SYNTHESIS OF 1-[ω-[(ARYLAMINO)CARBONYL]ALKYL]-4-(BENZOCYCLOALKYL)PIPERAZINES

Youssef El-Ahmad, Philippe Maillet, Elisabeth Laurent, Akram Talab, Gilles Tran, and Roland Ollivier*

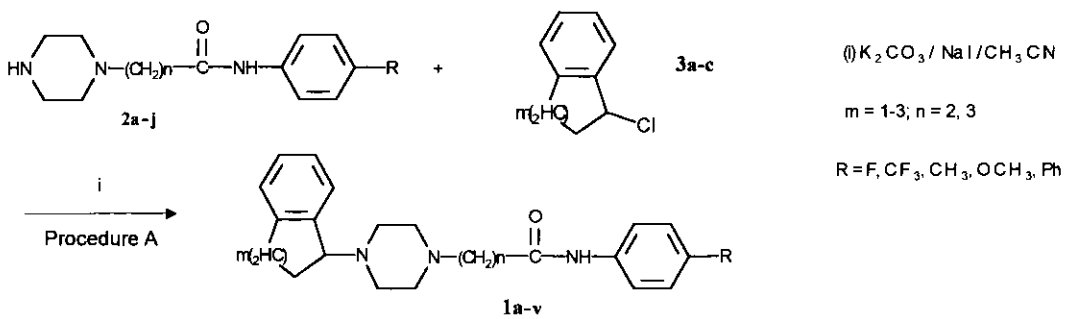
Centre de Recherche, Coopération Pharmaceutique Française,
13-15 rue Benjamin Franklin, 77000 La Rochette, France

Abstract- A series of 1-[ω-[(arylamino)carbonyl]alkyl]-4-(benzocycloalkyl)-piperazines (**1a-v**) was prepared either by reacting the precursor 4-[ω-[(arylamino)carbonyl]alkyl]piperazine (**2a-j**) with 1-chlorobenzocycloalkanes (**3a-c**) (Procedure A) or by reacting the *N*-aryl-ω-chloroalkanamides (**5a-j**) with the 4-(benzocycloalkyl)piperazines (**10a-c**) (Procedure B). The best yields were obtained using procedure A.

Aminotetralins exhibit various pharmacological activities, for example antidepressant[1], anxiolytic[2] or antipsychotic.[3] In connection with our ongoing work on the synthesis of potential central-nervous-system active compounds,[3] we were interested in the preparation of a series of 1-[ω-[(arylamino)carbonyl]alkyl]-4-(benzocycloalkyl)piperazines (**1a-v**).

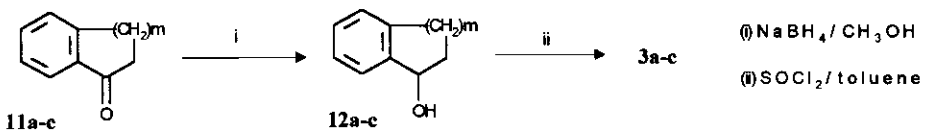
Derivatives (**1a-v**) were prepared by condensing the compounds (**2a-j**) with 1-chlorobenzocycloalkanes (**3a-c**) as described in Scheme 1 (Procedure A).

Scheme 1



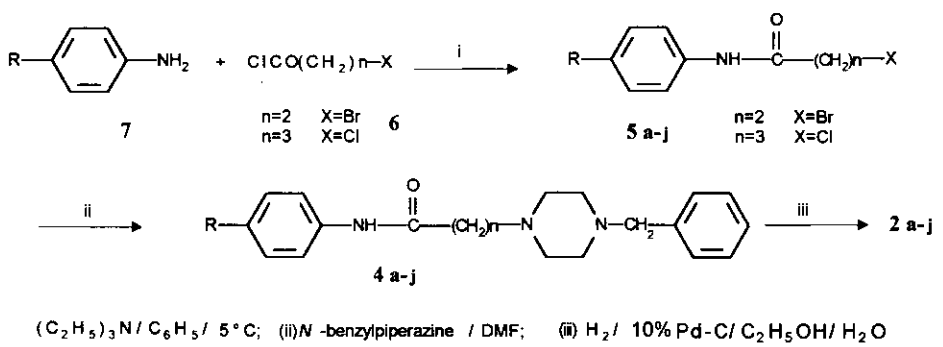
1-Chlorobenzocycloalkanes (**3a-c**) were synthesised by the method described by Bogeso[4] consisting in reducing the corresponding ketones (**11a-c**) with sodium borohydride, then by the treatment of the formed alcohols (**12a-c**) with thionyl chloride. (See Scheme 2).

Scheme 2



4-[(Arylaminocarbonyl)alkyl]piperazines (**2a-j**) were obtained according to the route illustrated in Scheme 3. The reaction of ω-halo-*N*-alkanoyl chlorides (**6**) with the appropriate arylamines (**7**) in the presence of Et_3N gave the ω-halo-*N*-arylalkanoylamides (**5a-j**),[5] which after condensation with two equivalents of 1-benzylpiperazine (one equivalent was used as the basic agent for the neutralization of the halogen hydride formed in the reaction) yielded the 1-[(arylaminocarbonyl)alkyl]-4-benzylpiperazines (**4a-j**),[5] which upon debenzylation under palladium on active carbon gave the desired **2a-j**.[6]

