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Synthesis and preliminary behavioural evaluation in mice of new 3-aryl-3-pyrrol-1-ylpropanamides, analogues of FGIN-1-27 and FGIN-1-43

J. Guillon, M. Boulouard, V. Lelong, P. Dallemagne, S. Rault and C. Jarry

Abstract

The 2-aryl-3-indoleacetamides FGIN-1-27 and FGIN-1-43 have already been characterized in-vitro as potent and specific ligands for the mitochondrial DBI receptor. This affinity was associated with psychotropic properties in several rodent behavioural tasks (in particular anxiolytic action) via enhancement of GABA transmission through neurosteroid production. The synthesis of new 3-aryl-3-pyrrol-1-ylpropanamides **1a–i**, analogues of FGIN-1-27 and FGIN-1-43, is described in four steps starting from the corresponding arylaldehydes. Preliminary evaluation of these compounds in behavioural studies (spontaneous locomotor activity and anxiolytic activity) in mice was also undertaken.

Introduction

The mitochondrial DBI receptor complex (mDRC; previously described as the peripheral benzodiazepine receptors) is linked to the production of neurosteroids such as pregnenolone sulfate, dehydroepiandrosterone sulfate and others. 2-Aryl-3-indoleacetamides (FGIN-1-27 and FGIN-1-43) (Auta et al 1993; Kozikowski et al 1993; Romeo et al 1993a, b) are potent and specific ligands for the mitochondrial DBI receptor. In fact, these compounds bind specifically and with high affinity to the peptide DBI receptor on mitochondrial membranes. They induce the production of neurosteroids, which modulate GABA receptors, thus influencing behaviour such as anxiety.

As part of our program concerning the 3-amino-3-arylpropionic acid derivatives of therapeutic interest (Alsaidi et al 1994; Guillon et al 1996a, b, 1998a, b), we now report the synthesis and preliminary behavioural evaluation in mice of new 3-aryl-3-pyrrol-1-ylpropanamides **1a–i**, analogues of FGIN-1-27 and FGIN-1-43. All compounds were first evaluated in a large range of doses for spontaneous motor activity in order to detect global psychotropic activity. An anxiolytic test was undertaken in a model of unconditioned behaviour for the two most active compounds. Variations in the length and number of the alkyl groups on the amide nitrogen were probed together with the effects of halogen substituents on the aryl ring to determine structure–activity relationships in comparison with the reference compounds (Figure 1).

EA 2962–Pharmacochimie, UFR des Sciences Pharmaceutiques, Université Victor Segalen Bordeaux 2, 146 Rue Léo Saignat, 33076 Bordeaux cedex, France

J. Guillon, C. Jarry

Centre d'Etudes et de Recherche sur le Médicament de Normandie, Laboratoire de Pharmacochimie, UFR des Sciences Pharmaceutiques, 1 Rue Vaubénard, 14032 Caen cedex, France

M. Boulouard, V. Lelong, P. Dallemagne, S. Rault

Correspondence: J. Guillon, EA 2962 – Pharmacochimie, UFR des Sciences Pharmaceutiques, Universitié Victor Segalen Bordeaux 2, 146 Rue Léo Saignat, 33076 Bordeaux cedex, France.

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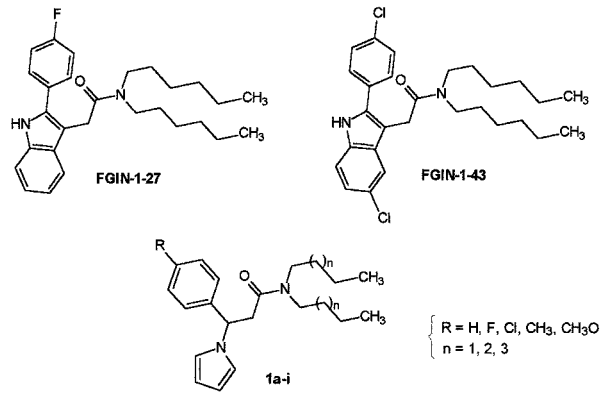


Figure 1 Structures of FGIN-1-27 and FGIN-1-43 and general structure of new compounds **1a**–**i**.

Materials and Methods

Chemical procedures

Melting points were determined with an SM-LUX-POL Leitz hot-stage microscope and are uncorrected. The IR spectra were recorded on a Bruker IFS-25 spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer (200 MHz) using deuteriochloroform as solvent. Chemical shifts (δ ppm) refer to tetramethylsilane, which was used as an internal reference. OH appeared as singlets exchangeable with D_2O. Key: t = triplet, s = singlet, d = doublet, dd = double doublet, m = multiplet. Elemental analyses (C, H, N) were performed by CNRS, Vernaison, France and agreed with the proposed structures to within $\pm$0.3% of the theoretical values.

