Synthesis and Hypocholesterolemic Activity of Some *N*-Diphenylmethylpiperazine Derivatives[+)]

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The synthesis and preliminary assays as hypocholesterolemic agents of five *N*-diphenylmethylpiperazines are described. The evaluations were carried out in hypercholesterolemic mice and two of these compounds were more effective than bezafibrate in the test employed. The di-*p*-chlorosubstituted compounds showed higher activity than their corresponding dechlorinated analogs.

Synthese und hypocholesterolemische Aktivität von einigen *N*-Diphenylmethylpiperazin-Derivaten

Fünf *N*-Diphenylmethylpiperazine wurden synthetisiert und ihre hypocholesterolemische Aktivität an hypercholesterolaemischen Mäusen untersucht. Zwei Substanzen zeigten eine höhere Aktivität als Bezafibrat. Die di-*p*-chlorosubstituierten Verbindungen waren aktiver als die dechlorierten Analoga.

In the last three decades a large number of *N*-diphenylmethylpiperazine derivatives **1** with useful pharmacological properties has been reported. These activities exhibit a wide variation depending mainly upon substitution on the second piperazinic nitrogen. Among others, compounds with antibacterial[1)], anticonvulsant[2)], hypocholesterolemic[3,4)], sedative[5)], antihistaminic[5,6)], and vasodilator[7)] properties have been described.

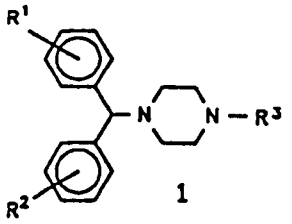
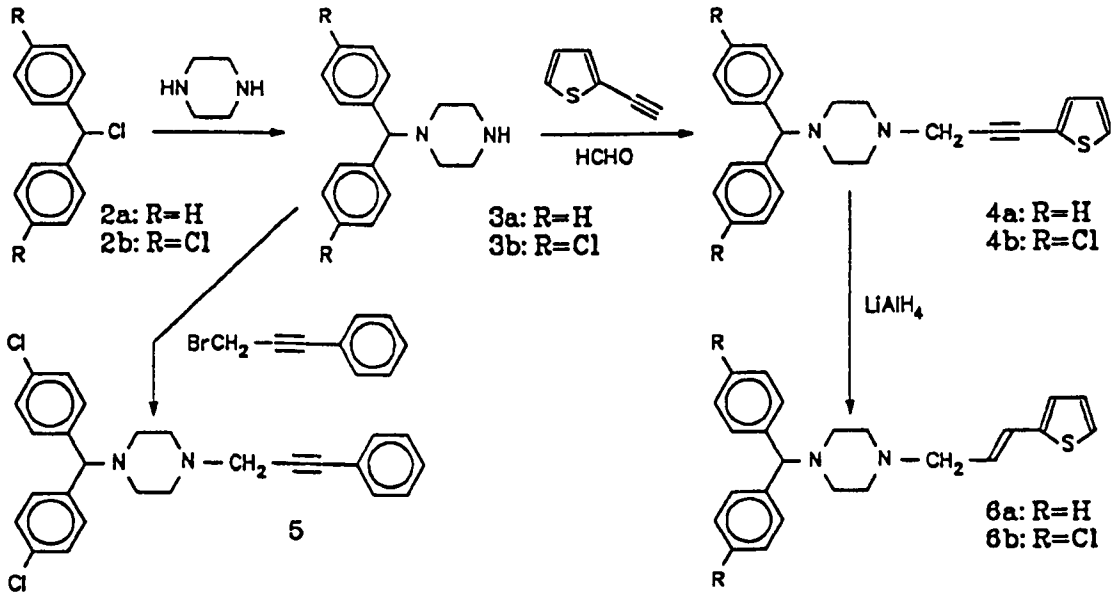


Fig. 1

Within this context, cinnarizine (1: $R^1 = R^2 = H$, R^3 = cinnamyl) is an interesting drug, pharmacologically characterized by its antivasoconstrictor activity, by its effects on red cell deformability and blood viscosity, and by its sedative action on vestibular labyrinth[8)]. This set of properties makes cinnarizine useful in the treatment of vascular disorders and of vertiginous symptoms. Several cinnarizine-related compounds have been prepared and tested, but no data are found in the literature about 2-thienyl analogs of cinnarizine. In the present paper we report on four of such compounds; they showed an interesting hypocholesterolemic activity, but no cinnarizine's characteristic properties were detected. For comparison the alkynylphenyl analog **5** was also prepared and tested.