Scheme 3

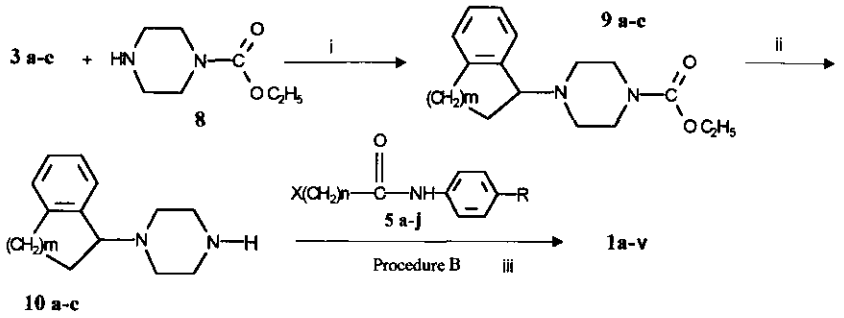


	a	b	c	d	e	f	g	h	i	j
n	2	2	2	2	2	3	3	3	3	3
R	F	CF_3	CH_3	Ph	OCH_3	F	CF_3	CH_3	Ph	OCH_3

As described in Scheme 4, the condensation of the *N*-aryl-ω-haloalkanamides (**5a-j**) with the benzocycloalkylpiperazines (**10a-c**) (procedure B) obtained by decarboxylation of 1-(benzocycloalkyl)-4-ethoxycarbonylpiperazines (**9a-c**) under basic conditions with potassium hydroxide, also permitted to obtain the benzocycloalkylpiperazines (**1a-v**). Compounds (**9a-c**) were obtained by the condensation of

(**3a-c**) with ethyl *N*-piperazinecarboxylate (**8**) (See Scheme 4).

Scheme 4



EXPERIMENTAL

Melting points were measured on a büchi 535 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer spectrophotometer; ^1H NMR spectra were recorded on a Hitachi 1500 FT spectrometer (60 MHz) with TMS as internal standard. Chemical shifts are given in ppm; s, d, t, q, m designated respectively singlet, doublet, triplet, quartet and multiplet. Thin layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualised with UV light (254 nM). Flash chromatography was conducted on Merck Kieselgel 60 (0.040-0.063). Elemental analyses were carried out by microanalysis laboratory in the faculty of pharmacy in Chatenay-Malabry, France.

1-Hydroxybenzocycloalkanes (12a-c)

Sodium borohydride (2.32 g, 61 mmol) was added in portions with stirring at 12 °C to a solution of **11** (183 mmol) in methanol (500 mL). The mixture was stirred for 2 h and then evaporated. The resulting oil was treated with water and ether, and the organic phase was separated, washed with water and 0.1 N HCl, dried over $MgSO_4$ and evaporated to dryness to give compounds (**12 a-c**). Compound **12a** (m = 1): yield 88%, ^1H NMR ($CDCl_3$): δ = 1.8-2.5 (m, 3H), 2.9 (t, 2H, J = 7 Hz), 5.2 (t, 1H, J = 7 Hz), 7.25 (m, 4H). Anal. Calcd for $C_9H_{10}O$: C, 80.57; H, 7.51. Found: C, 80.28; H, 7.45. Compound **12b** (m = 2): yield 97%, ^1H NMR ($CDCl_3$): δ = 1.6 -2.3 (m, 5H), 2.8 (t, 2H, J = 7 Hz), 4.95 (t, 1H, J = 7 Hz), 7.0-7.6 (m, 4H). Anal. Calcd for $C_{10}H_{12}O$: C, 81.06; H, 8.16. Found: C, 80.97; H, 8.22. Compound **12c** (m = 3): mp 102 °C (from 2-propanol), yield 85%, ^1H NMR ($CDCl_3$): δ = 1.4 -2.2 (m, 7H), 2.8 (t, 2H, J = 7 Hz), 4.75 (t, 1H, J = 7 Hz), 7.0-7.4 (m, 4H). Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.53; H,

8.62.

1-Chlorobenzocycloalkanes (3a-c)

Thionyl chloride (26 mL, 0.35 mol) was added with stirring and cooling at 15°C to a solution of **12** (0.238 mol) in toluene (340 mL). The mixture was stirred at room temperature for 30 min and then heated to 55°C for 1 h. The mixture was cooled, washed twice with ice-water, dried over $MgSO_4$ and evaporated to give a quantitative yield of **3** as an oil, which was used without any further purification in the following step. Compound **3a** (m = 1): ^{1}H NMR ($CDCl_3$): δ = 2.35 (q, 2H, J = 7 Hz), 2.95 (t, 2H, J = 7 Hz), 5.4 (t, 1H, J = 7 Hz), 7.1-7.5 (m, 4H). Anal. Calcd for C_9H_9Cl: C, 70.81; H, 5.94. Found: C, 70.53; H, 5.71. Compound **3b** (m = 2): ^{1}H NMR ($CDCl_3$): δ = 1.7-2.5 (m, 4H), 2.8 (t, 2H, J = 7 Hz), 5.3 (t, 1H, J = 7 Hz), 7.0-7.3 (m, 4H). Anal. Calcd for $C_{10}H_{11}Cl$: C, 72.06; H, 6.65. Found: C, 71.81; H, 6.42. Compound **3c** (m = 3): ^{1}H NMR ($CDCl_3$): δ = 1.4 -2.6 (m, 6H), 2.8 (t, 2H, J = 7 Hz), 5.2 (t, 1H, J = 7 Hz), 7.2 (m, 4H). Anal. Calcd for $C_{11}H_{13}Cl$: C, 73.11; H, 7.25. Found: C, 72.82; H, 6.96.