General procedure for the preparation of 3-aryl-3-(pyrrol-1-yl)propanoic acids (5a–e)

To a solution of 3-amino-3-arylpropionic acid (**2a**–**e**) (0.125 M) in 150 mL acetic acid, 2,5-dimethoxytetrahydrofuran (0.125 M) was added. The reaction mixture was refluxed for 1 h and then evaporated to dryness. The residue was triturated with water and then extracted twice with 150 mL diethyl ether. The organic layer was washed with 200 mL water, dried over sodium sulfate and evaporated under reduced pressure to give compounds **5a**–**e**, which were purified by chromatography on silica gel using ethyl acetate–cyclohexane (20:80, v/v) as eluent.

*3-Phenyl-3-(pyrrol-1-yl)propanoic acid (**5a**)*
White crystals (75%); mp 120–121°C (Carceller et al 1993; Tembo et al 1993).

*3-(4-Fluorophenyl)-3-(pyrrol-1-yl)propanoic acid (**5b**)*
White crystals (72%); mp 89–91°C; IR (KBr) ν: 3350–2600 (OH), 1705 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ: 3.22 (1H, dd, J = 16.30 and 6.95, *H*-2b), 3.34 (1H, dd, J = 16.30 and 8.35, *H*-2a), 5.71 (1H, dd, J = 8.35 and 6.95, *H*-3), 6.29 (2H, dd, J = 2.05 and 2.05, *H*-β), 6.82 (2H, dd, J = 2.05 and 2.05, *H*-α), 7.07 (2H, dd, J = 8.65 and 8.45, *H*-3′ and *H*-5′), 7.21 (2H, dd, J = 8.45 and 5.70, *H*-2′ and *H*-6′), 11.91 (1H, s, O*H*); ^{13}C NMR ($CDCl_3$) δ: 35.6 (*C*H$_2$), 53.1 (*C*H), 103.8 (*C*-β), 110.6 (d, ^{2}J = 21.4, *C*-3′ and *C*-5′), 114.3 (*C*-α), 122.8 (d, ^{3}J = 8.0, *C*-2′ and *C*-6′), 131.0 (d, ^{4}J = 2.15, *C*-1′), 157.2 (d, ^{1}J = 245.4, *C*-4′), 171.4 (*C*O). Anal. calcd. for $C_{13}H_{12}FNO_2$: C, 66.94; H, 5.18; N, 6.00. Found: C, 66.88; H, 5.14; N, 6.09%.

*3-(4-Chlorophenyl)-3-(pyrrol-1-yl)propanoic acid (**5c**)*
Beige crystals (29%); mp 84–86°C; IR (KBr) ν: 3385–2700 (OH), 1715 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ: 3.15 (1H, dd, J = 16.30 and 6.85, *H*-2b), 3.27 (1H, dd, J = 16.30 and 8.20, *H*-2a), 5.62 (1H, dd, J = 8.20 and 6.85, *H*-3), 6.20 (2H, dd, J = 2.05 and 2.05, *H*-β), 6.73 (2H, dd, J = 2.05 and 2.05, *H*-α), 7.09 (2H, d, J = 8.45, *H*-3′ and *H*-5′), 7.31 (2H, d, J = 8.45, *H*-2′ and *H*-6′), 11.74 (1H, s, O*H*); ^{13}C NMR ($CDCl_3$) δ: 39.9 (*C*H$_2$), 57.7 (*C*H), 108.4 (*C*-β), 118.9 (*C*-α), 126.9 (*C*-3′ and *C*-5′), 128.4 (*C*-2′ and *C*-6′), 133.4 (*C*-1′), 138.2 (*C*-4′), 175.6 (*C*O). Anal. calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.47; H, 4.69; N, 5.43%.

*3-(4-Methylphenyl)-3-(pyrrol-1-yl)propanoic acid (**5d**)*
White crystals (69%); mp 97–98°C; IR (KBr) ν: 3320–2700 (OH), 1710 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ: 2.41 (3H, C*H*$_3$), 3.23 (1H, dd, J = 16.30 and 7.00, *H*-2b), 3.33 (1H, dd, J = 16.30 and 8.30, *H*-2a), 5.69 (1H, dd, J = 8.30 and 7.00, *H*-3), 6.27 (2H, dd, J = 2.10 and 2.10, *H*-β), 6.82 (2H, dd, J = 2.10 and 2.10, *H*-α), 7.15 (2H, d, J = 8.15, *H*-2′ and *H*-6′), 7.22 (2H, d, J = 8.15, *H*-3′ and *H*-5′), 11.19 (1H, s, O*H*); ^{13}C NMR ($CDCl_3$) δ: 21.1 (*C*H$_3$), 40.8 (*C*H$_2$), 58.8 (*C*H), 108.7 (*C*-β), 119.6 (*C*-α), 126.3 (*C*-2′ and *C*-6′), 129.6 (*C*-3′ and *C*-5′), 137.3 (*C*-4′), 137.9 (*C*-1′), 176.7 (*C*O). Anal. calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.50; H, 6.69; N, 6.19%.