Scheme 1

[+)] Dedicated to Professor *Kurt Schaffner* on the occasion of his 60th birthday.

  0365-6233/91/090.

Results and Discussion

Chemistry

As is outlined in Scheme 1, the first step to all products were the corresponding monosubstituted piperazines 3, which were prepared by a known procedure'), reacting the appropriate benzhydryl chloride 2 with an excess of pip erazine.

The 2-thienylpropynylpiperazines 4 were prepared through a *Mannich* reaction between 2-thienylacetylene, formaldehyde and the adequate 3 in the presence of anhydrous cupric sulfate, 2-thienylacetylene was obtained by coupling 2-iodothiophene and trimethylsilylacetylene according to[10].

The 2-thienylpropenylpiperazines 6 were prepared by reduction of the corresponding alkynyl compounds 4 using lithium aluminium hydride*). The resulting products show *E* configuration.

The 1-[bis(4-chlorophenyl)methyl]-4-(3-phenyl-2-propynyl) piperazine (5) was prepared reacting 3b with 3-phenyl-2-propynyl bromide in the presence of anhydrous sodium carbonate and using potassium iodide as catalyst.

Most of the final products (except 5) showed quick decomposition signs at room temp., for this reason all of them were stored and pharmacologically tested as their maleic acid salts. The physical and pharmacological data of these salts are summarized in Table 1.

Pharmacology

The assays were carried out in groups of six mice made hypercholesterolemic by being fed a high cholesterol-cholic acid diet for seven days. The test compound was administered orally in the sixth and seventh days a half dose each time. After fasting overnight, serum cholesterol and heparin precipitating lipoproteins (HPL, corresponding to LDL and VLDL fractions) concentrations were measured. Reduction in these concentrations, in relation to hypercholesterolemic control animals, by more than 15 and 20%. respectively, indicates significant activity (*Student's* confidence test). Values obtained for each of the tested compounds are displayed in Table 1. The ratio of the HPL/cholesterol rates between treated and control animals ($[L/C]_{RT}$), calculated from the observed data, are also shown in this table. A value for this ratio below 0.92 suggests a possible increase in serum HDL fraction.

Except 6a, the tested compounds were able, in more or less extent, to reduce both cholesterol and HPL serum levels. Two of them (5 and 6b) were more potent than a commercial drug as bezafibrate and showed also better $[L/C]_{RT}$ values.

Dichlorosubstituted compounds were more active than chlorine lacking ones (4b vs. 4a and 6b vs. 6a). A similar observation has been reported for the monochlorinated compounds chlorcyclizine (1: R^1 = 4-Cl, R^2 = H, R^3 = methyl) and norchlorcyclizine (1: R' = 4-Cl, $R^2 = R^3$ = H). These drugs are more effective than their corresponding dechlorinated analogs in lowering serum cholesterol level in normocholesterolemic mice[3]. Moreover, whilst no reports are found about hypocholesterolemic activity in cinnarizine, its monochlorinated analog clocinizine (1: R' = 4-Cl, R^2 = H, R^3 = cinnamyl) slightly reduces serum cholesterol concentration, also in normocholesterolemic mice[4]:

Clocinizine's activity seems to be weaker than the observed for the dichlorinated compounds reported in the present paper, but no direct comparison is possible because the different model employed and, thus, further experiments are required to elucidate whether the second chlorine atom contributes to an enhancement of the activity.

Experimental Part

Chemistry

Melting points: in open capillaries, Biichi-Tottoli apparatus, uncorrected.- Chromatography: silica gel (Merck 60. 230-400 mesh), 5 cm diameter columns. N_2 pressure. Flow rate ≅ 100 mL/min.- IR spectra: Perkin-Elmer 638 spectrophotometer.- 'H-NMR spectra: Perkin-Elmer R-24 spectrometer, TMS as internal standard.- Elemental analyses: Institut de Química Bio-orgànica de Catalunya. C.S.I.C. Barcelona (Spain).