3-Bromo-*N*-(4-fluorophenyl)propionamide (5a)

A mixture of 4-fluoroaniline (22.2 g, 0.2 mol), 20 mL of triethylamine and 50 mL of benzene was cooled to 5°C. 3-Bromopropionyl chloride (34.3 g, 0.2 mol) dissolved in 150 mL of benzene was then added dropwise. When the addition was complete, the reaction medium was left to stand for 4 h. The benzene was evaporated off under vacuum. The solid was taken up with dichloromethane and then washed with ice water. The organic phase was dried over $MgSO_4$ and then concentrated under vacuum to give 39 g of **5a** (79%). Compounds (**5b-j**) were synthesised similarly. Compound **5a** (n = 2): mp 108 °C (from toluene); yield 79%; ^{1}H NMR ($CDCl_3$): δ = 2.9 (t, 2H, J = 7 Hz), 3.6 (t, 2H, J = 7 Hz), 6.8-7.65 (m, 4H), 8 (s, NH). Anal. Calcd for C_9H_9NOBrF: C, 43.93; H, 3.68; N, 5.69. Found: C, 43.71; H, 3.58; N, 5.56. Compound **5b** (n = 2): mp 106 °C (from 2-propanol); yield 86%; ^{1}H NMR ($CDCl_3$): δ = 2.9 (t, 2H, J = 7 Hz), 3.7 (t, 2H, J = 7 Hz), 7.6 (m, 4H), 7.95 (s, NH). Anal. Calcd for $C_{10}H_9NOBrF_3$: C, 40.56; H, 3.06; N, 4.73. Found: C, 40.32; H, 3.12; N, 4.56. Compound **5c** (n = 2): mp 137 °C (fom 2-propanol); yield 70%; ^{1}H NMR ($CDCl_3$): δ = 2.3 (s, 3H, CH_3), 2.9 (t, 2H, J = 7 Hz), 3.7 (t, 2H, J = 7 Hz), 7.1 (d, 2H, J = 9 Hz), 7.4 (d, 2H, J = 9 Hz), 7.6 (s, NH). Anal. Calcd for $C_{10}H_{12}NOBr$: C, 49.60; H, 4.99; N, 5.78. Found: C, 49.47; H, 4.81; N, 5.58. Compound **5d** (n = 2): mp 160 °C (from toluene); yield 78%; ^{1}H NMR ($CDCl_3$): δ = 2.95 (t, 2H, J = 7 Hz), 3.65 (t, 2H, J = 7 Hz), 7.3-7.7 (m, 9H), 7.9 (s, NH). Anal. Calcd for $C_{15}H_{14}NOBr$: C, 59.22; H, 4.60; N, 4.60. Found: C, 59.02; H, 4.43; N, 4.56. Compound **5e** (n = 2): mp 112 °C (from toluene); yield 95%; ^{1}H NMR ($CDCl_3$): δ = 2.85 (t, 2H, J = 7 Hz), 3.65 (t, 2H,

J = 7 Hz), 3.8 (s, 3H, OCH_3), 6.8 (d, 2H, J = 9 Hz), 7.4 (d, 2H, J = 9 Hz), 8.1 (s, NH). Anal. Calcd for $C_{10}H_{12}NO_2Br$: C, 46.52; H, 4.69; N, 5.43. Found: C, 46.41; H, 4.73; N, 5.56. Compound **5f** (n = 3): mp 98 °C (from toluene); yield 85%; ^{1}H NMR ($CDCl_3$): δ = 2.2 (m, 2H), 2.5 (t, 2H, J = 7 Hz), 3.6 (t, 2H, J = 7 Hz), 6.8-7.6 (m, 4H), 7.8 (s, NH). Anal. Calcd for $C_{10}H_{11}NOClF$: C, 55.70; H, 5.14; N, 6.49. Found: C, 55.56; H, 5.12; N, 6.56. Compound **5g** (n = 3): mp 118 °C (from pentane); yield 98%; ^{1}H NMR ($CDCl_3$): δ = 2.2 (m, 2H), 2.5 (t, 2H, J = 7 Hz), 3.65 (t, 2H, J = 7 Hz), 7.6 (m, 4H), 8.1 (s, NH). Anal. Calcd for $C_{11}H_{11}NOClF_3$: C, 49.74; H, 4.17; N, 5.27. Found: C, 49.63; H, 4.12; N, 5.11. Compound **5h** (n = 3): mp 87 °C (from 2-propanol); yield 89%; ^{1}H NMR ($CDCl_3$): δ = 2.1 (m, 2H), 2.3 (s, 3H, CH_3), 2.5 (t, 2H, J = 7 Hz), 3.6 (t, 2H, J = 7 Hz), 7.1 (d, 2H, J = 9 Hz), 7.35 (d, 2H, J = 9 Hz), 7.75 (s, NH). Anal. Calcd for $C_{11}H_{14}NOCl$: C, 62.40; H, 6.67; N, 6.62. Found: C, 62.32; H, 6.59; N, 6.56. Compound **5i** (n = 3): mp 151 °C (from 2-propanol); yield 80%; ^{1}H NMR ($CDCl_3$): δ = 2.2 (m, 2H), 2.55 (t, 2H, J = 7 Hz), 3.65 (t, 2H, J = 7 Hz), 7.3-7.7 (m, 9H), 7.85 (s, NH). Anal. Calcd for $C_{16}H_{16}NOCl$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.32; H, 5.93; N, 4.95. Compound **5j** (n = 3): mp 75 °C (from 2-propanol); yield 96%; ^{1}H NMR ($CDCl_3$): δ = 2.1 (m, 2H), 2.45 (t, 2H, J = 7 Hz), 3.6 (t, 2H, J = 7 Hz), 3.8 (s, 3H, OCH_3), 6.8 (d, 2H, J = 9 Hz), 7.35 (d, 2H, J = 9 Hz), 7.9 (s, NH). Anal. Calcd for $C_{11}H_{14}NO_2Cl$: C, 58.03; H, 6.20; N, 6.15. Found: C, 58.15; H, 6.28; N, 6.05.