*3-(4-Methoxyphenyl)-3-(pyrrol-1-yl)propanoic acid (**5e**)*
White crystals (71%); mp 102–104°C; IR (KBr) ν: 3300–2550 (OH), 1715 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ: 3.14 (1H, dd, J = 16.20 and 8.00, *H*-2b), 3.23 (1H, dd, J = 16.20 and 7.05, *H*-2a), 3.77 (3H, s, C*H*$_3$O), 5.59 (1H,

dd, J = 8.00 and 7.05, *H*-3), 6.15 (2H, dd, J = 2.00 and 2.00, *H*-β), 6.71 (2H, dd, J = 2.00 and 2.00, *H*-α), 6.85 (2H, d, J = 8.25, *H*-3′ and *H*-5′), 7.12 (2H, d, J = 8.25, *H*-2′ and *H*-6′), 11.19 (1H, s, O*H*); ^{13}C NMR ($CDCl_3$) δ: 40.8 (*C*H_2), 55.3 (*C*H_3O), 58.4 (*C*H), 108.6 (*C*-β), 114.2 (*C*-α), 119.4 (*C*-3′ and *C*-5′), 127.5 (*C*-2′ and *C*-6′), 132.2 (*C*-1′), 159.3 (*C*-4′), 176.4 (*C*O). Anal. calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.47; H, 6.05; N, 5.56%.

General procedure for the preparation of *N,N*-dialkyl-3-aryl-3-(pyrrol-1-yl)propanamides (1a–i)

To a stirred solution of compounds **5a**–**e** (21 mM) in 80 mL acetone at 0°C, triethylamine (21 mM) was added dropwise. After 30 min, ethyl chloroformate (21 mM) was added dropwise at 0°C. After 30 min, dialkylamine (21 mM) was added under the same conditions. The reaction mixture was refluxed for 3 h and then cooled at room temperature. After filtration of the precipitate, the filtrate was evaporated to dryness. The oily residue was taken up in 150 mL methylene chloride. The organic layer was washed with a 1 M aqueous hydrochloric acid solution (2 × 100 mL), then with a saturated aqueous sodium hydrogenocarbonate solution (2 × 100 mL), dried over sodium sulfate and evaporated to dryness. The oily residue was purified by chromatography on silica gel using chloroform as eluent.

N,N-*Dihexyl-3-phenyl-3-(pyrrol-1-yl)propanamide (**1a**)*
Pale yellow oil (38%); IR (KBr) ν: 1640 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ: 0.85 (3H, t, J = 6.35, C*H*$_3$), 0.88 (3H, t, J = 6.35, C*H*$_3$), 1.39 (12H, m, C*H*$_2$), 1.45 (4H, m, C*H*$_2$), 3.11 (4H, m, NC*H*$_2$), 3.24 (2H, m, *H*-2), 5.85 (1H, dd, J = 8.10 and 7.00, *H*-3), 6.13 (2H, dd, J = 2.10 and 2.10, *H*-β), 6.70 (2H, dd, J = 2.10 and 2.10, *H*-α), 7.18 (2H, m, *H*-arom), 7.26 (3H, m, *H*-arom); ^{13}C NMR ($CDCl_3$) δ: 13.6 (*C*H_3), 13.7 (*C*H_3), 22.1 (*C*H_2), 26.1 (*C*H_2), 26.2 (*C*H_2), 27.2 (*C*H_2), 28.7 (*C*H_2), 31.1 (*C*H_2), 31.2 (*C*H_2), 39.1 (*C*H_2), 46.0 (N*C*H_2), 47.6 (N*C*H_2), 59.3 (*C*H), 107.8 (*C*-β), 119.4 (*C*-α), 126.2 (*C*-3′ and *C*-5′), 127.3 (*C*-1′), 128.2 (*C*-2′ and *C*-6′), 140.8 (*C*-4′), 168.4 (*C*O). Anal. calcd. for $C_{25}H_{38}N_2O$: C, 78.48; H, 10.01; N, 7.32. Found: C, 78.19; H, 9.70; N, 7.21%.

N,N-*Dihexyl-3-(4-fluorophenyl)-3-(pyrrol-1-yl)propanamide (**1b**)*
Pale yellow oil (52%); IR (KBr) ν: 1640 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ: 0.86 (3H, t, J = 6.30, C*H*$_3$), 0.88 (3H, t, J = 6.30, C*H*$_3$), 1.25 (12H, m, C*H*$_2$), 1.42 (4H, m, C*H*$_2$), 3.11 (4H, m, NC*H*$_2$), 3.26 (2H, m, *H*-2), 5.84 (1H, dd, J = 8.00 and 6.95, *H*-3), 6.13 (2H, dd, J = 2.10 and 2.10, *H*-β), 6.69 (2H, dd, J = 2.10 and 2.10, *H*-α), 6.96 (2H, dd, J = 8.70 and 8.55, *H*-3′ and *H*-5′), 7.16 (2H, dd, J = 8.55 and 5.35, *H*-2′ and *H*-6′); ^{13}C NMR ($CDCl_3$) δ: 14.0 (*C*H_3), 22.6 (*C*H_2), 26.5 (*C*H_2), 26.6 (*C*H_2), 27.6 (*C*H_2), 29.1 (*C*H_2), 29.7 (*C*H_2), 31.5 (*C*H_2), 31.6 (*C*H_2), 39.6 (*C*H_2), 46.4 (N*C*H_2), 48.0 (N*C*H_2), 59.1 (*C*H), 108.4 (*C*-β), 115.4 (d, ^{2}J = 21.3, *C*-3′ and *C*-5′), 119.7 (*C*-α), 128.3 (d, ^{3}J = 8.10, *C*-2′ and *C*-6′), 137.1 (d, ^{4}J = 2.05, *C*-1′), 162.2 (d, ^{1}J = 245.05, *C*-4′), 168.6 (*C*O). Anal. calcd. for $C_{25}H_{37}FN_2O$: C, 74.96; H, 9.31; N, 6.99. Found: C, 74.67; H, 9.36; N, 6.87%.