1-Benzhydryl-4-[3-(2-thienyl)-2-propynyl]piperazine (4a)

A mixture of 2-thienylacetylene (3.15 g. 29.2 mmol), 1-benzhydrylpiperazine (3a) (7.37 g. 29.2 mmol), paraformaldehyde (1.19 g, 39.5 mmol HCHO), anhydrous $CuSO_4$ (0.34 g). and dry peroxide-free THF (120 mL) was stirred and heated under reflux for 5 h 45 min. After cooling, the resulting mixture was diluted with EtOEt (400 mL), filtered, and extracted with HCl 2.5 M/EtOH (5:1) (2 x 250 mL). The acid extract was treated with enough 5 M NaOH ro render pH > 12 and extracted with $CHCl_3$ (4 x 100 mL). The org. layer was dried (Na_2CO_3) and the solvent evaporated to give a brown oil (10.55 g). Chromatography on 100 g of silica gel, using cyclohexane/EtOAc (3:2), gave the title product as a clear oil (9.88 g. 91%) which was convetted in the corresponding dimaleate. A sample of the free base recovered from an analytical sample of the dimaleate showed the following data: IR (neat): 3060; 3020; 2930; 2810; 1595: 1490: 1450; 1005: 845; 755; 745; 700 cm^{-1}.- 'H-NMR ($CDCl_3$): δ = 2.25 (m, 8H, $N-CH_2-CH_2-N$), 3.5 (s, 2H. $N-CH_2-C{\equiv}C$), 4.2 (s, IH, $N-CH-Ar_2$), 6.9-7.5 (m. 13 H. arom.).

1-[Bis(4-chlorophenyl)methyl]-4-[3-(2-thienyl)-2-propynyl]piperazine (4b)

In a similar way as in the previous case, 4b (6.77 g, 87%) was prepared from 3b (5.63 g, 17.5 mmol). 2-thienylacetylene (1.89 g. 17.5 mmol), paraformaldehyde (0.76 g, 25.2 mmol HCHO), $CuSO_4$ (0.52 g). and THF (90 mL). 4b was obtained as a low melting point solid: mp. ≅ 47°C (d).- IR (neat): 2930; 2810; 1590; 1485; 1130; 1090; 1005; 805; 700 cm".- ^{1}H-NMR ($CDCl_3$): δ = 2.5 (m, 8H, $N-CH_2-CH_2-N$), 3.45 (s, 2H, $N-CH_2-C{\equiv}C$), 4.1 (s. 1H, $N-CH-Ar_2$), 6.8-7.1 (m. 11 H, arom.).

1-[Bis(4-chlorophenyl)methyl]-4-(3-phenyl-2-propynyl)piperazine (5)

In a flask fitted with a *Dean-Stark* separator were. poured 1-[bis(4-chlorophenyl)methyl]piperazine (3a) (6.00 g, 18.7 mmol), 3-phenyl-2-propynyl bromide (4.92 g. 25.2 mmol), anhydrous Na_2CO_3 (8.32 g), several crystals of KI, and toluene (175 mL). This mixture was stirred and heated under

*) The *tert*-3-aryl-2-propynylamines are reduced by $LiAlH_4$ to the corresponding property] compounds in good yields and under mild conditions. This is a recent finding of our laboratory and experiments to elucidate the scope and features of this reaction are in progress. The results will be published soon.

reflux for I h 30 min. The warm suspension was filtered and the filtrate extracted with HCl 2.5 M/EtOH (5:1) (2 x 250 mL). The acid extract was worked up as described above. Removal of the solvent gave a brown oil (6.48 g) which was chromatographed on 150 g of silica gel using cyclohexane/EtOAc (4:1). Thus. **5** was obtained as a yellowish oil (5.91 g, 72%) which was converted in its dimaleate. A sample of the free base recovered from an analytical sample of the dimaleate showed the following data: IR (neat): 3060; 2930; 2810; 1595; 1485; 1090; 1010; 810; 755; 690 cm.'.- 'H-NMR ($CDCl_3$): δ = 2.55 (m, 8H. N-CH_2-CH_2-N), 3.55 (s, 2H. N-CH_2-C≡C), 4.15 (s, I H, N-CH-Ar_2), 7.3 (m. 13 H. atom.).

(E)-1-[Bis(4-chlorophenyl)methyl]-4-[3-(2-thienyl)-2-propenyl]piperazine (6b)

A solution of 4b (3. IO g, 7 mmol) in dry peroxide-free THF (30 mL) was added to a suspension of $LiAlH_4$ (0.65 g. 17. I mmol) in THF (IO mL) and the mixture was stirred and heated under reflux for 7 h. After cooling, 5 M NaOH solution (20 mL) was carefully added. When hydrogen evolution sub sided, enough EtOEt and 5 M NaOH solution to render two clear layers were added. The phases were separated and the aqueous one extracted with EtOEt (3 x 100 mL). The combined ethereal fractions were. dried (Na_2CO_3). After filtration, saturated maleic acid ethereal solution was added until no more precipitation was observed. The whith solid obtained (4.62 g) was identified as 6b dimaleate. Recrystallization from ethanol/petroleum ether afforded pure material (3.98 g, 84%). A sample of the free base recovered from an analytical sample of the dimaleate showed the following data: mp. ≅ 30°C (d).- IR (neat): 2960; 2810; 1640; 1590; 1485: 1135; 1090; 1010; 1005; 955; 870; 850; 810; 800; 695 cm.'.- ^{1}H-NMR ($CDCl_3$): δ = 2.5 (broad, 8H. N-CH_2-CH_2-N), 3. 15 (d, 2H. J = 7 Hz, N-CH_2-CH=CH), 4.25 (s, 1 H, N-CH-Ar_2), 5.9-6.4 (m, 1H, N-CH_2-CH=CH), 6.7 (d. 1H, J = 16 Hz. N-CH_2-CH=CH), 6.95 -7.35 (m, 11 H. arom.).

(E)-1-Benzhydryl-4-[3-(2-thienyl)-2-propenyl]piperazine (6a)

The title compound was prepared, as described above, from **4a** (5.54 g, 14.8 mmol), $LiAlH_4$ (I .37 g. 36.2 mmol), and THF (60 mL). When the crude 6a was treated with an excess of maleic acid ethereal solution, two crystalline compounds were obtained. They were separated by crystallization from EtOH and were identified, by spectroscopic and titration methods, as **6a** monomaleate (needles. 4.22 g. 58%) and **6a** dimaleate (plates. I .26 g, 14%). A sample of the free base recovered from an analytical sample of the mono. maleate showed the following data: IR (neat): 3050; 3020; 2950; 2800; 1640; 1590; 1485; 1445; 1140; 1130; 1000; 950; 850; 750; 740; 700 cm.'.- 'H-NMR ($CDCl_3$): δ = 2.45 (broad. 8H. N-CH_2-CH_2-N), 3. I (d, 2H, J = 7 Hz, N-CH_2-CH=CH), 4.2 (s, 1H, N-CH-Ar_2), 5.9-6.3 (m. I H. N-CH_2-CH=CH), 6.55 (d, 1H, J= 16 Hz, N-CH_2-CH=CH), 6.8-7.3 (m, 13 H, arom.).

Pharmacology.- Pharmacological evaluations were performed by Panlabs, Inc. Laboratories, Taipei (Taiwan). as a part of its Pharmacological Screening Program.

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Tablel: Physical data and hypocholestemlemic activity.

Compd.[a]	mp[b] (°C)	Mol. formula	Analytical Data %	C	H	N	Dose[c] (mg/Kg)	Chol. % reduction[d]	HPL % reduction[d]	$[L/C]_{ar}$[e]
4a (dm)	176(A)	$C_{32}H_{32}N_2O_8S$	C:	63.6	5.33	4.6	400	22	19	1.04
			F:	63.9	5.37	4.7	200	0	0	.....
4b (dm)	186(B)	$C_{32}H_{30}Cl_2N_2O_8S$	c:	57.1	4.49	4.2	400	37	34	1.05
			F:	57.0	4.59	4.3	200	24	24	1.00
							100	6	12	.....
5 (dm)	174(C)	$C_{34}H_{32}Cl_2N_2O_8$	C:	61.2	4.84	4.2	400	62	67	0.87
			F:	61.1	4.96	4.3	200	48	53	0.90
							100	36	37	0.98
							50	1	2	.....
6a *(mm)*	191(B)	$C_{25}H_{24}N_2O_4S$	c:	68.5	6.16	5.7	200	0	0	.....
			F:	68.3	6.38	5.7				
6b (dm)	159-60(A)	$C_{32}H_{32}Cl_2N_2O_8S$	C:	56.9	4.78	4.2	400	62	62	1.00
			F:	57.0	4.97	4.2	200	57	62	0.88
							100	45	54	0.84
							50	13	16	.....
Bezafibrate							200	33	38	0.93

a) dm: dimaleate; mm: monomaleate. b) Recrystallization solvents: A: ethanol/petroleum ether; B: ethanol: C: ethanol/chloroform. c) *p.o.* d) Reduction levels higher 15% (Chol. %) and 20% (HPL %) are significant according to the Student's test. e) Calculated as (HPL/Chol) treated/(HPL/Chol) control. Values below 0.92 suggest a possible increase in HDL fraction