1-[2-[(4-Fluorophenylamino)carbonyl]ethyl]-4-benzylpiperazine (4a)

Compound (**5a**) (20.15 g, 0.1 mol) in solution in 50 mL of DMF was added dropwise to a mixture of 1-benzylpiperazine (35.2 g, 0.2 mol) and sodium iodide (1 g, 6.6 mmol) in 150 mL of DMF. The reaction mixture was stirred for 4 h and then for 2 h at 60-70 °C. After cooling, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed several times with water, dried over $MgSO_4$ and then evaporated to give 29 g of crude base (yield 85%). This base was dissolved in ethanol, a solution of hydrogen chloride in ethanol was then added, the dihydrochloride crystallised out. Compounds **4b-j** were synthesised similarly. ^{1}H NMR spectra were carried out on the crude base. Compound **4a** (n = 2): mp 226 °C (from ethanol); yield 77%; ^{1}H NMR ($CDCl_3$): δ = 2.3-2.8 (m, 12H), 3.6 (s, 2H), 6.8-7.6 (m, 9H), 11.0 (s, NH). Anal. Calcd for $C_{20}H_{26}N_3OCl_2F$: C, 57.98; H, 6.32; N, 10.14. Found: C, 58.12; H, 6.12; N, 9.97. Compound **4b** (n = 2): mp 229 °C (from ethanol); yield 91%; ^{1}H NMR ($CDCl_3$): δ = 2.3-2.8 (m, 12H), 3.6 (s, 2H), 7.3 (m, 5H), 7.6 (m, 4H), 11.4 (s, NH). Anal. Calcd for $C_{21}H_{26}N_3OCl_2F_3$: C, 54.32; H, 5.64; N, 9.05. Found: C, 54.12; H, 5.53; N, 9.17. Compound **4c** (n = 2): mp 234 °C (from ethanol); yield 90%; ^{1}H NMR ($CDCl_3$): δ = 2.3 (s, 3H, CH_3), 2.4-2.6 (m, 12H), 3.55 (s, 2H), 7.1 (d, 2H, J = 9 Hz), 7.25-7.55 (m, 7H), 9.8 (s, NH). Anal. Calcd for $C_{21}H_{29}N_3OCl_2$: C, 61.46; H, 7.12; N, 10.24. Found: C, 61.31; H, 7.02; N, 10.07. Compound **4d** (n = 2): mp > 250 °C (from methanol); yield 88%; ^{1}H

NMR ($CDCl_3$): δ = 2.3-2.7 (m, 12H), 3.55 (s, 2H), 7.2-7.7 (m, 14H), 11.1 (s, NH). Anal. Calcd for $C_{26}H_{31}N_3OCl_2$: C, 66.10; H, 6.61; N, 8.89. Found: C, 66.23; H, 6.54; N, 9.97. Compound **4e** (n = 2): mp 236 °C (from ethanol); yield 91%; ^{1}H NMR ($CDCl_3$): δ = 2.3-2.7 (m, 12H), 3.55 (s, 2H), 3.8 (s, 3H, OCH_3), 6.8 (d, 2H, J = 9 Hz), 7.3 (m, 5H), 7.45 (d, 2H, J = 9 Hz), 10.8 (s, NH). Anal. Calcd for $C_{21}H_{29}N_3O_2Cl_2$: C, 59.16; H, 6.86; N, 9.85. Found: C, 59.12; H, 6.70; N, 9.95. Compound **4f** (n = 3): mp 245 °C (from ethanol); yield 82%; ^{1}H NMR ($CDCl_3$): δ = 2 (m, 2H), 2.2-2.6 (m, 12H), 3.5 (s, 2H), 6.5-7.5 (m, 9H), 7.7 (s, NH). Anal. Calcd for $C_{21}H_{28}N_3OCl_2F$: C, 58.89; H, 6.59; N, 9.81. Found: C, 58.75; H, 6.42; N, 9.92. Compound **4g** (n = 3): mp > 250 °C (from methanol); yield 92%; ^{1}H NMR ($CDCl_3$): δ = 1.95 (m, 2H), 2.3-2.6 (m, 12H), 3.55 (s, 2H), 7.3-7.7 (m, 9H), 9.2 (s, NH). Anal. Calcd for $C_{22}H_{28}N_3OCl_2F_3$: C, 55.25; H, 5.90; N, 8.78. Found: C, 55.10; H, 6.12; N, 8.71. Compound **4h** (n = 3): mp 220 °C (from ethanol); yield 85%; ^{1}H NMR ($CDCl_3$): δ = 1.9 (m, 2H), 2.3 (s, 3H, CH_3), 2.35-2.9 (m, 12H), 3.55 (s, 2H), 6.95 (d, 2H, J = 9 Hz), 7.2-7.5 (m, 7H), 9.2 (s, NH). Anal. Calcd for $C_{22}H_{31}N_3OCl_2$: C, 62.26; H, 7.36; N, 9.90. Found: C, 62.12; H, 7.12; N, 9.73. Compound **4i** (n = 3): mp 230 °C (from ethanol); yield 77%; ^{1}H NMR ($CDCl_3$): δ = 1.9 (m, 2H), 2.2-2.7 (m, 12H), 3.5 (s, 2H), 7.2-7.7 (m, 14H), 8.6 (s, NH). Anal. Calcd for $C_{27}H_{33}N_3OCl_2$: C, 66.65; H, 6.84; N, 8.84. Found: C, 66.50; H, 6.90; N, 8.71. Compound **4j** (n = 3): mp 215 °C (from ethanol); yield 83%; ^{1}H NMR ($CDCl_3$): δ = 2.0 (m, 2H), 2.2-2.7 (m, 12H), 3.55 (s, 2H), 3.8 (s, 3H, OCH_3), 6.8 (d, 2H, J = 9 Hz), 7.25 (m, 5H), 7.6 (d, 2H, J = 9 Hz), 8.6 (s, NH). Anal. Calcd for $C_{22}H_{31}N_3O_2Cl_2$: C, 60.00; H, 7.09; N, 9.54. Found: C, 60.12; H, 7.18; N, 9.63.

