Journal of Enzyme Inhibition and Medicinal Chemistry, 2003 Vol. 18 (2), pp. 147–153

Taylor & Francis
healthsciences

Synthesis and Initial Results for MAO-B Inhibition by New *N*-Propargyl-3-pyrrol-1-ylindanamine Derivatives, Analogues of Rasagiline

JEAN GUILLON[a], GUILLAUME HÉBERT[b], PATRICK DALLEMAGNE[c], JEAN-MICHEL LÉGER[a], CÉLINE VIDAILLAC[a], CORINNE THÉ[a], VINCENT LISOWSKI[c], SYLVAIN RAULT[c], JACQUES DEMOTES-MAINARD[b] and CHRISTIAN JARRY[a,*]

[a]*EA 2962—Pharmacochimie, UFR des Sciences Pharmaceutiques, Université Victor Segalen Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France;* [b]*INSERM U-394, Neurobiologie Intégrative, Institut François Magendie, Université Victor Segalen Bordeaux 2, rue Camille Saint-Saens, 33077 Bordeaux Cedex, France;* [c]*Centre d'Etudes et de Recherche sur le Médicament de Normandie, UFR des Sciences Pharmaceutiques, 1 rue Vaubénard, 14032 Caen Cedex, France*

(Received 1 July 2002; In final form 15 October 2002)

The synthesis of new *N*-propargyl-3-pyrrol-1-ylindanamine derivatives, analogues of rasagiline, is described in ten steps starting from the corresponding arylaldehydes *via* the corresponding *cis*-3-pyrrol-1-ylindanamines. The *cis*-configuration of some intermediates has been established using X-ray analysis and NOE experiments. The new *N*-propargyl-3-pyrrol-1-ylindanamine derivatives were evaluated for their potential MAO-B inhibitor activity in an *in vivo* model of MPTP-induced Parkinsonism in mice with respect to the potent MAO-B inhibitor rasagiline.

Keywords: MAO-B; *N*-Propargyl-3-pyrrol-1-ylindanamine; *N*-Propargyl-3-pyrrol-1-ylcyclopenta[*b*]thiophenamine, 3-Amino-3-arylpropionic acids; Rasagiline

INTRODUCTION

Parkinson's disease is a neurodegenerative disorder characterised by the progressive loss of striatal dopaminergic innervation, leading to the emergence of three major symptoms: tremor, akinesia and rigidity.[1] In order to restore a sufficient striatal dopamine level, either L-DOPA substitutive treatment, or blockade of the dopamine inactivation process by monoamine oxidase B (MAO-B) inhibitors like selegiline (L-deprenyl), are currently used as symptomatic treatment for Parkinson's disease.[2]

However, Parkinson's disease can be modelled by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injection in primates and rodents. After transformation by MAO-B into its active metabolite salt, 1-methyl-4-phenyl-pyridinium (MPP^+), this drug induces a rapid striatal dopaminergic denervation.[3] Rasagiline, a restricted analogue of selegiline, is a novel selective and irreversible monoamine oxidase-B (MAO-B) inhibitor that can then protect against MPTP-induced neurotoxicity.[4–7] MPTP-induced striatal dopaminergic denervation can thus be used as a bioassay for the *in vivo* activity of MAO-B.

As part of our program concerning 3-amino-3-arylpropionic acid derivatives of therapeutic interest,[8–10] we now report the synthesis and initial results of MAO-B inhibition by the new *N*-propargyl-3-pyrrol-1-ylindanamine hydrochloride **1a** and *N*-propargyl-3-pyrrol-1-ylcyclopenta[*b*]thiophenamine hydrochloride **1b**. These compounds could be regarded as pyrrolyl analogues of rasagiline, keeping a part of the required pharmacophore (Figure 1). These new compounds **1a**–**b** might protect against the MPTP-induced dopaminergic neuronal death and striatum denervation. In order to investigate a putative MAO-B inhibitory activity of these new derivatives, **1a**–**b** and rasagiline have been injected intraperitoneally in mice during a period overlapping the MPTP injection at different doses. Striatal dopamine transporter (DAT) quantification was then

*Corresponding author. Tel.: +(0) 5-57-57-11-76. Fax: +(0) 5-57-57-13-52. E-mail: christian.jarry@chimphys.u-bordeaux2.fr

ISSN 1475-6366 print/ISSN 1475-6374 online
DOI: 10.1080/1475636032000069800

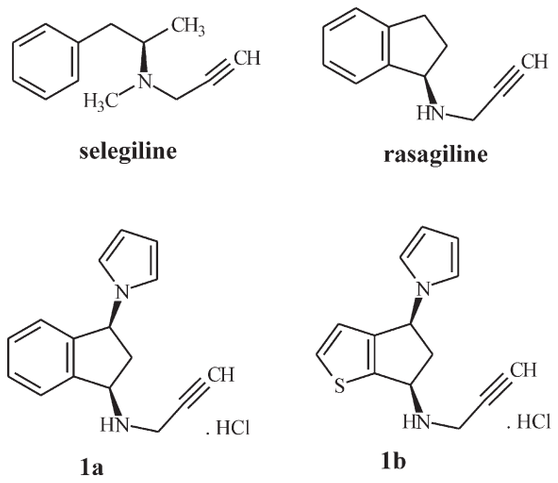


FIGURE 1 Structure of selegiline, rasagiline, *N*-propargyl-3-pyrrol-1-ylindanamine and *N*-propargyl-3-pyrrol-1-ylcyclopenta[*b*]thiophenamine hydrochlorides **1a**–**b**.

performed by measuring [^{3}H]-GBR-12935 binding on striatal slices to assess striatal dopaminergic denervation.

MATERIALS AND METHODS

Chemistry

Melting points were determined with an SM-LUX-POL Leitz hot-stage microscope and are reported uncorrected. Infrared (IR) spectra were determined in KBr discs on a BRUKER IFS-25 spectrometer. NMR spectra were recorded on a BRUKER AC 200 spectrometer (200 MHz). Chemical shifts refer to tetramethylsilane which was used as an internal reference. Elemental analyses were conducted by CNRS, Vernaison, France and the results were within ±0.3% of their calculated values. Rasagiline was synthesized in analogy to described procedures.[6–7]

General Procedure for the Preparation of 3-Pyrrol-1-ylindanone 7a and 3-Pyrrol-1-yl-cyclopenta[b]thiophenone 7b

To a solution of 3-aminoindanone **6a** or 3-amino-cyclopenta[*b*]thiophenone **6b** (70 mmol) in acetic acid (120 ml), was added 2,5-dimethoxytetrahydrofuran (70 mmol). The reaction mixture was refluxed for 1 h and then evaporated to dryness. The residue was triturated with water and then extracted twice with diethyl ether (150 ml). The organic layer was washed with a saturated aqueous sodium bicarbonate solution, then with water, dried over sodium sulfate and evaporated under reduced pressure to give compounds **7a**–**b**.

3-Pyrrol-1-ylindanone **7a**

As beige crystals (44%), m.p. 73°C (diethyl ether/hexane). IR (KBr), cm^{-1}: 1715 (CO); ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 2.78 (dd, J = 19.10 and 3.75, 1H, H-2a), 3.28 (dd, J = 19.10 and 7.65, 1H, H-2b), 5.75 (dd, J = 7.65 and 3.75, 1H, H-3), 6.18 (dd, J = 2.05 and 2.05, 2H, H-β), 6.62 (dd, J = 2.05 and 2.05, 2H, H-α), 7.41 (d, J = 7.50, 1H, H-4), 7.51 (t, J = 7.50, 1H, H-5), 7.60 (t, J = 7.50, 1H, H-6), 7.82 (d, J = 7.50, 1H, H-7); ^{13}C NMR ($CDCl_3$), δ, ppm: 45.9 (C-2), 56.6 (C-3), 109.1 (C-β), 119.3 (C-α), 123.3 (C-4), 126.1 (C-5), 129.5 (C-6), 135.4 (C-7), 136.6 (C-3a), 152.6 (C-7a), 202.3 (CO). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.32; H, 5.65; N, 7.02%.

3-Pyrrol-1-ylcyclopenta[*b*]thiophenone **7b**

As beige crystals (66%), m.p. 83–85°C (diethyl ether/hexane). IR (KBr), cm^{-1}: 1700 (CO); ^{1}H NMR (d_6-DMSO), δ, ppm; J, Hz: 2.95 (dd, J = 18.25 and 2.70, 1H, H-2a), 3.54 (dd, J = 18.25 and 6.90, 1H, H-2b), 5.90 (dd, J = 6.90 and 2.70, 1H, H-3), 6.05 (dd, J = 2.05 and 2.05, 2H, H-β), 6.77 (dd, J = 2.05 and 2.05, 2H, H-α), 7.07 (d, J = 4.85, 1H, H-thiophene), 8.27 (d, J = 4.85, 1H, H-thiophene); ^{13}C NMR (d_6-DMSO), δ, ppm: 50.1 (C-2), 53.5 (C-3), 108.5 (C-β), 119.2 (C-α), 123.6 (C-4), 141.4 (C-5), 142.4 (C-6a), 166.7 (C-3a), 192.8 (CO). Anal. Calcd for $C_{11}H_9SNO$: C, 65.00; H, 4.46; N, 6.89. Found: C, 65.21; H, 4.56; N, 6.85%.

General Procedure for the Preparation of 3-Pyrrol-1-ylindanone Oxime 8a and 3-Pyrrol-1-ylcyclopenta[b]thiophenone Oxime 8b

To a stirred solution of **7a**–**b** (40 mmol) in ethanol (90 ml) was added a solution of hydroxylamine hydrochloride (80 mmol) and sodium acetate (80 mmol) in water (20 ml). The reaction mixture was refluxed for 3 h and the ethanol was removed under reduced pressure. The residue was extracted with diethyl ether. The organic layer was washed with water (4 × 100 ml), dried over sodium sulfate and evaporated to dryness.

3-Pyrrol-1-ylindanones Oxime **8a**

As beige crystals (63%), m.p. 88°C (methanol). IR (KBr), cm^{-1}: 3250–2800 (= NOH), 1665 (C = N); ^{1}H NMR ($CDCl_3$), δ, ppm; J, Hz: 3.04 (dd, J = 19.05 and 3.90, 1H, H-2a), 3.65 (dd, J = 19.05 and 8.35, 1H, H-2b), 5.67 (dd, J = 8.35 and 3.90, 1H, H-3), 6.18 (dd, J = 2.05 and 2.05, 2H, H-β), 6.64 (dd, J = 2.05 and 2.05, 2H, H-α), 7.24–7.26 (m, 1H, H-4), 7.36 7.39 (m, 2H, H-5 and H-6), 7.78 7.80 (m, 1H, H-7), 9.61 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$), δ, ppm: 36.5 (C-2), 59.5 (C-3), 108.8 (C-β), 119.5 (C-α), 121.6 (C-6), 125.5 (C-4), 129.3 (C-7), 131.2 (C-5), 135.3 (C-7a), 146.4 (C-3a), 160.2 (C-1). Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.67; H, 5.78; N, 13.38%.

3-Pyrrol-1-ylcyclopenta[*b*]thiophenone Oxime **8b**

As beige crystals (89%), m.p. 68–69°C (methanol). IR (KBr), cm^{-1}: 3300–2850 (=NOH), 1655 (C=N); ^1H NMR (d_6-DMSO), δ, ppm; J, Hz: 2.96–2.99 (m, 1H, H-2a), 3.68–3.70 (m, 1H, H-2b), 5.78–5.81 (m, 0.3H, H-3-*Z*), 5.82–5.84 (m, 0.7H, H-3-*E*), 6.02 (dd, J = 1.95 and 1.95, 2H, H-β), 6.66 (dd, J = 1.95 and 1.95, 2H, H-α), 6.91 (d, J = 4.95, 0.7H, H-thiophene-*E*), 7.11 (d, J = 4.95, 0.3H, H-thiophene-*Z*), 7.68 (d, J = 4.95, 0.3H, H-thiophene-*Z*), 7.83 (d, J = 4.95, 0.7H, H-thiophene-*E*), 10.97 (s, 0.3H, OH-*Z*), 11.14 (s, 0.7H, OH-*E*). Anal. Calcd for $C_{11}H_{10}SN_2O$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.71; H, 4.64; N, 12.95%.

General Procedure for the Preparation of cis-3-Pyrrol-1-ylindanamine 9a and cis-3-Pyrrol-1-ylcyclopenta[b]thiophenamine 9b

To a suspension of $LiAlH_4$ (180 mmol) in anhydrous diethyl ether (150 ml) was added dropwise a solution of **8a–b** (30 mmol) in a mixture of diethyl ether and benzene (120 ml) [Care-carcinogenic]. The reaction mixture was heated for 2 h, then diethyl ether was replaced with benzene (180 ml) and it was refluxed for 4 h. After cooling, the excess of lithium aluminium hydride was decomposed by careful addition of ice. The reaction mixture was stirred for an additional 10 min, filtered and the solid was washed with several portions of diethyl ether. The organic layer was extracted with an 1 N aqueous hydrochloric acid solution. The aqueous layer was made alkaline with NaOH, and the product was then extracted with diethyl ether. The organic layer was dried over sodium sulfate and evaporated to dryness to afford **9a–b**.

cis-3-Pyrrol-1-ylindanamine **9a**

As pale-yellow oil (73%). IR (KBr), cm^{-1}: 3360 and 3310 (NH_2); ^1H NMR ($CDCl_3$), δ, ppm; J, Hz: 1.66 (bs, 2H, NH_2), 1.89 (ddd, J = 12.65, 9.30 and 8.70, 1H, H-2a), 3.09 (ddd, J = 12.65, 7.70 and 7.50, 1H, H-2b), 4.32 (dd, J = 9.30 and 7.50, 1H, H-1), 5.40 (dd, J = 8.70 and 7.70, 1H, H-3), 6.19 (dd, J = 2.10 and 2.10, 2H, H-β), 6.73 (dd, J = 2.10 and 2.10, 2H, H-α), 7.03 (d, J = 7.45, 1H, H-4), 7.24 (t, J = 7.45, 1H, H-5), 7.35 (t, J = 7.45, 1H, H-6), 7.44 (d, J = 7.45, 1H, H-7). Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.89; H, 7.14; N, 14.31%.

cis-3-Pyrrol-1-ylcyclopenta[*b*]thiophenamine **9b**

As pale-yellow oil (60%). IR (KBr), cm^{-1}: 3370 and 3310 (NH_2); ^1H NMR (d_6-DMSO), δ, ppm; J, Hz: 2.04 (ddd, J = 13.05, 6.70 and 6.40, 1H, H-2a), 2.20 (bs, 2H, NH_2), 3.28 (ddd, J = 13.05, 7.50 and 7.10, 1H, H-2b), 4.32 (dd, J = 7.50 and 6.40, 1H, H-1), 5.38 (dd, J = 7.10 and 6.70, 1H, H-3), 6.01 (dd, J = 2.15 and 2.15, 2H, H-β), 6.63 (d, J = 4.95, 1H, H-thiophene), 6.79 (dd, J = 2.15 and 2.15, 2H, H-α), 7.43 (d, J = 4.95, 1H, H-thiophene); ^{13}C NMR (d_6-DMSO), δ, ppm: 50.9 (C-2), 52.1 (C-1), 57.5 (C-3), 107.7 (C-β), 119.1 (C-5 and C-α), 121.1 (C-4), 130.2 (C-3a), 144.5 (C-6a). Anal. Calcd for $C_{11}H_{12}SN_2$: C, 64.67; H, 5.92; N, 13.71. Found: C, 64.73; H, 6.07; N, 13.88%.

General Procedure for the Preparation of cis-3-Pyrrol-1-ylindanamine and cis-3-Pyrrol-1-ylcyclopenta[b]thiophenamine Hydrochlorides 10a–b

Through a solution of the amines **9a–b** (20 mmol) in diethyl ether (60 ml) was bubbled hydrochloric acid gas. The precipitate was filtered, washed with diethyl ether and dried to give **10a–b** as white crystals.

cis-3-Pyrrol-1-ylindanamine Hydrochloride **10a**

As white crystals (69%), m.p. 184–186°C (AcOEt/methanol). IR (KBr), cm^{-1}: 3150–2800 (NH_3^+); ^1H NMR (d_6-DMSO), δ, ppm; J, Hz: 2.22 (ddd, J = 12.90, 9.50 and 8.95, 1H, H-2a), 3.11 (ddd, J = 12.90, 8.00 and 7.80, 1H, H-2b), 4.71 (dd, J = 9.50 and 7.80, 1H, H-1), 5.66 (dd, J = 8.95 and 8.00, 1H, H-3), 6.06 (dd, J = 1.90 and 1.90, 2H, H-β), 6.85 (dd, J = 1.90 and 1.90, 2H, H-α), 6.87 (d, J = 7.15, 1H, H-4), 7.34 (t, J = 7.15, 1H, H-5), 7.41 (t, J = 7.15, 1H, H-6), 7.83 (d, J = 7.15, 1H, H-7), 8.97 (bs, 3H, NH_3^+). Anal. Calcd for $C_{13}H_{15}ClN_2$: C, 66.52; H, 6.44; N, 11.93. Found: C, 66.75; H, 6.57; N, 12.10%.

cis-3-Pyrrol-1-ylcyclopenta[*b*]thiophenamine Hydrochloride **10b**

As white crystals (58%), m.p. 214°C (AcOEt/methanol). IR (KBr), cm^{-1}: 3150–2650 (NH_3^+); ^1H NMR (d_6-DMSO), δ, ppm; J, Hz: 2.40 (ddd, J = 13.20, 6.85 and 6.45, 1H, H-2a), 3.47 (ddd, J = 13.20, 7.80 and 7.15, 1H, H-2b), 4.72-4.74 (m, 1H, H-1), 5.55 (dd, J = 7.15 and 6.85, 1H, H-3), 6.03 (dd, J = 2.10 and 2.10, 2H, H-β), 6.69 (d, J = 4.90, 1H, H-thiophene), 6.86 (dd, J = 2.10 and 2.10, 2H, H-α), 7.64 (d, J = 4.90, 1H, H-thiophene), 8.89 (bs, 3H, NH_3^+). Anal. Calcd for $C_{11}H_{13}ClSN_2$: C, 54.88; H, 5.44; N, 11.64. Found: C, 54.90; H, 5.54; N, 11.73%.

General Procedure for the Preparation of cis-N-Propargyl-3-pyrrol-1-ylindanamine 11a and cis-N-propargyl-3-pyrrol-1-yl-cyclopenta[b]thiophenamine 11b

The racemic amines **9a–b** (0.005 mole) and potassium carbonate (0.005 mole) were added to acetonitrile (15 ml). The resulting suspension was heated to 60°C and propargyl chloride (0.004 mole) was added dropwise. The mixture was stirred at 60°C for 16 h, whereafter most of the volatiles were removed by distillation *in vacuo*. The residue was partitioned between a 10 % aqueous sodium hydroxide solution and methylene chloride. The organic layer was dried

over sodium sulfate and the solvent removed by distillation. The residue was flash chromatographed on silica gel, eluting with 40% ethyl acetate/60% hexane to give **11a–b**.

cis-N-propargyl-3-pyrrol-1-ylindanamine **11a**

As white crystals (32%), m.p. 24°C (petroleum ether). IR (KBr), cm^{-1}: 3290 (NH), 2140 (C≡C); ^1H NMR ($CDCl_3$), δ, ppm; J, Hz: 1.72 (s, 1H, NH), 2.06 (ddd, J = 12.95, 8.65 and 8.30, 1H, H-2a), 2.31 (t, J = 2.40, 1H, ≡CH), 3.14 (ddd, J = 12.95, 7.80 and 7.15, 1H, H-2b), 3.61 (d, J = 2.40, 2H, CH_2), 4.44 (dd, J = 8.65 and 7.15, 1H, H-1), 5.45 (dd, J = 8.30 and 7.80, 1H, H-3), 6.25 (dd, J = 2.10 and 2.10, 2H, H-β), 6.80 (dd, J = 2.10 and 2.10, 2H, H-α), 7.12 (d, J = 7.30, 1H, H-4), 7.35 (t, J = 7.30, 1H, H-5), 7.39 (t, J = 7.30, 1H, H-6), 7.50 (d, J = 7.30, 1H, H-7); ^{13}C NMR ($CDCl_3$), δ, ppm: 35.8 (C-2), 43.3 (NCH_2), 58.7 (C-1), 61.1 (C-3), 71.2 (≡CH), 81.8 (C≡), 107.8 (C-β), 119.2 (C-α), 123.4 (C-4), 123.8 (C-5), 127.7 (C-6), 127.9 (C-7), 141.5 (C-3a), 143.5 (C-7a). Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.39; H, 6.96; N, 11.92%.

cis-*N*-propargyl-3-pyrrol-1-yl-cyclopenta[*b*]thiophenamine **11b**

As colorless oil (45%). IR (KBr), cm^{-1}: 3295 (NH), 2110 (C ≡ C); ^1H NMR ($CDCl_3$), δ, ppm; J, Hz: 1.56 (s, 1H, NH), 2.24-2.26 (m, 1H, H-2a and ≡CH), 3.45 (ddd, J = 13.25, 7.60 and 6.90, 1H, H-2b), 3.56 (d, J = 2.45, 2H, CH_2), 4.47 (dd, J = 6.90 and 5.65, 1H, H-1), 5.38 (dd, J = 7.60 and 5.45, 1H, H-3), 6.16 (dd, J = 2.10 and 2.10, 2H, H-β), 6.70 (dd, J = 2.10 and 2.10, 2H, H-α), 6.76 (d, J = 5.00, 1H, H-thiophene), 7.31 (d, J = 5.00, 1H, H-thiophene); ^{13}C NMR ($CDCl_3$), δ, ppm: 36.5 (C-2), 48.0 (NCH_2), 57.4 (C-1), 58.1 (C-3), 71.9 (≡CH), 81.7 (C≡), 108.4 (C-β), 119.2 (C-α), 121.7 (C-4 and C-5), 130.7 (C-3a), 145.1 (C-6a). Anal. Calcd for $C_{14}H_{14}SN_2$: C, 69.38; H, 5.82; N, 11.56. Found: C, 69.44; H, 5.96; N, 11.62%.

General Procedure for the Preparation of cis-N-Propargyl-3-pyrrol-1-ylindanamine and cis-N-Propargyl-3-pyrrol-1-ylcyclopenta[b] thiophenamine Hydrochlorides 1a–b

Through a solution of the amines **9a–b** (20 mmol) in diethyl ether (60 ml) was bubbled hydrochloric acid gas. The precipitate was filtered, washed with diethyl ether and dried to give **1a–b** as white crystals.

cis-N-Propargyl-3-pyrrol-1-ylindanamine Hydrochloride **1a**

As white crystals (94%), m.p. 30°C (methanol). IR (KBr), cm^{-1}: 3220 (NH), 2850–2550 (NH^+), 2130 (C≡C); ^1H NMR (d_6-DMSO), δ, ppm; J, Hz: 2.44-2.46 (m, 1H, H-2a), 3.09-3.11 (m, 1H, H-2b), 3.41-3.43 (m, 1H, ≡CH), 4.04 (s, 2H, CH_2), 4.86–4.88 (m, 1H, H-1), 5.67–5.69 (m, 1H, H-3), 6.07 (dd, J = 1.95 and 1.95, 2H, H-β), 6.86 (d, J = 6.95, 1H, H-4), 6.88 (dd, J = 1.95 and 1.95, 2H, H-α), 7.38–7.40 (m, 2H, H-5 and H-6), 8.01 (d, J = 6.95, 1H, H-7), 10.48 (bs, 2H, NH_2^+). Anal. Calcd for $C_{16}H_{17}ClN_2$: C, 70.45; H, 6.28; N, 10.27. Found: C, 70.53; H, 6.31; N, 10.36%.

cis-N-Propargyl-3-pyrrol-1-yl-cyclopenta[*b*]thiophenamine Hydrochloride **1b**

As white crystals (84%), m.p. 110°C (ethanol). IR (KBr), cm^{-1}: 3230 (NH), 2900–2450 (NH^+), 2130 (C≡C); ^1H NMR (d_6-DMSO), δ, ppm; J, Hz: 2.57 (ddd, J = 13.20, 7.20 and 6.60, 1H, H-2a), 3.41 (m, 2H, H-2b and ≡CH), 3.98 (s, 2H, CH_2), 4.85 (dd, J = 6.85 and 6.60, 1H, H-1), 5.57 (dd, J = 7.30 and 7.20, 1H, H-3), 6.03 (dd, J = 2.05 and 2.05, 2H, H-β), 6.71 (d, J = 5.00, 1H, H-thiophene), 6.89 (dd, J = 2.05 and 2.05, 2H, H-α), 7.68 (d, J = 5.00, 1H, H-thiophene), 10.54 (bs, 2H, NH_2^+). Anal. Calcd for $C_{14}H_{15}ClSN_2$: C, 60.31; H, 5.42; N, 10.05. Found: C, 60.45; H, 5.54; N, 10.20%.

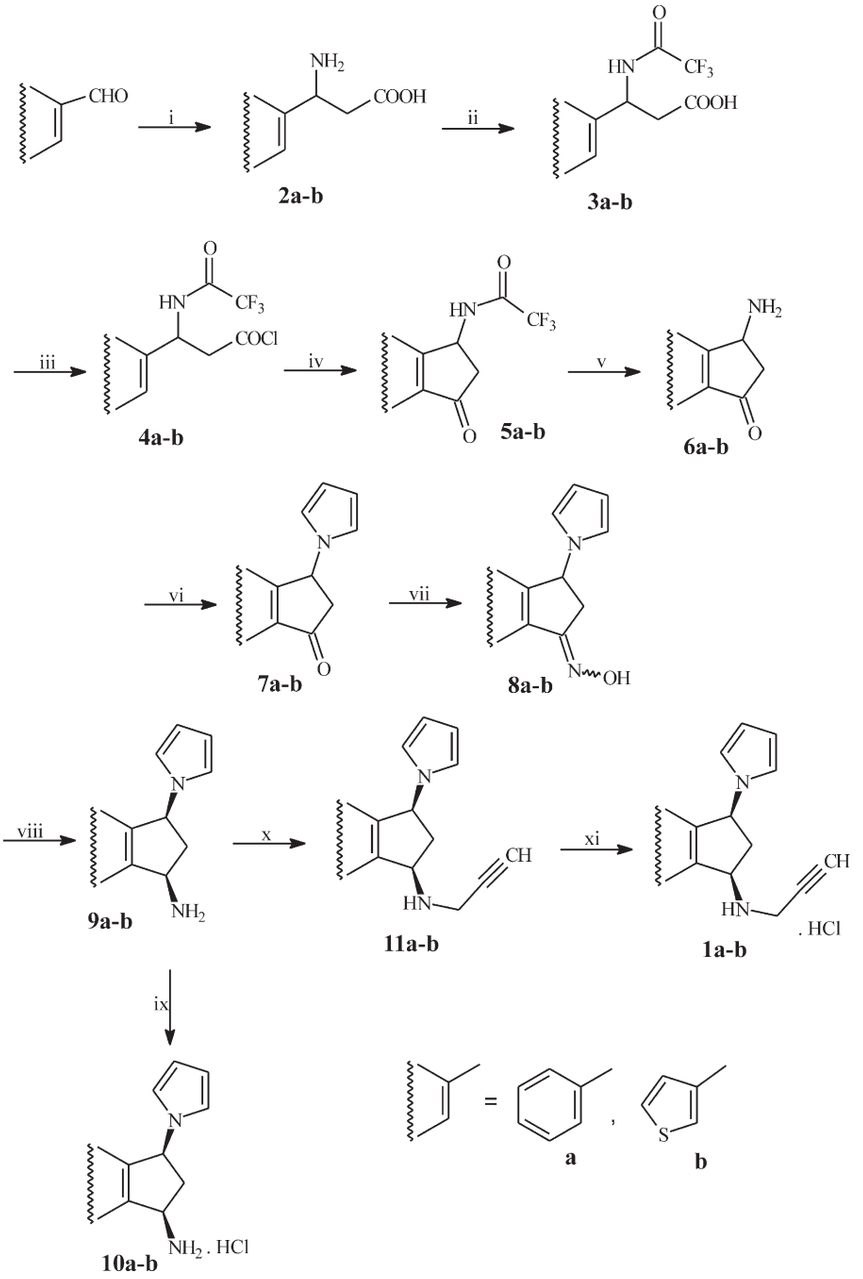
Animal Studies

Eight-week-old male C57BL/6 mice (Iffa Credo, France) were subcutaneously injected with MPTP hydrochloride (RBI, Natick, MA, USA) in a single 40 mg/kg dose on day 0. On day −1, 0 and +1, twelve different mice groups (n = 5/group) were intraperitoneally injected with rasagiline at 0, 0.1, 1 and 10 mg/kg, and compounds **1a–b** at 0, 0.2, 2 and 20 mg/kg. Animals were sacrificed 10 days after MPTP treatment.

Dopamine Transporter Binding Autoradiography

Frozen coronal cryostat sections (30 μm) were thaw-mounted on gelatined slides. [^3H]GBR-12935 binding was performed according to the method of Mennicken.[11] Sections were pre-incubated in 50 mM Tris–HCl pH 07.5, 450 mM NaCl, 1 μM cis-flupentixol (Fluka) and 0.02% bovine serum albumin for 30 min. Tissue sections were then incubated at 4°C in 50 mM Tris-HCl pH 7.5, 450 mM NaCl, 1 μM *cis*-flupentixol (Fluka), 0.02% bovine serum albumin and 2 nM [^3H]GBR-12935 for 20 h. Then, sections were rapidly rinsed in distilled water at 0°C. Slides were washed four times at 4°C in 50 mM Tris-HCl pH 7.5 and 450 mM NaCl for 5 min. Finally, slides were rapidly rinsed in distilled water at 4°C and dried with a stream of cold air for 4 min. Non-specific binding was determined in the presence of 50 μM mazindol during incubation. Sections were apposed on Biomax MS films (Kodak) placed on an intensifying screen (Biomax transcreen LE, Kodak) for 21 days. The optical density of autoradiograms was analysed using a computerized image analysis system (GS-800, Biorad, France).

Statistical analysis was performed using Analysis of Variance (ANOVA) followed by a Student-Newman-Keuls *post hoc* test. Means observed for groups treated with the lowest dose (0.1 or 0.2 mg/kg) of



SCHEME 1 Synthesis of compounds **1a–b**. Reagents: (i) CH_3COONH_4, $CH_2(COOH)_2$; (ii) $(CF_3CO)_2O$; (iii) $SOCl_2$; (iv) $AlCl_3$; (v) NaOH; (vi) 2,5-dimethoxyTHF, CH_3COOH; (vii) H_2NOH; (viii) $LiAlH_4$; (ix) HCl; (x) propargyl chloride, K_2CO_3; (xi) HCl.

rasagiline or **1a–b**, respectively, are statistically different (*) from the mean of the NaCl-treated group. The risk of differences being due to chance is below 5% ($p < 0.05$).

RESULTS AND DISCUSSION

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 **2** in 35–60% yields starting from commercial arylaldehydes.[12,13] The synthetic pathway involved the Rodionow–Johnson reaction using malonic acid and ammonium acetate in an ethanolic solution of starting material (Scheme 1).[14,15] The obtained β-amino-acids **2a–b** were involved in an intramolecular cyclization reaction using the Friedel–Crafts method after protection of the amino group with trifluoroacetic anhydride at 0°C in diethyl ether. The resulting

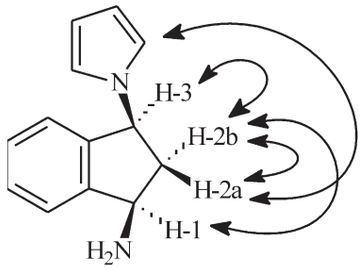


FIGURE 2 NOE experiments on compound **9a**.

trifluoroacetamides **3a**–**b** were then treated with thionyl chloride to afford the acid chlorides **4a**–**b** which were immediately engaged in the Friedel–Crafts cyclization using excess aluminium chloride in refluxing dichloromethane.[16,17] After acidic hydrolysis, the expected amides **5a**–**b** were isolated. Deprotection of the amino group in an aqueous sodium hydroxide solution yielded the aminoindanone **6a** and aminocyclopenta[*b*]thiophenone **6b**. These aminoindanones **6a**–**b** in a Clauson-Kaas reaction using 2,5-dimethoxytetrahydrofuran in acetic acid, led to the pyrrolylindanone **7a** and pyrrolylcyclopenta[*b*]thiophenone **7b** in good yields (60–74%).[18,19] Reaction of **7a**–**b** with hydroxylamine afforded the oximes **8a**–**b**. On the basis of previous results noticed in the indane series [20], a study of the ^{1}H NMR spectra of the latter oximes revealed the presence of the *E* isomers as major products. Reduction of the oximes **8a**–**b** with an excess of lithium aluminium hydride in refluxing benzene gave the pyrrolylindanamine **9a** and pyrrolylcyclopenta[*b*]thiophenamine **9b**.[21] Assignment of the relative configuration in **9a**–**b** was made on the basis of NOE experiments. Specifically, irradiation of H-2b in **9a** led to an NOE with H-2a, H-1 and H-3, while similar irradiation of H-2a showed an NOE with either H-2b and H-α of the pyrrole (Figure 2). These observations were consistent with a *cis* stereochemical relationship between the NH_2 group and the pyrrole moiety in **9a**. The amines **9a**–**b** were converted into their hydrochlorides **10a**–**b** for X-ray crystallography purpose. Unfortunately, suitable crystals were only obtained for **10a**. Its molecular structure, depicted in Figure 3, confirms the all-*cis* conformation. Moreover, **10a** appeared as an enantiomeric mixture of 1(*R*)-3(*S*)- and 1(*S*)-3(*R*)-3-pyrrol-1-ylindanamines according to the determined spatial group from the crystallographic data (Pbca).[22] Finally, the alkylation of the amines **9a**–**b** with propargyl chloride and potassium carbonate in hot acetonitrile gave the secondary amines **11a**–**b**, which were converted into their hydrochlorides **1a**–**b** by treatment with hydrochloric acid gas in diethyl ether (Scheme 1).[6,7]

Pharmacology

This study was designed to assess a putative, physiologically relevant, inhibitory effect of compounds **1a**–**b** on MAO-B enzymatic activity. This was assessed through its anti-Parkinsonian potential in the MPTP model, which can be viewed as an *in vivo* bioassay for MAO-B activity and racemic compounds **1a**–**b** were compared to rasagiline, an already studied MAO-B inhibitor. For this purpose, intraperitoneal injection of compounds **1a**–**b** and rasagiline was performed in a dose range allowing inhibition of MPTP-induced striatal denervation, as already shown for several MAO-B inhibitors.[23] The 0.1 mg/kg rasagiline-treated group showed a significantly higher striatal [^{3}H]-GBR-12935 binding following MPTP injection (Figure 4). At the equivalent 0.2 mg/kg dose of the racemic compounds **1a**–**b**, a similar beneficial effect was observed, indicative of a significant neuroprotective effect of **1a**–**b** at the dose of 0.2 mg/kg on

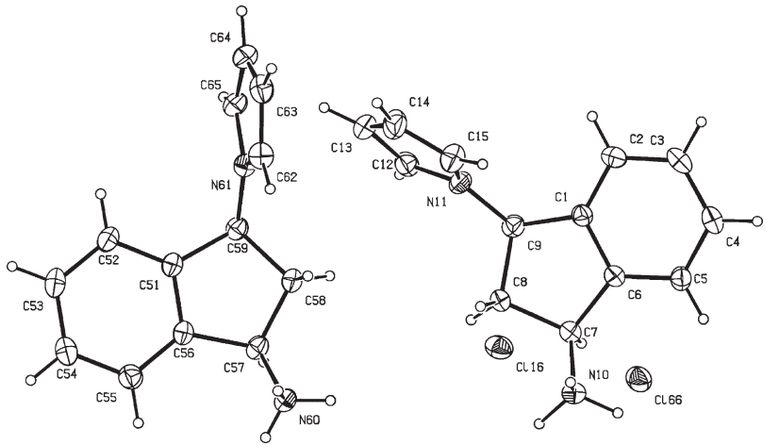


FIGURE 3 A view of **10a** with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

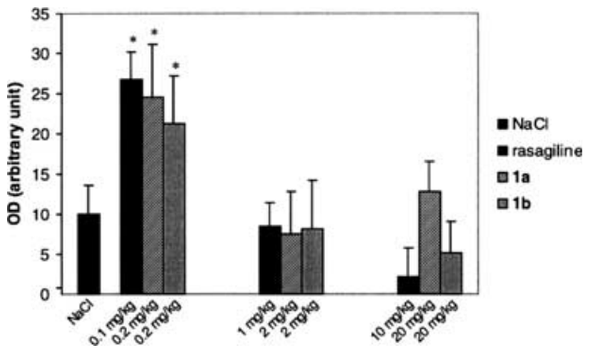


FIGURE 4 Striatal dopaminergic innervation measured by [^{3}H]-GBR-12935 binding quantification after MPTP treatment and injection of NaCl, rasagiline, **1a** and **1b** at different doses (means ± SEM). (*) Observed means are statistically different from that of NaCl-treated group with a risk below 5% ($p < 0.05$).

MPTP-induced striatum denervation. However, this effect was no longer observed either for the 2 mg/kg or for the 20 mg/kg doses, as well as with equivalent doses of rasagiline. This suggests that all tested compounds are ineffective or even neurotoxic at high dose, as already hypothesized for other MAO-B inhibitors.[5]. These data, observed from the MPTP bioassay model, point to an *in vivo* activity pattern similar to other MAO-B inhibitors already used to prevent Parkinson's disease progression in this animal model. Nevertheless, further *in vitro* analysis of MAO-B activity is now required to more precisely determine the MAO-B inhibitory potential of compounds **1a**–**b**.

References

[1] Zagnoli, F. and Rouhart, F. (2000) *Maladie de Parkinson* (Dion; Paris).
[2] Foley, P., Gerlach, M., Youdim, M.B.H. and Riederer, P. (2000) *Parkinsonism Relat. Disord.* **6**, 25–47.
[3] Przedborski, S. and Jackson-Lewis, V. (1998) *Mov. Disord.* **13**, 35–38.
[4] Heikkila, R.E., Duvoisin, R.C., Finberg, J.P. and Youdim, M.B. (1985) *Eur. J. Pharmacol.* **116**, 313–317.
[5] Kupsch, A., Sautter, J., Gotz, M.E., Breithaupt, W., Schwarz, J., Youdim, M.B., Riederer, P., Gerlach, M. and Oertel, W.H. (2001) *J. Neural. Transm.* **108**, 985–1009.
[6] Graul, A. and Castaner, J. (1996) *Drugs Fut.* **21**, 903–905.
[7] Youdim, M.B.H., Finberg, J.P.M., Levy, R., Sterling, J., