19.4 (CH_2, C-7). Anal $C_{17}H_{18}ClN$ (C, H, Cl).

(±)-5-(2′,4′-Dichlorophenethyl)-5,6,7,8-tetrahydroisoquinoline 12 and 5,5-bis-(2′,4′-dichlorophenethyl)-5,6,7,8-tetrahydroisoquinoline ***43****.* Freshly distilled 5,6,7,8-tetrahydroisoquinoline (5.63 g, 42.3 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (1.66 g, 42.3 mmol) in ammonia (200 mL) in the presence of $Fe(NO_3)_3{\cdot}9H_2O$ (42 mg)]. The resulting carbanion was treated as above with 1,5-dichloro-2-(2-iodoethyl)benzene (12.7 g, 42.3 mmol) and worked up as previously described. Distillation under reduced pressure gave unreacted 5,6,7,8-tetrahydroisoquinoline (1.75 g, 31% recovery), and a higher boiling fraction which crystallized. The solid was triturated with diethyl ether and crystallized twice from ethyl acetate to give **12**; (2.12 g, 16%), mp: 87–99 °C; *m*/*z*: 307, 305, 270, 175, 173, 159, 146, 133, 132, 130, 117, 77 and 51; (found: M^+, 305.0737; $C_{17}H_{17}$ $^{35}Cl_2N$ requires M, 305.0738); ^{1}H-NMR δ: 8.29 (1H, s , 1-H), 8.28 (1H, d, *J* = 5.0 Hz, 3-H), 7.33 (1H, s, 3'-H), 7.13 (2H, s, Ar-H), 7.03 (1H, d, *J* = 5.0 Hz, 4-H), 2.90–2.60 (5H, m) and 2.05–1.65 (6H, m); ^{13}C-NMR δ: 150.4 (CH, C-1), 149.0 (C, C-4a), 146.6 (CH, C-3), 138.1 (C, C-1'), 134.3 (C, C-2'), 132.6 (C), 132.2 (C), 130.8 (CH, C-6'), 129.2 (CH, C-3'), 127.0 (CH, C-5'), 122.6 (CH, C-4) , 36.8 (CH, C-5), 35.7 (CH_2, CH_2Ar), 30.6 (CH_2, C-8), 26.9 (CH_2), 26.4 (CH_2) and 19.7 (CH_2, C-7). Anal $C_{17}H_{17}Cl_2N$ (C, H, N, Cl).

The mother liquors of the above crystallizations were purified by column chromatography and the product was distilled to give a further yield (1.24 g, 10%), bp: 181–183 °C/0.1 mmHg.

The distillation residue was passed down a column of silica using ethyl acetate as eluent to give **43** as an oil (0.81 g, 4%). Anal $C_{25}H_{23}Cl_4N$ (C, H, N).

(±)-5-(3′,4′-Dichlorophenethyl)-5,6,7,8-tetrahydroisoquinoline 13. Freshly distilled 5,6,7,8-tetrahydroisoquinoline (5.76 g, 43.3 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (1.69 g, 43.3 mmol) in ammonia (200 mL) in the presence of $Fe(NO_3)_3{\cdot}9H_2O$ (43 mg)]. The resulting carbanion was treated as above with 1,2-dichloro-4-(2-iodoethyl)benzene (13.0 g, 43.3 mmol) and worked up as previously described. Distillation under reduced pressure gave unreacted 5,6,7,8-tetrahydroisoquinoline (1.97 g, 34% recovery), and a higher boiling fraction which was distilled a further two times to give **13** as an oil (2.26 g, 17%), bp: 170–172 °C/0.05 mmHg; *m*/*z*: 307, 305, 159, 146, 133, 132, 130, 125, 117, 77 and 51; ^{1}H-NMR δ: 8.29 (1H, s, 1-H), 8.28 (1H, d, *J* = 5.0 Hz, 3-H), 7.32 (1H, d, *J* = 8.5 Hz, 5'-H), 7.27 (1H, d, *J* = 2.0 Hz, 2'-H), 7.02 (1H, d, *J* = 5.0 Hz, 4-H) 7.02 (1H, d, *J* = 8.5 Hz, 6'-H), 2.80–2.50 (5H, m) and 2.05–1.60 (6H, m); ^{13}C-NMR δ: 150.3 (CH, C-1), 148.9 (C, C-4a), 146.5 (CH, C-3), 142.1 (C, C-1'), 132.6 (C, C-8a), 132.1 (C, C-3'), 130.1 (CH), 130.0 (CH), 129.6 (C, C-4'), 127.6 (CH, C-6'), 122.5 (CH, C-4), 37.1 (CH_2, CH_2Ar), 36.3 (CH, C-5), 32.2 (CH_2, C-8), 26.8 (CH_2), 26.3 (CH_2) and 19.5 (CH_2, C-7). Anal $C_{17}H_{17}Cl_2N$ (C, H, Cl).