4-[2-(4-Fluorophenylamino)carbonyl]ethylpiperazine (2a)

Compound (**4a**) (25 g, 0.06 mol) was dissolved in a mixture of 100 mL of water and 100 mL of ethanol. 3 g of 10% Pd/C were added. Hydrogenolysis was carried out until the absorption of the theoretical hydrogen volume. The reaction mixture was filtered and the filtrate was neutralised with 2N NaOH and evaporated to dryness. The residue was taken up with dichloromethane and filtered. The filtrate was dried over $MgSO_4$, filtered and concentrated under vacuum to give crude (**2a**).

Compounds (**2b-j**) were synthesised similarly. Compound **2a** (n = 2): mp 132 °C (from ethyl acetate); yield 93%; ^{1}H NMR ($CDCl_3$): δ = 2.3-2.6 (m, 8H), 2.8-3.0 (m, 4H), 3.7 (s, NH amine), 6.7-7.7 (m, 4H). 10.1 (s, NH amide). Anal. Calcd for $C_{13}H_{18}N_3OF$: C, 62.13; H, 7.22; N, 16.72. Found: C, 61.89; H, 7.12; N, 16.71. Compound **2b** (n = 2): mp 103 °C (from 2-propanol); yield 67%; ^{1}H NMR ($CDCl_3$): δ = 2.4-2.7 (m, 8H), 2.8-3.1 (m, 4H), 3.4 (s, NH amine), 7.3-7.6 (m, 4H), 11.3 (s, NH amide). Anal. Calcd for $C_{14}H_{18}N_3OF_3$: C, 55.80; H, 6.02; N, 13.95. Found: C, 55.72; H, 5.95; N, 13.78. Compound **2c** (n =

2): mp 116 °C (from ethyl acetate); yield 71%; ^{1}H NMR ($CDCl_3$): δ = 2.3 (s, 3H, CH_3), 2.4-2.6 (m, 8H), 2.8-3.0 (m, 4H), 3.9 (s, NH amine), 7.1 (d, 2H, J = 9 Hz), 7.4 (d, 2H, J = 9 Hz), 10.6 (s, NH amide). Anal. Calcd for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.57; N, 17.00. Found: C, 67.85; H, 8.43; N, 16.86. Compound **2d** (n = 2): mp 159 °C (from 2-propanol); yield 87%; ^{1}H NMR ($CDCl_3$): δ = 2.3-2.6 (m, 8H), 2.8-3.0 (m, 4H), 3.75 (s, NH amine), 7.3-7.7 (9H), 10.8 (s, NH amide). Anal. Calcd for $C_{19}H_{23}N_3O$: C, 73.76; H, 7.49; N, 13.58. Found: C, 73.63; H, 7.56; N, 13.47. Compound **2e** (n = 2): mp 127 °C (from 2-propanol); yield 84%; ^{1}H NMR ($CDCl_3$): δ = 2.4-2.6 (m, 8H), 2.8-3.0 (m, 4H), 3.6 (s, NH amine), 3.8 (s, 3H, OCH_3), 6.8 (d, 2H, J = 9 Hz), 7.6 (d, 2H, J = 9 Hz), 10.0 (s, NH amide). Anal. Calcd for $C_{14}H_{21}N_3O_2$: C, 63.85; H, 8.04; N, 15.96. Found: C, 63.75; H, 7.90; N, 15.86. Compound **2f** (n = 3): mp 146 °C (from ethyl acetate); yield 89%; ^{1}H NMR ($CDCl_3$): δ = 1.8 (m, 2H), 2.2-2.6 (m, 8H), 2.7-3.0 (m, 4H), 3.8 (s, NH amine), 6.8-7.6 (m, 4H), 9.0 (s, NH amide). Anal. Calcd for $C_{14}H_{20}N_3OF$: C, 63.37; H, 7.60; N, 15.84. Found: C, 63.45; H, 7.46; N, 15.78. Compound **2g** (n = 3): mp 132 °C (from 2-propanol); yield 90%; ^{1}H NMR ($CDCl_3$): δ = 1.95 (m, 2H), 2.2-2.6 (m, 8H), 2.7-3.1 (m, 4H), 3.2 (s, NH amine), 7.4-7.8 (m, 4H), 9.45 (s, NH amide). Anal. Calcd for $C_{15}H_{20}N_3OF_3$: C, 57.14; H, 6.39; N, 13.33. Found: C, 57.03; H, 6.25; N, 13.21. Compound **2h** (n = 3): mp 124 °C (from 2-propanol); yield 94%; ^{1}H NMR ($CDCl_3$): δ = 1.9 (m, 2H), 2.3 (s, 3H, CH_3), 2.35-2.7 (m, 8H), 2.75-3.1 (m, 4H), 4.0 (s, NH amine), 7.0 (d, 2H, J = 9 Hz), 7.4 (d, 2H, J = 9 Hz), 8.65 (s, NH amide). Anal. Calcd for $C_{15}H_{23}N_3O$: C, 68.93; H, 8.87; N, 16.08. Found: C, 68.72; H, 8.75; N, 15.92. Compound **2i** (n = 3): mp 183 °C (from 2-propanol); yield 91%; ^{1}H NMR ($CDCl_3$): δ = 1.9 (m, 2H), 2.2-2.7 (m, 8H), 3.0 (m, 4H), 3.5 (s, NH amine), 7.3-7.8 (m, 9H), 10.1 (s, NH amide). Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.27; H, 7.79; N, 13.00. Found: C, 74.44; H, 7.67; N, 13.12. Compound **2j** (n = 3): mp 115 °C (from ethyl acetate); yield 81%; ^{1}H NMR ($CDCl_3$): δ = 1.9 (m, 2H), 2.2-2.6 (m, 8H), 2.7-3.0 (m, 4H), 3.8(s, 3H, OCH_3), 5.0 (s, NH amine), 6.8 (d, 2H, J = 9 Hz), 7.4 (d, 2H, J = 9 Hz), 8.4 (s, NH amide). Anal. Calcd for $C_{15}H_{23}N_3O_2$: C, 64.95; H, 8.36; N, 15.15. Found: C, 64.80; H, 8.23; N, 14.95.