N,N-*Dihexyl-3-(4-chlorophenyl)-3-(pyrrol-1-yl)propanamide (**1c**)*
Orange oil (28%); IR (KBr) ν: 1645 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ: 0.86 (3H, t, J = 6.40, C*H*$_3$), 0.88 (3H, t, J = 6.40, C*H*$_3$), 1.23 (12H, m, C*H*$_2$), 1.43 (4H, m, C*H*$_2$), 3.10 (4H, m, NC*H*$_2$), 3.25 (2H, m, *H*-2), 5.82 (1H, dd, J = 8.20 and 7.00, *H*-3), 6.13 (2H, dd, J = 2.05 and 2.05, *H*-β), 6.67 (2H, dd, J = 2.05 and 2.05, *H*-α), 7.09 (2H, d, J = 8.20, *H*-3′ and *H*-5′), 7.25 (2H, d, J = 8.20, *H*-2′ and *H*-6′); ^{13}C NMR ($CDCl_3$) δ: 13.4 (*C*H_3), 21.9 (*C*H_2), 25.9 (*C*H_2), 26.0 (*C*H_2), 26.9 (*C*H_2), 28.5 (*C*H_2), 30.8 (*C*H_2), 30.9 (*C*H_2), 38.7 (*C*H_2), 45.7 (N*C*H_2), 47.3 (N*C*H_2), 58.4 (*C*H), 107.8 (*C*-β), 119.0 (*C*-α), 127.3 (*C*-3′ and *C*-5′), 128.1 (*C*-2′ and *C*-6′), 132.8 (*C*-1′), 139.2 (*C*-4′), 167.8 (*C*O). Anal. calcd. for $C_{25}H_{37}ClN_2O$: C, 72.00; H, 8.94; N, 6.72. Found: C, 71.88; H, 9.12; N, 6.85%.

N,N-*Dihexyl-3-(4-methylphenyl)-3-(pyrrol-1-yl)propanamide (**1d**)*
Colourless oil (27%); IR (KBr) ν: 1645 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6.30, C*H*$_3$), 0.90 (3H, t, J = 6.30, C*H*$_3$), 1.27 (12H, m, C*H*$_2$), 1.43 (4H, m, C*H*$_2$), 3.12 (4H, m, NC*H*$_2$), 3.26 (2H, m, *H*-2), 5.83 (1H, dd, J = 8.05 and 7.00, *H*-3), 6.13 (2H, dd, J = 2.00 and 2.00, *H*-β), 6.71 (2H, dd, J = 2.00 and 2.00, *H*-α), 7.09 (2H, d, J = 8.00, *H*-2′ and *H*-6′), 7.12 (2H, d, J = 8.00, *H*-3′ and *H*-5′); ^{13}C NMR ($CDCl_3$) δ: 14.0 (*C*H_3), 14.1 (*C*H_3), 21.0 (*C*H_2), 22.5 (*C*H_2), 26.5 (*C*H_2), 26.6 (*C*H_2), 27.5 (*C*H_2), 29.1 (*C*H_2), 31.5 (*C*H_2), 31.6 (*C*H_2), 39.5 (*C*H_2), 46.3 (N*C*H_2), 47.9 (N*C*H_2), 59.5 (*C*H), 108.1 (*C*-β), 119.7 (*C*-α), 126.5 (*C*-2′ and *C*-6′), 129.3 (*C*-3′ and *C*-5′), 137.3 (*C*-4′), 138.2 (*C*-1′), 168.9 (*C*O). Anal. calcd. for $C_{26}H_{40}N_2O$: C, 78.74; H, 10.16; N, 7.06. Found: C, 78.90; H, 10.05; N, 6.91%.

N,N-*Dihexyl-3-(4-methoxyphenyl)-3-(pyrrol-1-yl)propanamide (**1e**)*
Colourless oil (25%); IR (KBr) ν: 1645 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ: 0.85 (3H, t, J = 6.60, CH_3), 0.87 (3H, t, J = 6.60, CH_3), 1.24 (12H, m, CH_2), 1.35 (4H, m, CH_2), 3.12 (4H, m, NCH_2), 3.24 (2H, m, *H*-2), 5.79 (1H, dd, J = 8.10 and 7.00, *H*-3), 6.10 (2H, dd, J = 2.00 and 2.00, *H*-β), 6.68 (2H, dd, J = 2.00 and 2.00, *H*-α), 6.82 (2H, d, J = 6.90, *H*-3′ and *H*-5′), 7.12 (2H, d, J = 6.90, *H*-2′ and *H*-6′); ^{13}C NMR ($CDCl_3$) δ: 14.0 (CH_3), 22.5 (CH_2), 26.5 (CH_2), 26.6 (CH_2), 27.5 (CH_2), 29.1 (CH_2), 31.4 (CH_2), 31.6 (CH_2), 39.6 (CH_2), 46.3 (NCH_2), 47.9 (NCH_2), 55.2 (CH_3O), 59.2 (*C*H), 108.1 (*C*-β), 113.9 (*C*-3′ and *C*-5′), 119.6 (*C*-α), 127.8 (*C*-2′ and *C*-6′), 133.2 (*C*-1′), 159.0 (*C*-4′), 168.9 (*C*O). Anal. calcd. for $C_{26}H_{40}N_2O_2$: C, 75.68; H, 9.77; N, 6.79. Found: C, 75.49; H, 10.02; N, 6.85%.

N,N-*Dipentyl-3-phenyl-3-(pyrrol-1-yl)propanamide (**1f**)*
White crystals (31%); mp 37–39°C; IR (KBr) ν: 1630 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ: 0.86 (3H, t, J = 6.55, CH_3), 0.89 (3H, t, J = 6.55, CH_3), 1.21 (8H, m, CH_2), 1.43 (4H, m, CH_2), 3.08 (4H, m, NCH_2), 3.25 (2H, m, *H*-2), 5.86 (1H, dd, J = 8.10 and 7.05, *H*-3), 6.13 (2H, dd, J = 2.05 and 2.05, *H*-β), 6.71 (2H, dd, J = 2.05 and 2.05, *H*-α), 7.18 (2H, m, *H*-arom), 7.27 (3H, m, *H*-arom); ^{13}C NMR ($CDCl_3$) δ: 13.9 (CH_3), 22.3 (CH_2), 22.4 (CH_2), 27.2 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 39.4 (CH_2), 46.2 (NCH_2), 47.9 (NCH_2), 59.7 (*C*H), 108.1 (*C*-β), 119.7 (*C*-α), 126.5 (*C*-3′ and *C*-5′), 127.6 (*C*-1′), 128.6 (*C*-2′ and *C*-6′), 141.1 (*C*-4′), 168.8 (*C*O). Anal. calcd. for $C_{23}H_{34}N_2O$: C, 77.92; H, 9.66; N, 7.90. Found: C, 78.10; H, 9.76; N, 8.05%.

N,N-*Dipentyl-3-(4-fluorophenyl)-3-(pyrrol-1-yl)-propanamide (**1g**)*
White crystals (25%); mp 44–45°C; IR (KBr) ν: 1630 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ: 0.85 (3H, t, J = 7.00, CH_3), 0.89 (3H, t, J = 7.00, CH_3), 1.24 (8H, m, CH_2), 1.39 (4H, m, CH_2), 3.11 (4H, m, NCH_2), 3.25 (2H, m, *H*-2), 5.83 (1H, dd, J = 8.05 and 6.95, *H*-3), 6.13 (2H, dd, J = 2.10 and 2.10, *H*-β), 6.68 (2H, dd, J = 2.10 and 2.10, *H*-α), 6.96 (2H, dd, J = 8.60 and 8.50, *H*-3′ and *H*-5′), 7.15 (2H, dd, J = 8.50 and 5.45, *H*-2′ and *H*-6′); ^{13}C NMR ($CDCl_3$) δ: 13.9 (CH_3), 22.3 (CH_2), 22.4 (CH_2), 27.2 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 39.5 (CH_2), 46.3 (NCH_2), 47.9 (NCH_2), 59.1 (*C*H), 108.4 (*C*-β), 115.4 (d, ^2J = 21.2, *C*-3′ and *C*-5′), 119.6 (*C*-α), 128.2 (d, ^3J = 8.50, *C*-2′ and *C*-6′), 137.1 (d, ^4J = 2.95, *C*-1′), 162.1 (d, ^1J = 245.9, *C*-4′), 168.6 (*C*O). Anal. calcd. for $C_{23}H_{33}FN_2O$: C, 74.15; H, 8.93; N, 7.52. Found: C, 74.44; H, 9.10; N, 7.44%.

N,N-*Dibutyl-3-phenyl-3-(pyrrol-1-yl)propanamide (**1h**)*
White crystals (26%); mp 40–41°C; IR (KBr) ν: 1640 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ: 0.89 (3H, t, J = 7.00, CH_3), 0.92 (3H, t, J = 7.00, CH_3), 1.23 (4H, m, CH_2), 1.43 (4H, m, CH_2), 3.10 (4H, m, NCH_2), 3.28 (2H, m, *H*-2), 5.88 (1H, dd, J = 7.90 and 6.95, *H*-3), 6.14 (2H, dd, J = 2.10 and 2.10, *H*-β), 6.72 (2H, dd, J = 2.10 and 2.10, *H*-α), 7.19 (2H, m, *H*-arom), 7.29 (3H, m, *H*-arom); ^{13}C NMR ($CDCl_3$) δ: 13.8 (CH_3), 13.9 (CH_3), 20.1 (CH_2), 20.2 (CH_2), 29.7 (CH_2), 31.2 (CH_2), 39.4 (CH_2), 46.1 (NCH_2), 47.7 (NCH_2), 59.8 (*C*H), 108.2 (*C*-β), 119.8 (*C*-α), 125.6 (*C*-3′ and *C*-5′), 127.7 (*C*-1′), 128.6 (*C*-2′ and *C*-6′), 141.2 (*C*-4′), 168.9 (*C*O). Anal. calcd. for $C_{21}H_{30}N_2O$: C, 77.25; H, 9.26; N, 8.58. Found: C, 77.50; H, 9.36; N, 8.57%.

N,N-*Dibutyl-3-(4-fluorophenyl)-3-(pyrrol-1-yl)-propanamide (**1i**)*
White crystals (41%); mp 35–37°C; IR (KBr) ν: 1635 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ: 0.87 (3H, t, J = 7.05, CH_3), 0.91 (3H, t, J = 7.05, CH_3), 1.19 (4H, m, CH_2), 1.40 (4H, m, CH_2), 3.08 (4H, m, NCH_2), 3.27 (2H, m, *H*-2), 5.84 (1H, dd, J = 7.95 and 7.00, *H*-3), 6.13 (2H, dd, J = 2.10 and 2.10, *H*-β), 6.69 (2H, dd, J = 2.10 and 2.10, *H*-α), 6.96 (2H, dd, J = 8.85 and 8.65, *H*-3′ and *H*-5′), 7.17 (2H, dd, J = 8.65 and 5.30, *H*-2′ and *H*-6′); ^{13}C NMR ($CDCl_3$) δ: 13.7 (CH_3), 13.8 (CH_3), 20.0 (CH_2), 20.1 (CH_2), 29.7 (CH_2), 31.2 (CH_2), 39.5 (CH_2), 46.1 (NCH_2), 47.7 (NCH_2), 59.1 (*C*H), 108.4 (*C*-β), 115.4 (d, ^2J = 21.3, *C*-3′ and *C*-5′), 119.6 (*C*-α), 128.3 (d, ^3J = 7.80, *C*-2′ and *C*-6′), 137.1 (d, ^4J = 1.95, *C*-1′), 162.1 (d, ^1J = 245.0, *C*-4′), 168.6 (*C*O). Anal. calcd. for $C_{21}H_{29}FN_2O$: C, 73.22; H, 8.48; N, 8.13. Found: C, 73.03; H, 8.64; N, 8.11%.

Pharmacological procedures

Animals

Male OF-1 mice (Iffa Credo), 20–24 g, were used for the pharmacological studies. The animals were allowed free access to food and water. They were housed at a temperature of 21–22°C and maintained under a 12-h light–dark cycle. Behavioural testing was conducted during the dark phase of the cycle (1300–1800 h). All

experiments were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication No. 85-23, revised 1985), European directives and French laws on animal experimentation.

Drugs

The test compounds **1a**–**1i** and the pharmacological references (chlorpromazine (Specia) for the photoactimetry test and diazepam (Roche) for light/dark exploration test) were suspended in a 1% carboxymethylcellulose suspension and administered intraperitoneally in a volume of 10 mL kg^{-1}. Controls received the same amount of vehicle.

Locomotor activity

Locomotor activity (Boissier & Simon 1965) was recorded for 15 min with a photocell activity meter beginning 30 min after intraperitoneal administration of each test drug (n = 12 for each dose).

Light/dark exploration test

For the light/dark exploration test (Costall et al 1989), test boxes, constructed entirely of perspex, had two compartments with 270-mm high walls. One compartment (coloured matt black) measured 270 × 180 mm, and the other (coloured matt white) measured 270 × 270 mm (interior dimensions). Both compartments were separated by a wall (470 mm high, to act as a light separator) with a 70 × 70-mm opening in the base. The boxes did not have a top cover. Each compartment was independently illuminated: the white compartment with a 100-W white bulb and the black compartment with a 40-W red bulb. Both bulbs were located 370 mm from the floor of the box. Each mouse (n = 12 for each dose) was placed in the center of the light/dark box, and then measurements of the number of transitions between light and dark compartments and of the time spent in the light compartment were made over a 5-min period starting 30 min after intraperitoneal administration of the test compounds.

Statistical analysis

The result are expressed as mean ± s.e.m. of the scores (number of interrupted beams in the photoactimetry test and number of transitions and time in the light compartment in the light/dark exploration test). The results were analysed using analysis of variance followed by the Fischer's protected least significant difference (PLSD) test. P values < 0.05 were considered significant.

Results

Chemistry

During the course of our work on the synthesis of new heterocyclic compounds of potential therapeutic interest, we recently described the access to numerous 3-amino-3-arylpropionic acids (**2a**–**e**) in 35–60% yields starting from commercial arylaldehydes (Dallemagne et al 1986; Rault et al 1987, 1991). The β-amino-acids **2a**–**e** were synthesized by the Rodionow-Johnson reaction (Rodionow & Malewinskaja 1926; Johnson & Livak 1936; Profft & Becker 1965; Guillon et al 1998a, b; Sonnet et al 2000) via the corresponding imines **3a**–**e** (Figure 2). Moreover, a not-negligible quantity (10–25%) of dicarboxylic acids **4a**–**e** was isolated as the intermediate product of the well-known Knoevenagel synthesis of cinnamic acids (Johnson 1942). Treatment of **2a**–**e** with 2,5-dimethoxytetrahydrofuran in boiling acetic acid according to the Clauson-Kaas method (Elming & Clauson-Kaas 1952; Clauson-Kaas & Tyle 1952), led to the arylpyrrolylpropanoic acids **5a**–**e** (Carceller et al 1993; Tembo et al 1993). The Clauson-Kaas reaction represented an easy method for the preparation of *N*-substituted pyrroles from primary amino derivatives. The acids were converted to their mixed anhydrides **6a**–**e** with ethyl chloroformate in presence of triethylamine, and these intermediates **6a**–**e** reacted in-situ with the dialkylamine of choice to afford the amides **1a**–**i**, which were purified by chromatography on silica gel using chloroform as eluent (Kozikowski et al 1993;

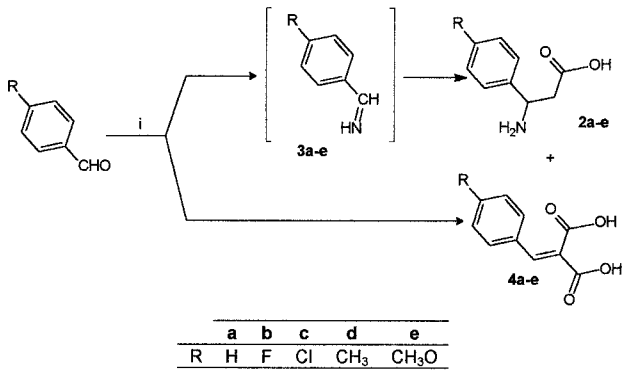
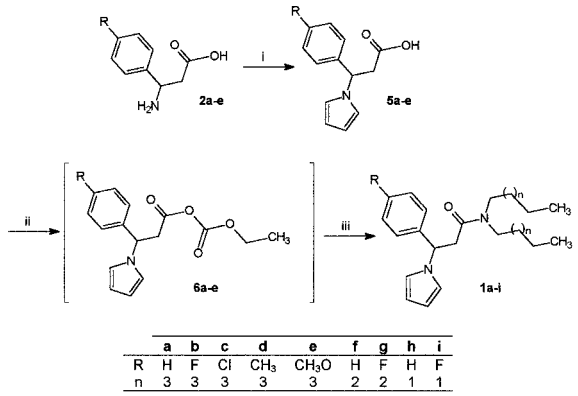


Figure 2 Synthesis of the β-amino-acids **2a**–**e**. Reagents: i. CH_3COONH_4, $CH_2(COOH)_2$, C_2H_5OH.



	a	b	c	d	e	f	g	h	i
R	H	F	Cl	CH_3	CH_3O	H	F	H	F
n	3	3	3	3	3	2	2	1	1

Figure 3 Synthesis of amides **1a**–**i**. Reagents: i. 2,5-dimethoxytetrahydrofuran, AcOH; ii. $(C_2H_5)_3N$, CH_3COCH_3, $ClCOOC_2H_5$; iii. $[CH_3CH_2(CH_2)_nCH_2]_2NH$.

Renault et al 1999) (Figure 3). In the ^{13}C NMR spectra of the fluorine compounds **5b** and **1b**, **g**, **f**, the aromatic carbon absorption exhibited four typical doublets at 110.6–115.4 ppm for C-3′ and C-5′ ($^2J_{CF} = 21.2$–21.4 Hz), 122.8–128.2 ppm for C-2′ and C-6′ ($^3J_{CF} = 7.8$–8.5 Hz), 131.0–137.1 ppm for C-1′ ($^4J_{CF} = 1.95$–2.95 Hz) and 157.2–162.2 ppm for C-4′ ($^1J_{CF} = 245.0$–245.9 Hz). The different measured aromatic coupling constant values (J_{CF}) were in accordance with those described in the literature for para-fluorobenzene derivatives (Stothers 1972; Pretsch et al 1989).

Pharmacology

Compounds **1a**–**i** were first evaluated in a large range of doses for spontaneous motor activity to detect global psychotropic activity. Two pharmacological tests were used for the evaluation of the in-vivo central potential activity – the photoactimetry test (Boissier & Simon 1965) measuring spontaneous activity, and the black and white test box (Costall et al 1989), a model based on fear of novelty. All compounds were evaluated in the first model at four doses (0.1, 1, 10 and 100 mg kg^{-1}). These doses were selected in accordance with those previously used for FGIN compounds in behavioural studies (Romeo et al 1993a, b). At the upper dose (100 mg kg^{-1}), none of the compounds **1a**–**i** revealed strong acute toxic effects (i.e. no prostration no convulsion and no tremor) and no mortality was observed at 48 h. The pharmacological data for the 100 mg kg^{-1} dose are given in Table 1. They distinguished between compounds **1f** and **1g** with no sedative activity, compounds **1a**, **1h** and **1i** with mild sedative activity and compounds **1b**, **1c**, **1d** and **1e**, which presented high central depressive activity. Compound **1b** appeared to be the most active compound because at 10 mg kg^{-1} it produced a decrease of spontaneous activity similar to that induced by chlorpromazine at 4 mg kg^{-1} (68 ± 19 interrupted beams vs 66 ± 17 for chlorpromazine).

Anxiolytic properties of two of the most sedative compounds, **1b** and **1c**, were tested in a model of unconditioned behaviour using the light/dark exploration test. This model is known to be sensitive to numerous antineophobic drugs (such as benzodiazepines or 5-HT_{1A} agonists) and also to many compounds that increase neurosteroid production. Under the experimental conditions, at doses of 1, 2.5 and 5 mg kg^{-1} (no sedative effect), the compounds did not present significant anxiolytic activity (Table 2). Under the same conditions, diazepam, which was used as a reference compound, induced anxiolytic behaviour at doses of 2.5 and 5 mg kg^{-1} (Table 2).

Table 1 Effects of tested compounds **1a**–**i** and chlorpromazine on spontaneous activity in mice[a].

Compounds	Dose (mg kg^{-1})	Number of interrupted beams (mean ± s.e.m.)
Control	–	383 ± 45
1a	100	90 ± 23***
Chlorpromazine	4	51 ± 28***
Control	–	259 ± 42
1b	100	54 ± 11**
Chlorpromazine	4	66 ± 17**
Control	–	400 ± 54
1c	100	133 ± 31***
Chlorpromazine	4	64 ± 11***
Control	–	367 ± 65
1d	100	34 ± 9**
Chlorpromazine	4	33 ± 13**
Control	–	320 ± 37
1e	100	149 ± 21**
Chlorpromazine	4	34 ± 6***
Control	–	279 ± 37
1f	100	244 ± 48
Chlorpromazine	4	24 ± 7**
Control	–	306 ± 44
1g	100	249 ± 37
Chlorpromazine	4	16 ± 6***
Control	–	435 ± 33
1h	100	87 ± 29***
Chlorpromazine	4	68 ± 15***
Control	–	282 ± 74
1i	100	35 ± 9*
Chlorpromazine	4	28 ± 8**

[a]All the compounds were tested at 0.1, 1, 10 and 100 mg kg^{-1}, but only results at 100 mg kg^{-1} are given. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with control.

Table 2 Pharmacological data of compounds **1b**, **1c** and diazepam in the light/dark exploration test.

Compounds	Dose (mg kg^{-1})	Number of transitions (mean ± s.e.m.)	Time in light (white) compartment(s) (mean ± s.e.m.)
Control	–	12 ± 2.7	57 ± 13
1b	1	9.6 ± 1.8	46 ± 17
1b	2.5	11.5 ± 2.5	52 ± 16
1b	5	7.5 ± 1.7	39 ± 15
Control	–	11.5 ± 2.7	46 ± 13
1c	1	11.2 ± 1.9	49 ± 17
1c	2.5	9.5 ± 2.4	41 ± 14
1c	5	10.6 ± 2.1	52 ± 15
Control	–	8.5 ± 1.5	36.3 ± 7.5
Diazepam	1	6.7 ± 1.3	39.5 ± 8.2
Diazepam	2.5	18 ± 4.4*	89.9 ± 12*
Diazepam	5	12 ± 2.5	85.6 ± 17*

*$P < 0.05$ compared with control.

Discussion

In this work, we synthesized new analogues of compounds FGIN-1-27 and F-GIN-1-43 previously characterized in-vitro as potent and specific ligands for the mitochondrial DBI receptor. We chose to change the indole ring for a pyrrole ring, whereas we preserved the dialkylation on the amide nitrogen by long and alkyl chains as the para substitution of the phenyl ring on the indole nitrogen. The presence of those two last structural items in FGIN-1 derivatives appears to be essential for binding to the mitochondrial DBI receptor complex (Romeo et al 1993a, b). In mice, the in-vivo preliminary pharmacological studies of the new products **1a–i** showed a central depressive activity characterized by a decrease of the spontaneous activity. As a general rule, we noted that the most active compounds, **1b–e**, bore two *n*-hexyl groups on the amide nitrogen and substituents located at the para position of the 3-aryl ring. Moreover, compounds **1b** and **1c**, which present some structural similarities with FGIN-1-27 and FGIN-1-43 (with fluoro and chloro substituents on the phenyl ring, respectively), exhibited the most intensive depressive activity. However, they showed no significant anxiolytic activity in the black and white test box. This is probably related to a different psychotropic profile compared with those of the FGIN-1 reference compounds.

In conclusion, the preliminary structure–activity relationship results indicated that the replacement of the indole ring in FGIN-1 compounds by a pyrrole ring in **1a–i** led to compounds with various sedative profiles, but without anxiolytic activity. Among these new 3-aryl-3-pyrrolylpropanamides, compounds **1b** and **1c**, which are structurally similar to FGIN-1-27 and FGIN-1-43, presented the highest sedative activity. These results suggest a psychotropic profile different from that of the FGIN-1 references and further investigations are required to specify the mechanism of central depressive activity.

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