(±)-5-(2′,6′-Dichlorophenethyl)-5,6,7,8-tetrahydroisoquinoline ***14*** *and 5,5-bis-(2′,6′-dichlorophenethyl)-5,6,7,8-tetrahydroisoquinoline* ***44****.* Freshly distilled 5,6,7,8-tetrahydroisoquinoline (11.7 g, 88.2 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (3.45 g, 88.2 mmol) in ammonia (400 mL) in the presence of $Fe(NO_3)_3{\cdot}9H_2O$ (88 mg)]. The resulting carbanion was treated as above with 1,3-dichloro-2-(2-iodoethyl)benzene (26.5 g, 88.2 mmol) and worked up as previously described. Distillation under reduced pressure gave unreacted 5,6,7,8-tetrahydroisoquinoline (3.52 g, 30% recovery), and a higher boiling fraction containing two compounds. Purification by column chromatography using the eluent ethyl acetate/hexane, 2:1 gave **14** as a solid (2.23 g, 8%). A sample was crystallized from ethyl acetate/hexane, 2:1 for analysis, mp: 73–75 °C; R_f 0.45 (EtOAc); *m*/*z*: 307, 305, 270, 175, 173, 159, 146, 133, 132, 130, 117 and 77; (found: M^+, 305.0739; $C_{17}H_{17}$ $^{35}Cl_2N$ requires M, 305.0738); ^{1}H-NMR δ: 8.30 (1H, d, *J* = 5.0 Hz, 3-H), 8.29 (1H, s, 1-H), 7.24 (2H, d, *J* = 8.0 Hz, 3'-H, 5'-H), 7.10 (1H, d, *J* = 5.0 Hz, 4-H), 7.03 (1H, t, *J* = 8.0 Hz, 4'-H), 3.10–2.60 (5H, m) and 2.10–1.70 (6H, m); ^{13}C-NMR δ: 150.3 (CH, C-1), 149.0 (C, C-4a), 146.6 (CH, C-3), 137.9 (C, C-1'), 135.0 (C, C-2'), 132.7 (C, C-8a), 128.2 (CH), 127.8 (CH), 122.6 (CH, C-4), 37.2 (CH, C-5), 33.8 (CH_2, C-8), 29.0 (CH_2), 26.7 (CH_2), 26.5 (CH_2) and 19.8 (CH_2, C-7).

The distillation residue above was applied to a column of silica and eluted with ethyl acetate/hexane, 2:1, then ethyl acetate. The product was crystallized from ethyl acetate to give **44** (0.90 g, 2%), mp: 170–174 °C; ^{1}H-NMR δ: 8.40 (1H, d, J = 5.0 Hz, 3-H), 8.36 (1H, s, 1-H), 7.35 (1H, d, J = 5.0 Hz, 4-H), 7.26 (2H, d, J = 8.0 Hz, 3'-H, 5'-H), 7.25 (2H, d, J = 8.0 Hz, 3'-H, 5'-H), 7.01 (1H, t, J = 8.0 Hz, 4'-H), 7.00 (1H, t, J = 8.0 Hz, 4'-H), 2.95–2.50 (4H, m), 2.65 (2H, dt, J = 4.5 and 12.5 Hz, C*H*H'CH_2Ar), 2.10–1.80 (6H, m) and 1.78 (2H, dt, J = 4.5 and 12.5 Hz, CH*H'*CH_2Ar); ^{13}C-NMR δ: 150.8 (C, C-4a), 150.5 (CH, C-1), 147.0 (CH, C-3), 137.8 (C, C-1'), 135.0 (C, C-2'), 133.2 (C, C-8a), 128.0 (CH), 127.5 (CH), 121.7 (CH, C-4), 40.1 (C, C-5), 39.4 (CH_2, CH_2Ar), 30.5 (CH_2, C-8), 27.2 (CH_2), 26.7 (CH_2), and 19.6 (CH_2, C-7). Anal $C_{25}H_{23}Cl_4N$ (C, H, N).

*(±)-5-(4'-Methoxyphenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **18**.* The tetrahydroisoquinoline **7** (7.35 g, 27.5 mmol) was taken up in anhydrous diethyl ether (125 mL); the solution was treated with iodomethane (2.70 mL, 6.15 g, 43.0 mmol) and stirred at room temp for 7 days to give the methiodide salt as a precipitate (10.5 g, 93%).

The methiodide salt was taken up in ethanol (250 mL) without further purification and cooled in an ice bath. The solution was stirred and sodium borohydride (1.94 g, 51.4 mmol) was added in portions. The reaction solution was allowed to reach room temp and was stirred overnight. The solvent was removed under reduced pressure and the residue was taken up in a mixture of dilute aq sodium hydroxide. The phases were separated and the aqueous phase was extracted twice with diethyl ether. The organic extracts were combined and extracted twice with dilute hydrochloric acid. The acidic extracts were washed with diethyl ether, neutralized to litmus paper with sodium hydrogen carbonate, then basified with aq sodium hydroxide and extracted twice with diethyl ether. The organic extracts were dried, filtered, and concentrated to give a residue which was distilled under reduced pressure to give **18** as a slightly yellow oil (5.83 g, 74%), bp: 150–153 °C/0.04 mmHg; m/z: 285, 270, 176, 164, 162, 150, 134, 122, 121, 110, 91, 83, 77 and 44; ^{1}H-NMR δ: 7.08 (2H, d, J = 8.0 Hz, 2'-H), 6.80 (2H, d, J = 8.0 Hz, 3'-H), 3.75 (3H, s, OMe), 3.10–2.10 (11H, m), 2.30 (3H, s, NMe) and 2.10–1.40 (6H, m); ^{13}C-NMR δ: 157.4 (C, C-4'), 134.6 (C, C-1') 129.1 (C), 128.9 (CH, C-2' and -6'), 127.1 (C), 113.5 (CH, C-3' and -5'), 58.9 (CH_2, C-1), 54.9 (CH_3, OMe), 52.6 (CH_2, C-3), 45.6 (CH_3, NMe), 37.6 (CH, C-5), 34.3 (CH_2), 32.4 (CH_2), 28.7 (CH_2), 27.8 (CH_2), 27.4 (CH_2) and 19.9 (CH_2, C-7). Anal $C_{19}H_{27}NO$ (C, H).

*(±)-5-(3',4'-Dimethoxyphenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **19**.* The tetrahydroisoquinoline **8** (8.51 g, 28.7 mmol) was taken up in anhydrous diethyl ether (150 mL) and treated with iodomethane (2.50 mL, 5.69 g, 40.0 mmol) at room temperature for 3 days to give the methiodide salt as a precipitate (7.2 g, 57%). Treatment of the filtrate with a further portion of iodomethane gave a second crop (4.6 g, 37%).

The two crops were combined and taken up in ethanol (250 mL) and treated with sodium borohydride (2.04 g, 53.8 mmol) as described above to give **19** as an oil (7.10 g, 78.4%), bp: 161 °C/0.05 mmHg; m/z: 315, 300, 284, 176, 164, 151, 150, 149, 136, 134, 122, 110, 91, 83 and 64; ^{1}H-NMR δ: 6.82–6.65 (3H, m, Ar-H), 3.84 (3H, s, OMe), 3.81 (3H, s, OMe), 3.00–2.10 (m), 2.30 (3H, s, NMe) and 2.10–1.40 (m); ^{13}C-NMR δ: 148.4 (C, C-3') 146.6 (C, C-4'), 135.0 (C, C-1'), 128.7 (C), 126.8 (C), 119.6 (CH, C-6'), 111.3 (CH), 110.9 (CH), 58.6 (CH_2, C-1), 55.4 (CH_3, OMe), 55.3 (CH_3, OMe), 52.3 (CH_2, C-3), 45.4 (CH_3, NMe), 37.4 (CH, C-5), 33.9 (CH_2), 32.6 (CH_2), 28.4 (CH_2), 27.6 (CH_2), 27.2 (CH_2) and 19.7 (CH_2, C-7). Anal $C_{20}H_{29}NO_2$ (C, H, N).

*(±)-5-(3'-Methoxyphenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **20**.* The tetrahydroisoquinoline **9** (8.26 g, 30.9 mmol) was taken up in anhydrous diethyl ether (150 mL) and treated with iodomethane (2.70 mL, 6.15 g, 43.0 mmol) at room temperature for 7 days to give the methiodide salt as an oil (12.7 g, 100%).

The methiodide salt was taken up in ethanol (250 mL) and treated with sodium borohydride (2.35 g, 62.0 mmol) as described above to give **20** as a yellow oil (6.94 g, 78.8%), bp: 145–146 °C/0.05 mmHg; m/z: 285, 164, 150, 134, 122, 121, 110, 108, 93, 91, 83, 79, 77 and 44; ^{1}H-NMR δ: 7.16 (1H, t, J = 7.5 Hz, 5'-H), 6.77–6.67 (2H, m, 4'-H, 6'-H), 6.72 (1H, s, 2'-H), 3.75 (3H, s, OMe), 2.95–2.10 (11H, m), 2.30 (3H, s, NMe) and 2.10–1.40 (6H, m); ^{13}C-NMR δ: 159.4 (C, C-3'), 144.2 (C, C-1'), 128.9 (C), 128.9 (CH, C-5'), 127.2 (C), 120.5 (CH, C-6'), 113.9 (CH, C-2'), 110.6 (CH, C-4'), 58.9 (CH_2, C-1), 54.3 (CH_3, OMe), 52.6 (CH_2, C-3), 45.6 (CH_3, NMe), 37.6 (CH, C-5), 33.9 (CH_2), 33.3 (CH_2), 28.6 (CH_2), 27.8 (CH_2), 27.4 (CH_2) and 19.9 (CH_2, C-7). Anal $C_{19}H_{27}NO$ (C, H).

A sample of the free base was converted into the hydrochloride salt. Anal $C_{19}H_{28}ClNO$ (C, H, N, Cl).

*(±)-5-(2'-Chlorophenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **22**.* The tetrahydroisoquinoline **10** (1.26 g, 4.63 mmol) was taken up in anhydrous diethyl ether (25 mL) and treated with iodomethane (0.40 mL, 0.91 g, 6.42 mmol) at room temperature for 7 days to give the methiodide salt as a yellow precipitate (1.63 g, 85%).

The methiodide salt was taken up in ethanol (50 mL) and treated with sodium borohydride (0.30 g, 7.90 mmol) as described above to give **22** as an oil (0.77 g, 67%), bp: 140–144 °C/0.04 mmHg; R_f 0.40 [MeOH/AcOH, 5:1]; m/z: 291, 289, 164, 150, 122, 110, 108, 93, 91, 79, 77 and 44; (found: M$^+$, 289.1598; $C_{18}H_{24}{}^{35}ClN$ requires M, 289.1597); ^{1}H-NMR δ: 7.29 (1H, dd, J = 7.0 and 2.0 Hz, 3'-H), 7.25–7.00 (3H, m, Ar-H), 2.90–2.20 (m), 2.30 (3H, s, NMe) and 2.00–1.40 (m); ^{13}C-NMR δ: 140.2 (C, C-1'), 133.6 (C, C-2'), 129.9 (CH, C-6'), 129.1 (C), 128.9 (CH, C-3'), 127.2 (C), 126.8 (CH, C-4'), 126.4 (CH, C-5'), 58.8 (CH_2, C-1), 52.6 (CH_2, C-3), 45.6 (CH_3, NMe), 37.9 (CH, C-5), 32.4 (CH_2), 31.4 (CH_2), 28.6 (CH_2), 27.8 (CH_2), 27.3 (CH_2) and 19.8 (CH_2, C-7). Anal $C_{18}H_{24}ClN$ (Cl).

*(±)-5-(3'-Chlorophenethyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **23**.* The tetrahydroisoquinoline **11** (1.86 g, 6.85 mmol) was taken up in anhydrous diethyl ether (35 mL) and treated with iodomethane (0.60 mL, 1.36 g, 9.63 mmol) at room temperature for 7 days to give the methiodide salt as a yellow precipitate (2.69 g, 95%).

The methiodide salt was taken up in ethanol (50 mL) and treated with sodium borohydride (0.49 g, 13.0 mmol) as described above to give **23** as a pale yellow oil (2.69 g, 95%), bp: 144–148 °C/0.03 mmHg; m/z: 291, 289, 164, 150, 122, 110, 108, 93, 91, 79, 77 and 44; ^{1}H-NMR δ: 7.16–7.09 (2H, m, 4'-H, 5'-H), 7.12 (1H, s, 2'-H), 7.02 (1H, d, J = 6.5 Hz, 6'-H), 2.90–2.25 (m), 2.30 (3H, s, NMe), 2.00–1.65 (m) and 1.65–1.46 (m); ^{13}C-NMR δ: 144.7 (C, C-1'), 133.8 (C, C-3'), 129.3 (CH, C-5'), 128.7 (C), 128.2 (CH, C-2'), 127.4 (C), 126.3 (CH, C-6'), 125.6 (CH, C-4'), 58.9 (CH_2, C-1), 52.6 (CH_2, C-3), 45.6 (CH_3, NMe), 37.6 (CH, C-5), 33.9 (CH_2), 32.9 (CH_2), 28.6 (CH_2), 27.8 (CH_2), 27.4 (CH_2) and 19.9 (CH_2, C-7). Anal $C_{18}H_{24}ClN$ (C, H, Cl).

(±)-5-(2',4'-Dichlorophenethyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline ***24****.* The tetrahydroisoquinoline **12** (2.60 g, 8.51 mmol) was taken up in anhydrous diethyl ether (45 mL) and treated with iodomethane (0.80 mL, 1.82 g, 12.8 mmol) at room temperature for 7 days to give the methiodide salt as a yellow precipitate (3.32 g, 87%).

The methiodide salt was taken up in ethanol (100 mL) and treated with sodium borohydride (0.56 g, 14.8 mmol) as described above to give **24** as a yellow oil (0.95 g, 40%), bp: 148–150 °C/0.04 mmHg; R_f 0.40 [MeOH/AcOH, 5:1]; *m/z*: 325, 323, 164, 150, 122, 110, 108, 93, 91, 79, 77 and 44; (found: M^+, 323.1206; $C_{18}H_{23}{}^{35}Cl_2N$ requires M, 323.1208); ^1H-NMR δ: 7.31 (1H, s, 3'-H), 7.11 (2H, s, 5'-H, 6'-H), 2.90–2.20 (m) 2.30 (3H, s, NMe) and 2.00–1.40 (m); ^{13}C-NMR δ: 138.9 (C, C-1'), 134.3 (C, C-2'), 131.8 (C, C-4'), 130.7 (CH, C-6'), 129.0 (CH, C-3'), 128.7 (C), 127.5 (C), 126.8 (CH, C-5'), 58.9 (CH_2, C-1), 52.6 (CH_2, C-3), 45.6 (CH_3, NMe), 37.9 (CH, C-5), 32.4 (CH_2), 30.9 (CH_2), 28.7 (CH_2), 27.8 (CH_2), 27.4 (CH_2) and 19.9 (CH_2, C-7). Anal $C_{18}H_{23}Cl_2N$ (Cl).

(±)-5-(3',4'-Dichlorophenethyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline ***25****.* The tetrahydroisoquinoline **13** (1.48 g, 4.84 mmol) was taken up in anhydrous diethyl ether (25 mL) and treated with iodomethane (0.40 mL, 0.91 g, 6.42 mmol) at room temperature for 7 days to give the methiodide salt as a yellow precipitate (2.08 g, 72%).

The methiodide salt was taken up in ethanol (50 mL) and treated with sodium borohydride (0.35 g, 9.30 mmol) as described above to give **25** as a yellow oil (1.44 g, 95%), bp: 154–156 °C/0.04 mmHg; *m/z*: 325, 323, 164, 150, 122, 110, 108, 93, 91, 79, 77 and 44; (found: M^+, 323.1206; $C_{18}H_{23}Cl_2N$ requires M, 323.1208); ^1H-NMR δ: 7.28 (1H, d, *J* = 8.0 Hz, 5'-H), 7.24 (1H, d, *J* = 2.0 Hz , 2'-H), 6.98 (1H, dd, *J* = 8.5 and 2.0 Hz, 6'-H), 2.90–2.20 (m), 2.30 (3H, s, NMe), 2.00–1.60 (m) and 1.60–1.40 (m); ^{13}C-NMR δ: 142.8 (C, C-1'), 131.8 (C, C-3'), 129.9 (CH, C-2'), 129.9 (CH, C-5'), 129.1 (C, C-4'), 128.4 (C), 127.5 (CH, C-6'), 58.8 (CH_2, C-1), 52.5 (CH_2, C-3), 45.5 (CH_3, NMe), 37.5 (CH, C-5), 33.7 (CH_2), 32.3 (CH_2), 28.6 (CH_2), 27.7 (CH_2), 27.4 (CH_2) and 19.9 (CH_2, C-7). Anal $C_{18}H_{23}Cl_2N$ (C, H, Cl).

(±)-5-(2',6'-Dichlorophenethyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline ***26****.* The tetrahydroisoquinoline **14** (1.43 g, 4.66 mmol) was taken up in anhydrous diethyl ether (25 mL) and treated with iodomethane (0.40 mL, 0.91 g, 6.42 mmol) at room temperature for 7 days to give the methiodide salt as a yellow precipitate (2.00 g, 96%).

The methiodide salt was taken up in ethanol (50 mL) and treated with sodium borohydride (0.34 g, 8.93 mmol) as described above to give **26** as a yellow oil (1.08 g, 75%), bp: 146–148 °C/0.025 mmHg; *m/z*: 325, 323, 164, 150, 122, 110, 108, 96, 93, 91, 79, 77 and 44; (found: M^+, 323.1206; $C_{18}H_{23}Cl_2N$ requires M, 323.1208); ^1H-NMR δ: 7.23 (2H, d, *J* = 8.0 Hz, 3'-H, 5'-H), 7.01 (1H, t, *J* = 8.0 Hz, 4'-H), 2.99 (dt, *J* = 12.5 and 5.5 Hz), 2.83 (dd, *J* = 12.0 and 5.0 Hz), 2.72 (brd, *J* = 7.5 Hz), 2.55–2.35 (m), 2.31 (3H, s, NMe) and 2.20–1.50 (m); ^{13}C-NMR δ: 138.7 (C, C-1'), 135.0 (C, C-2' and -6'), 128.9 (C), 127.9 (CH, Ar-H), 127.3 (C), 127.1 (CH, Ar-H), 58.9 (CH_2, C-1), 52.7 (CH_2, Ar-H), 45.7 (CH_3, NMe), 38.3 (CH, C-5), 30.7 (CH_2), 29.5 (CH_2), 28.6 (CH_2), 27.9 (CH_2), 27.3 (CH_2) and 19.9 (CH_2, C-7). Anal $C_{18}H_{23}Cl_2N$ (C, H, Cl).

5-Benzyl-5,6,7,8-tetrahydroisoquinoline ***27****.* Freshly distilled 5,6,7,8-tetrahydroisoquinoline (9.2 , 69.2 mmol) was treated as previously described with an ammoniacal solution of potassium amide [prepared from potassium (3.52 g, 89.9 mmol) in ammonia (500 mL) in the presence of $Fe(NO_3)_3 \cdot 9H_2O$ (70 mg)]. The resulting carbanion was treated as above with benzyl chloride (8.67 g, 68.5 mmol) and worked up as previously described. Distillation under reduced pressure gave **27** as a clear oil (7.67 g, 50%); bp 128–130 °C/0.05mmHg; R_f 0.50 (EtOAc), 0.35 ($CHCl_3$/MeOH, 10:1); (found: M^+ 233.1360; $C_{16}H_{17}N$ requires M, 233.1361); ν_{max} (film)/cm^{-1} 2940s, 1593m, 1496m, 1455m, 1415m, 755m and 705s; *m/z* 223, 132, 117, 104, 91, 77, 65 and 51; ^1H-NMR δ (90 MHz): 8.30 (1 H, s, 1-H), 8.25 (1 H, d, *J* = 5.0 Hz, 3-H), 7.16–6.85 (5 H, m, Ar-H), 6.98 (1 H, d, *J* = 5.0 Hz, 4-H), 3.20–2.80 (2 H, m), 2.80–2.50 (3 H, m) and 2.00–1.80 (4 H, m); ^{13}C-NMR δ (90 MHz): 150.5 (CH, C-1), 148.9 (C, C-4a), 146.5 (CH, C-3), 139.9 (C, C-1'), 132.7 (C, C-8a), 129.1 (CH, C-2'), 128.4 (CH, C-3'), 126.2 (CH, C-4'), 123.1 (CH, C-4), 42.4 (CH_2, $ArCH_2$), 38.8 (CH, C-5), 26.5 (CH_2), 26.4 (CH_2) and 19.2 (CH_2, C-7).

5-Benzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline ***28****.* The tetrahydroisoquinoline **27** (7.67 g, 34.4 mmol) was taken up in anhydrous diethyl ether (125 mL); the solution was treated with iodomethane (5.05 g, 2.20 mL, 35.6 mmol) and stirred for 7 days to give the methiodide salt as a precipitate (9.44 g, 75%).

The methiodide salt (5.0 g, 13.7 mmol) was taken up in ethanol (100 mL), and the mixture was cooled in an ice bath and treated with sodium borohydride (1.06 g, 28.0 mmol) as described above to give **28** as an oil (2.77 g, 11.49 mmol, 84%); bp 124.0–126.0 °C/0.06 mmHg; R_f 0.25 ($CHCl_3$/MeOH, 10:1); (found: C, 84.43; H, 9.72; N, 5.78% M^+, 241.1667; $C_{17}H_{23}N$ requires C, 84.59; H, 9.60; N, 5.80% M, 241.1830); *m/z* 241, 150, 122, 107, 91, 79, 77 and 65; ν_{max} (film)/cm^{-1} 2950, 2850, 2795, 1610, 1500, 1460 and 1395; ^1H-NMR δ (200 MHz): 7.30–7.09 (5 H, m, Ar-H), 2.82 (1 H, brd, *J* = 13.5 Hz, 1-H'), 2.66 (1 H, brd, *J* = 13.5 Hz, 1-H''), 2.34 (3 H, s, NMe) and 2.60–1.30 (m); ^{13}C-NMR δ (90 MHz): 141.7 (C, C-1'), 129.2 (C, C-4a), 129.1 (CH, C-2' and -6'), 128.2 (CH, C-3' and -5'), 127.7 (C, C-8a), 125.7 (CH, C-4'), 59.0 (CH_2, C-1), 52.8 (CH_2, C-2), 45.8 (CH_3, NCH_3), 40.3 (CH, C-5), 39.1 (CH_2, $PhCH_2$), 29.1 (CH_2), 28.1 (CH_2), 27.0 (CH_2) and 19.3 (CH_2, C-7). Anal $C_{17}H_{23}N$ (C, H, N).

5,5-Bis-(3',4'-dimethoxyphenethyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline ***31****.* 5,5-Bis-(3',4'-dimethoxyphenethyl)-5,6,7,8-tetrahydroisoquinoline **41** (1.16 g, 2.52 mmol) was taken up in anhydrous diethyl ether (10 mL) and treated with iodomethane (0.73 mL, 1.67 g, 11.7 mmol) at room temperature for 7 days to give the methiodide salt as a precipitate (1.16 g, 76%).

The methiodide salt was taken up in ethanol (25 mL) and treated with sodium borohydride (0.14 g, 3.83 mmol) as described above. Final purification was carried out by column chromatography using methanol/acetic acid, 5:1 as eluent to give **31** as an oil (786 g, 85%); R_f 0.42 (MeOH/AcOH, 5:1); *m/z*: 479, 464, 448, 328, 314, 164, 162, 151, 136, 122, 110, 91, 79 and 77; (found M^+, 479.3038; $C_{30}H_{41}NO_4$ requires M, 479.3036); ^1H-NMR δ: 6.74–6.68 (6H, m, Ar-H), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.81 (3H, s, OMe), 3.81 (3H, s, OMe), 2.82 (brs), 2.65–2.35 (m), 2.33 (3H, s, NMe), 2.20 (brs) and 2.00–1.60 (m); ^{13}C-NMR δ: 148.5 (C, C-3'), 146.7 (C, C-4'), 135.6 (C, C-1'), 130.2 (C), 129.0 (C), 119.6 (CH, C-6'), 111.5 (CH, Ar-H), 111.1 (CH, Ar-H), 59.1 (CH_2, C-1), 55.5 (CH_3, OMe), 55.5 (CH_3, OMe), 52.7 (CH_2, C-3), 45.5 (CH_3, NMe), 41.3 (CH_2, CH_2Ar), 39.2 (C, C-5), 31.0 (CH_2), 30.2 (CH_2), 24.8 (CH_2) and 19.2 (CH_2, C-7).

4-[2-(4-Phenylbutyl)]pyridine ***33***. Freshly distilled 4-ethylpyridine (10.0 g, 93.3 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (3.64 g, 93.3 mmol) in ammonia (150 mL) in the presence of $Fe(NO_3)_3\cdot 9H_2O$ (93 mg)]. The resulting carbanion was treated as above with a solution of phenethyl bromide (17.62 g, 93.3 mmol) in toluene (20 mL) and worked up as previously described. Distillation under reduced pressure gave unreacted 4-ethylpyridine and a higher boiling fraction identified as **33** (7.57 g, 38%), bp: 136 °C/0.08 mmHg; R_f 0.4 (EtOAc); *m/z*: 211, 120, 107, 105, 92, 91, 79, 77, 65 and 51; ^{1}H-NMR δ: 8.49 (2H, dd, *J* = 5.5 and 1.5 Hz, 2- and 6-H), 7.25–6.95 (7H, m, Ar-H, 3- and 5-H), 2.65 (1H, q, *J* = 7.0 Hz, $CH(CH_3)$), 2.47 (2H, t, *J* = 8.0 Hz, CH_2 Ph), 1.87 (2H, q, *J* = 8.0 Hz, CH_2CH_2Ph) and 1.22 (3H, d, *J* = 7.0 Hz, $CHCH_3$); ^{13}C-NMR δ: 155.6 (C, C-4), 149.5 (CH, C-2 and -6), 141.4 (C, C-1'), 128.0 (CH, Ar-H), 127.9 (CH, Ar-H), 125.5 (CH, C-4'), 122.2 (CH, C-3 and -5), 38.7 (CH_2, CH_2Ph), 38.5 (CH, $CHCH_3$), 33.3 (CH_2, CH_2CH_2Ph) and 21.2 (CH_3, $CHCH_3$). Anal $C_{15}H_{17}N$ (C, H).

3-Methyl-4-(3-phenylpropyl)pyridine ***34***. Freshly distilled 3,4-dimethylpyridine (15.3 g, 142 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (5.56 g, 142 mmol) in ammonia (228 mL) in the presence of $Fe(NO_3)_3\cdot 9H_2O$ (142 mg)]. The resulting carbanion was treated as above with a solution of phenethyl bromide (26.34 g, 142 mmol) in toluene (25 mL) and worked up as previously described. Distillation under reduced pressure gave unreacted dimethylpyridine and a higher boiling fraction identified as **34** (4.64 g, 15%), bp: 136–138 °C/0.09 mmHg; R_f 0.6 (EtOAc); *m/z*: 211, 120, 107, 105, 92, 91, 77, 65 and 51; ^{1}H-NMR δ: 8.31 (1H, d, *J* = 5.0 Hz, 6-H), 8.30 (1H, s, 2-H), 7.40–7.10 (5H, m, Ar-H), 6.98 (1H, d, *J* = 5.0 Hz, 5-H), 2.65 (2H, t, *J* = 8.0 Hz), 2.55 (2H, t, *J* = 8.0 Hz), 2.17 (3H, s, CH_3) and 1.87 (2H, quintet, *J* = 8.0 Hz, CH_2CH_2Ph); ^{13} C-NMR δ: 150.4 (CH, C-2), 148.9 (C, C-4), 147.2 (CH, C-6), 141.3 (C, C-1'), 131.2 (C, C-3), 128.1 (CH, C-2' and -6'), 128.1 (CH, C-3' and -5'), 125.7 (CH, C-4'), 123.0 (CH, C-5), 55.3 (CH_2, CH_2Ph), 31.6 (CH_2), 30.4 (CH_2) and 15.7 (CH_3). Anal $C_{15}H_{17}N$ (C, H).

4-[3-(4'-Bromophenyl)propyl]-3-methylpyridine ***35***. Freshly distilled 3,4-lutidine (7.71 g, 72.0 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (2.80 g, 72.0 mmol) in ammonia (400 mL) in the presence of $Fe(NO_3)_3\cdot 9H_2O$ (72 mg)]. The resulting carbanion was treated as above with 1-bromo-4-(2-iodoethyl)benzene (10.6 g, 34.0 mmol) and worked up as previously described. Distillation under reduced pressure gave unreacted 5,6,7,8-tetrahydroisoquinoline, and a higher boiling fraction which was treated to column chromatography using the eluent ethyl acetate/hexane, 1:1. The major product was applied to a second column (eluent: diethyl ether/hexane, 3:1) to give **35** as a liquid (0.79 g, 4%), bp: 139–141 °C/0.02 mmHg; *m/z*: 291, 289, 171, 169, 120, 107, 104, 91, 90, 77, 65 and 51; (found: M$^+$, 289.0467, $C_{15}H_{16}BrN$ requires M, 289.0466); ^{1}H-NMR δ: 8.33 (1H, d, *J* = 5.0 Hz, 6-H), 8.32 (1H, s, 2-H), 7.39 (2H, d, *J* = 8.0 Hz, 3'- and 5'-H), 7.04 (2H, d, *J* = 8.0 Hz, 2'- and 6'-H), 6.99 (1H, d, *J* = 5.0 Hz, 5-H), 2.62 (2H, t, *J* = 7.5 Hz), 2.57 (2H, t, *J* = 7.5 Hz), 2.20 (3H, s, CH_3) and 1.86 (2H, quintet, *J* = 7.5 Hz, CH_2CH_2Ar); ^{13}C-NMR δ: 150.5 (CH, C-1), 148.7 (C, C-4), 147.4 (CH, C-6), 140.4 (C, C-1'), 131.3 (C, C-3), 131.3 (CH, C-3' and -5'), 129.9 (CH, C-2' and -6'), 123.1 (CH, C-5), 119.6 (C, C-4'), 34.8 (CH_2), 31.6 (CH_2), 30.2 (CH_2) and 15.8 (CH_3). Anal $C_{15}H_{16}BrN$ (C, H, Br).

4-[3-(4'-Fluorophenyl)propyl]-3-methylpyridine ***36*** *and 4-{3-[1,5-bis-(4'-fluorophenyl)pentyl]}-3-methylpyridine* ***45***. Freshly distilled 3,4-lutidine (16.0 g, 150 mmol) was treated as described above with an ammoniacal solution of potassium amide [prepared from potassium (5.84 g, 150 mmol) in ammonia (400 mL) in the presence of $Fe(NO_3)_3\cdot 9H_2O$ (150 mg)]. The resulting carbanion was treated as above with 1-fluoro-4-(2-iodoethyl)benzene (18.7 g, 74.8 mmol) and worked up as previously described. Distillation under reduced pressure gave unreacted 5,6,7,8-tetrahydroisoquinoline and a higher boiling fraction which was purified by column chromatography using ethyl acetate/hexane eluent of increasing polarity, then redistilled under reduced pressure to give **36** as a liquid (6.86 g, 40%), bp: 112–113 °C/0.02 mmHg; *m/z*: 229, 123, 120, 109, 107, 83, 77, 65 and 51; (found: M$^+$, 229.1266; $C_{15}H_{16}FN$ requires M, 229.1267); ^{1}H-NMR δ: 8.33 (1H, d, *J* = 5.0 Hz, 6-H), 8.32 (1H, s, 2-H), 7.20–6.95 (5H, m, 5-H and Ar-H), 2.64 (2H, t, *J* = 8.0 Hz), 2.57 (2H, t, *J* = 8.0 Hz), 2.20 (3H, s) and 1.86 (2H, quintet, *J* = 8.0 Hz, $CH_2CH_2CH_2$); ^{13} C-NMR δ: 161.1 (C, d, *J* = 242.0 Hz, C-4'), 150.6 (CH, C-2), 148.8 (C, C-4), 147.4 (CH, C-6), 137.1 (C, d, *J* = 3.0 Hz, C-1'), 131.3 (C, C-3), 129.6 (CH, d, *J* = 8.0 Hz, C-2' and -6'), 123.1 (CH, C-5), 114.9 (CH, d, *J* = 20.5 Hz, C-3' and -5'), 34.5 (CH_2, CH_2Ar), 31.6 (CH_2), 30.6 (CH_2) and 15.8 (CH_3). Anal $C_{15}H_{16}FN$ (C, H, F).

The distillation residue was applied to a column of silica and eluted with diethyl ether/hexane, 3:1, followed by diethyl ether to give **45** as an oil, (3.30 g, 13%); *m/z*: 351, 242, 229, 123, 120, 109, 107, 103, 83 and 77; (found: M$^+$, 351.1800; $C_{23}H_{23}F_2N$ requires M, 351.1799); ^{1}H-NMR δ: 8.44 (1H, d, *J* = 5.0 Hz, 6-H), 8.37 (1H, s, 2-H), 7.13 (1H, d, *J* = 5.0 Hz, 5-H), 7.05–6.80 (8H, m, Ar-H), 2.83 (1H, m, $CHCH_2CH_2$), 2.43 (4H, t, *J* = 8.0 Hz, CH_2CH_2Ar), 2.05 (3H, s, CH_3) and 2.15–1.80 (4H, m, $CHCH_2CH_2$); ^{13}C-NMR δ: 161.2 (C, d, *J* = 243.0 Hz, C-4'), 152.0 (CH, C-4), 151.1 (CH, C-2), 147.9 (CH, C-6), 137.1 (C, d, *J* = 3.0 Hz, C-1'), 131.9 (C, C-3), 129.5 (CH, d, *J* = 7.0 Hz, C-2' and -6'), 120.4 (CH, C-5), 115.0 (CH, d, *J* = 20.0 Hz, C-3' and -5'), 38.4 (CH, $CHCH_2CH_2$), 37.4 (CH_2, CH_2Ar), 32.4 (CH_2, $CHCH_2$) and 16.3 (CH_3). Anal $C_{23}H_{23}F_2N$ (C, H, F).

1-Methyl-4-[2-(4-phenylbutyl]-1,2,5,6-tetrahydropyridine ***37***. The pyridine **33** (7.09 g, 33.6 mmol) was taken up in anhydrous diethyl ether (125 mL) and treated with iodomethane (2.09 mL, 4.76 g, 33.6 mmol) at room temperature for 7 days to give the methiodide salt as an oily precipitate. Treatment of the filtrate with a further portion of iodomethane gave a further yield. The two crops were combined (9.91 g, 84%).

The methiodide salt was taken up in ethanol (125 mL) and treated with sodium borohydride (2.13 g, 56.2 mmol) as described previously to give **37** as a clear oil (4.21 g, 65%), bp: 104–106 °C/0.04 mmHg; R_f 0.4 (MeOH/AcOH, 5:1); *m/z*: 229, 228, 214, 157, 136, 124, 97, 96, 91, 82 and 67. Anal $C_{16}H_{23}N$ (C, H).

1,3-Dimethyl-4-(3-phenylpropyl)-1,2,5,6-tetrahydropyridine ***38***. The pyridine **34** (4.30 g, 20.4 mmol) was taken up in anhydrous diethyl ether (50 mL) and treated with iodomethane (1.45 mL, 3.30 g, 23.2 mmol) at room temperature for 7 days to give the methiodide salt as an oily precipitate (6.49 g, 18.4 mmol, 90%).

The methiodide salt (6.02 g, 17.1 mmol) was taken up in ethanol (250 mL) and treated with sodium borohydride (1.29 g, 34.2 mmol) as described previously to give **38** as a slightly yellow oil (2.98 g, 76%), bp: 95 °C/0.04 mmHg; R_f 0.4 (MeOH/AcOH, 5:1); *m/z*: 229, 214, 124, 110, 104, 91, and 82;

^{1}H-NMR δ: 7.35–7.10 (5H, m, Ar-H), 2.78 (2H, brs, 2-H_2), 2.60 (2H, t, J = 8.0 Hz, CH_2Ph), 2.47 (2H, t, J = 5.5 Hz, 6-H_2), 2.32 (3H, s, NMe), 2.20–2.10 (4H, m), 1.70 (2H, quintet, J = 8.0 Hz, CH_2CH_2Ph) and 1.56 (3H, s, =CCH_3); ^{13}C-NMR δ: 141.8 (C, C-1'), 128.2 (CH), 128.1 (CH), 127.8 (C, C-4), 125.5 (CH, C-4'), 124.4 (C, C-3), 59.7 (CH_2, C-2), 52.7 (CH_2, C-6), 45.6 (CH_3, NMe), 35.7 (CH_2, CH_2Ph), 31.6 (CH_2), 30.0 (CH_2), 29.6 (CH_2) and 16.2 (CH_3, =CCH_3). Anal $C_{16}H_{23}N$ (C, H).

4-[3-(4'-Fluorophenyl)propyl]-1,3-dimethyl-1,2,5,6-tetrahydropyridine ***39***. The pyridine **36** (5.00 g, 21.8 mmol) was taken up in anhydrous diethyl ether (125 mL) and treated with iodomethane (2.00 mL, 4.56 g, 32.1 mmol) at room temperature for 7 days to give the methiodide salt as a precipitate (6.30 g, 78%).

The methiodide salt (6.30 g, 17 mmol) was taken up in ethanol (100 mL) and treated with sodium borohydride (1.29 g, 34.2 mmol) as described previously to give an oil which was distilled under reduced pressure to give **39** as a clear oil (3.71 g, 88%), bp: 113–116 °C/0.03 mmHg; m/z: 247, 232, 124, 122, 110, 96, 82, 67 and 44; (found: M^+, 247.1737; $C_{16}H_{22}FN$ requires M, 247.1736); ^{1}H-NMR δ: 7.10 (2H, dd, J = 8.5 and 5.5 Hz, 2'- and 6'-H), 6.92 (2H, t, J = 9.0 Hz, 3'- and 5'-H), 2.75 (2H, brs, 2-H), 2.55 (2H, t, J = 7.5 Hz, CH_2Ar), 2.44 (2H, t, J = 6.0 Hz, 6-H_2), 2.30 (3H, s, NMe), 2.20–2.00 (4H, m), 1.66 (2H, quintet, J = 7.5 Hz, $CH_2CH_2CH_2$) and 1.53 (3H, s, =CCH_3); ^{13}C-NMR δ: 160.9 (C, d, J = 242.5 Hz, C-4'), 137.8 (C) (d, J = 3.0 Hz, C-1'), 129.4 (CH, d, J = 7.0 Hz, C-2' and -6'), 127.6 (C, C-3), 124.3 (C, C-4), 114.7 (CH, d, J = 22.0 Hz, C-3' and -5'), 59.7 (CH_2, C-2), 52.5 (CH_2, C-6), 45.5 (CH_3, NMe), 34.7 (CH_2, CH_2Ar), 31.7 (CH_2), 29.8 (CH_2), 29.4 (CH_2) and 16.1 (CH_3, =CCH_3). Anal $C_{16}H_{22}FN$ (C, H, F).

Pharmacology

In vitro antifungal activity was tested on fungi obtained from the Glaxo Culture Collection which were previously isolated from clinical infections. Minimum inhibitory concentrations (MICs) were determined by the agar dilution method with Iso-Sensitest agar as previously described [28]. To determine fungicidal or fungistatic inhibition, *C albicans* C316 was inoculated into Iso-Sensitest broth at 5 x 10^6 colony forming units/mL with compounds at a range of 100 to 0.1 µl/mL. After incubation with shaking at 37 °C, samples were removed at time intervals up to 24 h and plated onto Iso-Sensitest agar.

In vivo efficacy of compounds was assessed in mice with acute systemic *C albicans* infections as previously described [28]. Mice were infected intraperitoneally with an inoculum containing 2 x 10^7 cfu in 0.5 mL isosensitest broth containing 1% Yestamin as a virulence enhancer. Test compounds were weighed into tissue grinders, suspended in 0.5% sodium carboxymethyl cellulose in 0.85% saline to give 10 mg/mL and further diluted by three four-fold steps. These preparations were used for both po and sc administrations. Therapy in the dose range 100–1.6 mg/kg was given at 1, 3 and 5 h post infection to both infected and uninfected mice.

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