1-Ethoxycarbonyl-4-(benzocycloalkyl)piperazines (9a-c)

A mixture of 1-chlorobenzocycloalkanes (**3**) (0.65 mol), ethyl *N*-piperazinecarboxylate (124.8 g, 0.79 mol), potassium carbonate (197.34 g, 1.43 mol) and sodium iodide (10 g, 0.06 mol) in 900 mL of acetonitrile, was refluxed for 24 h. After cooling, the mixture was filtered and the solvent was evaporated off. The residual oil was taken up with ice water and the product was extracted 3 times with ethyl acetate. An ethanolic solution of 2N hydrogen chloride was then added. The hydrochloride formed was filtered off. The base was freed with sodium carbonate in a dichloromethane / water mixture. The organic layer was separated, dried over $MgSO_4$ and evaporated off under vacuum to give compounds (**9a-c**) as an oil. Compound **9a** (m = 1): yield 70%; ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 3H, J = 7 Hz), 2.1 (q, 2H, J = 7 Hz),

2.3-2.9 (m, 6H), 3.5 (t, 4H, J = 5 Hz), 4.15 (q, 2H, J = 7 Hz), 4.35 (t, 1H, J = 7 Hz), 7-7.7 (m, 4H). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.05; H, 8.08; N, 10.21. Found: C, 69.90; H, 7.88; N, 10.06. Compound **9b** (m = 2): yield 63%; ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 3H, J = 7 Hz), 1.6-2.1 (m, 4H), 2.3-2.9 (m, 6H), 3.5 (t, 4H, J = 5 Hz), 3.8 (t, 1H, J = 7 Hz), 4.15 (q, 2H, J = 7 Hz), 7.0-7.75 (m, 4H). Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.92; H, 8.24; N, 9.58. Compound **9c** (m = 3): yield 61%, ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 3H, J = 7 Hz), 1.4-2.0 (m, 6H), 2.4-2.9 (m, 6H), 3.15 (t, 1H, J = 7 Hz), 3.45 (t, 4H, J = 5 Hz), 4.15 (q, 2H, J = 7 Hz), 7-7.2 (m, 4H). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.38; H, 8.88; N, 9.10.

4-Benzocycloalkylpiperazines (10a-c)

Potassium hydroxide (300 g, 5.36 mol) was added slowly to a solution of 1-ethoxycarbonyl-4-(benzocycloalkyl)piperazine **9** (0.46 mol), water (100 mL) and methanol (400 mL). The reaction mixture was refluxed. The reaction was monitored by thin layer chromatography. After the starting material had disappeared, the mixture was cooled, filtered and extracted with dichloromethane. The organic layer was separated, dried over $MgSO_4$ and evaporated. The residual oil was taken up with ethanol, and oxalic acid (39.33 g, 0.44 mol) dissolved in ethanol (700 mL) was added. The oxalate formed was filtered off and then freed with sodium carbonate in a dichloromethane / water mixture. After decantation, the organic layer was dried over $MgSO_4$ and the solvent was evaporated off to give compounds (**10a-c**) as an oil. Compound **10a** (m = 1): yield 83%; ^{1}H NMR ($CDCl_3$): δ = 2.1 (t, 2H, J = 7 Hz), 2.4-2.85 (m, 7H), 2.9 (t, 4H, J = 5 Hz), 4.3 (t, 1H, J = 7 Hz), 7.0-7.7 (m, 4H). Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 76.94; H, 8.88; N, 13.72. Compound **10b** (m = 2): yield 84%; ^{1}H NMR ($CDCl_3$): δ = 1.5-2.1 (m, 4H), 2.0 (s, NH), 2.4-2.8 (m, 6H), 2.9 (t, 4H, J = 5 Hz), 3.75 (t, 1H, J = 7 Hz), 7.0-7.8 (m, 4H). Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.90; H, 9.18; N, 12.73. Compound **10c** (m = 3): yield 70%; ^{1}H NMR ($CDCl_3$): δ = 1.3-2.7 (m, 12H), 2.9 (t, 4H, J = 5 Hz), 3.2 (t, 1H, J = 7 Hz), 3.9 (s, NH), 7.1 (m, 4H). Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.06; H, 9.48; N, 12.05.

1-[2-[(4-Fluorophenylamino)carbonyl]ethyl]-4-(1,2,3,4-tetrahydronaphth-1-yl)piperazine dihydrochloride (1k)

Procedure A : A mixture of 4-[2-[(4-fluorophenylamino)carbonyl]ethyl]piperazine (**2a**) (4 g, 15.9 mmol), 1-chlorotetralin (**3b**) (2.65 g, 15.9 mmol), potassium carbonate (5.55 g, 40 mmol) and sodium iodide (0.5 g, 3.3 mmol) in 150 mL of acetonitrile was refluxed for 24 h. The solution was then evaporated to

dryness, the residue was taken up with water and extracted with ethyl acetate. The organic layer was separated, dried over $MgSO_4$ and evaporated and the residue was chromatographied over a silica gel column (eluent, 0.5% Et_3N / ethyl acetate) to yield 3.3 g of pure product (65%).

Procedure B : A mixture of 4-(1,2,3,4-tetrahydronaphth-1-yl)piperazine (**10b**) (5.4 g, 25 mmol), ω-bromo-*N*-(4-fluorophenyl)propionamide (**5a**) (5.04 g, 25 mmol) and 8 mL of triethylamine in 100 mL of DMF was heated at 60°C for 48 h. After cooling, the reaction mixture was poured all at once into 200 mL of water and then extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by column chromatography (eluent, 0.5% Et_3N / ethyl acetate) to yield 3 g of a pure product (31%).

Compounds (**1a-v**) were synthesised similarly. Analytical and physicochemical data are shown in Tables 1 and 2.

Preparation of the dihydrochloride : The base was dissolved in ethanol, and an ethanolic solution of hydrogen chloride was added and the salt crystallised out.

CONCLUSION

Compounds (**1a-v**) were prepared by two procedures. The best yields were obtained using procedure A. This probably should be due to the fact that the « pseudobenzylic » halogen of the intermediates (**3a-c**) is more reactive than that the « alkyl type » halogen of arylalkanoylamides derivatives (**5a-j**).

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Table 1. Analytical Data for Compounds (**1a-v**) Dihydrochlorides

	m	n	R	Yield (%) A	Yield (%) B	mp °C	Molecular Formula	Microanalyses (%) C Calcd / Found	H Calcd / Found	N Calcd / Found
1a	1	2	F	73	41	219	$C_{22}H_{28}N_3OCl_2F$	59.98	6.41	9.54
								60.11	6.47	9.61
1b	1	2	CF_3	54	36	249	$C_{23}H_{28}N_3OCl_2F_3$	56.32	5.76	8.57
								56.47	5.68	8.72
1c	1	2	CH_3	59	38	218	$C_{23}H_{31}N_3OCl_2$	63.30	7.16	9.63
								63.42	7.03	9.59
1d	1	2	Ph	63	35	256	$C_{28}H_{33}N_3OCl_2$	67.45	6.67	8.43
								67.56	6.63	8.56
1e	1	2	OCH_3	71	40	214	$C_{23}H_{31}N_3O_2Cl_2$	61.05	6.91	9.29
								60.92	7.05	9.21
1f	1	3	F	69	33	217	$C_{23}H_{30}N_3OCl_2F$	60.78	6.65	9.25
								60.69	6.76	9.33
1g	1	3	CF_3	48	36	256	$C_{24}H_{30}N_3OCl_2F_3$	57.14	5.99	8.33
								57.03	6.10	8.21
1h	1	3	CH_3	57	39	232	$C_{24}H_{33}N_3OCl_2$	63.98	7.38	9.33
								64.11	7.31	9.42
1i	1	3	Ph	68	41	217	$C_{29}H_{35}N_3OCl_2$	67.95	6.88	8.20
								68.07	6.96	8.13
1j	1	3	OCH_3	62	34	243	$C_{24}H_{33}N_3O_2Cl_2$	61.79	7.13	9.01
								61.68	7.25	9.14
1k	2	2	F	65	37	246	$C_{23}H_{30}N_3OCl_2F$	60.78	6.65	9.25
								60.91	6.74	9.09
1l	2	2	CF_3	70	42	249	$C_{24}H_{30}N_3OCl_2F_3$	57.14	5.99	8.33
								57.22	6.10	8.21
1m	2	2	CH_3	68	36	221	$C_{24}H_{33}N_3OCl_2$	63.98	7.38	9.33
								64.12	7.41	9.26
1n	2	2	Ph	64	32	215	$C_{29}H_{35}N_3OCl_2$	67.95	6.88	8.20
								68.07	6.79	8.34
1o	2	2	OCH_3	62	37	208	$C_{24}H_{33}N_3O_2Cl_2$	61.79	7.13	9.01
								61.74	7.21	9.13
1p	2	3	F	55	31	204	$C_{24}H_{32}N_3OCl_2F$	61.53	6.89	8.97
								61.47	6.95	9.06
1q	2	3	CF_3	66	38	227	$C_{25}H_{32}N_3OCl_2F_3$	57.91	6.22	8.10
								58.11	6.36	8.03
1r	2	3	CH_3	56	34	217	$C_{25}H_{35}N_3OCl_2$	64.64	7.60	9.05
								64.59	7.52	9.11
1s	2	3	Ph	58	32	194	$C_{30}H_{37}Cl_2N_3O$	68.43	7.08	7.98
								68.52	7.16	8.10
1t	2	3	OCH_3	51	30	202	$C_{25}H_{35}N_3O_2Cl_2$	62.49	7.34	8.75
								62.61	7.27	8.89
1u	3	2	F	46	31	218	$C_{24}H_{32}N_3OCl_2F$	61.53	6.89	8.97
								61.67	6.73	9.06
1v	3	3	F	53	35	236	$C_{25}H_{34}N_3OCl_2F$	62.23	7.10	8.71
								62.33	7.21	8.65

Table 2. Spectral data for compounds **(1a-v)**

	^{1}H NMR (base) ($CDCl_3$) δ (ppm)	IR (ν) (salt) cm^{-1}
1a	2.1 (q, 2H, J = 7 Hz), 2.4-3.0 (m, 14H), 4.4 (t, 1H, J = 7 Hz), 6.8-7.6 (m, 8H), 11.1 (s, NH)	3261, 1685
1b	2.1 (q, 2H, J = 7 Hz), 2.4-3.1 (m, 14H), 4.4 (t, 1H, J = 7 Hz), 7.2-7.7 (m, 8H), 11.4 (s, NH)	3248, 1697
1c	2.1 (q, 2H, J = 7 Hz), 2.3 (s, 3H, CH_3), 2.4-3.0 (m, 14H), 4.35 (t, 1H, J = 7 Hz), 6.9-7.45 (m, 8H), 10.9 (s, NH)	3261, 1696
1d	2.1 (q, 2H, J = 7 Hz), 2.4-3.1 (m, 14H), 4.4 (t, 1H, J = 7 Hz), 7.1-7.6 (m, 13H), 11.1 (s, NH)	3257, 1695
1e	2.1 (q, 2H, J = 7 Hz), 2.4-3.0 (m, 14H), 3.8 (s, 3H, OCH_3), 4.35 (t, 1H, J = 7 Hz), 6.7-7.5 (m, 8H), 10.8 (s, NH)	3254, 1678
1f	1.7-2.1 (m, 4H), 2.35-3.0 (m, 14H), 4.35 (t, 1H, J = 7 Hz), 6.8-7.6 (m, 8H), 9.0 (s, NH)	3251, 1688
1g	1.7-2.1 (m, 4H), 2.35-3.0 (m, 14H), 4.35 (t, 1H, J = 7 Hz), 7.1-7.6 (m, 8H), 9.2 (s, NH)	3246, 1696
1h	1.7-2.1 (m, 4H), 2.3 (s, 3H, CH_3), 2.35-2.9 (m, 14H), 4.3 (t, 1H, J = 7 Hz), 6.9-7.5 (m, 8H), 8.8 (s, NH)	3258, 1687
1i	1.7-2.1 (m, 4H), 2.2-3.0 (m, 14H), 4.35 (t, 1H, J = 7 Hz), 7.1-7.6 (m, 13H), 8.8 (s, NH)	3316, 1669
1j	1.7-2.1 (m, 4H), 2.2-3.0 (m, 14H), 3.8 (s, 3H, OCH_3), 4.35 (t, 1H, J = 7 Hz), 6.7-7.4 (m, 8H), 8.7 (s, NH)	3245, 1688
1k	1.6-2.1 (m, 4H), 2.4-2.9 (m, 14H), 3.85 (t, 1H, J = 7 Hz), 6.8-7.7 (m, 8H), 11.1 (s, 1H)	3175, 1688
1l	1.6-2.1 (m, 4H), 2.4-2.85 (m, 14H), 3.9 (t, 1H, J = 7 Hz), 7.0-7.7 (m, 8H), 11.5 (s, 1H)	3247, 1692
1m	1.6-2.1 (m, 4H), 2.3 (s, 3H, CH_3), 2.4-2.8 (m, 14H), 3.8 (t, 1H, J = 7 Hz), 7-7.7 (m, 8H), 11.1 (s, NH)	3258, 1691
1n	1.6-2.1 (m, 4H), 2.4-2.9 (m, 14H), 3.8 (t, 1H, J = 7 Hz), 7.0-7.6 (m, 13H), 11.2 (s, NH)	3255, 1690
1o	1.6-2.1 (m, 4H), 2.4-2.8 (m, 14H), 3.8 (s, 3H, OCH_3), 3.85 (t, 1H, J = 7 Hz), 6.8-7.7 (m, 8H), 10.85 (s, NH)	3251, 1679
1p	1.5-2.1 (m, 6H), 2.3-2.8 (m, 14H), 3.8 (t, 1H, J = 7 Hz), 6.8-7.7 (m, 8H), 9.1(s, NH)	3245, 1684
1q	1.5-2.1 (m, 6H), 2.3-2.9 (m, 14H), 3.8 (t, 1H, J = 7 Hz), 7.0-7.8 (m, 8H), 9.25(s, NH)	3245, 1695
1r	1.6-2.1 (m, 6H), 2.3 (s, 3H, CH_3), 2.4-2.8 (m, 14H), 3.8 (t, 1H, J = 7 Hz), 6.9-7.7 (m, 8H), 8.75 (s, NH)	3240, 1686
1s	1.6-2.1 (m, 6H), 2.3-2.8 (m, 14H), 3.8 (t, 1H, J = 7 Hz), 7.0-7.7 (m, 13H), 9.0 (s, NH)	3237, 1680
1t	1.6-2.1 (m, 6H), 2.3-2.8 (m, 14H), 3.7 (s, 3H, OCH_3), 3.8 (t, 1H, J = 7 Hz), 6.7-7.7 (m, 8H), 8.8 (s, NH)	3248, 1688
1u	1.2-2.15 (m, 6H), 2.2-2.8 (m, 14H), 3.2 (t, 1H, J = 7 Hz), 6.8-7.6 (m, 8H), 11.05 (s, NH)	3276, 1689
1v	1.5-2.1 (m, 8H), 2.3-2.8 (m, 14H), 3.2 (t, 1H, J = 7 Hz), 6.85-7.7 (m, 8H), 9 (s, NH)	3249, 1688

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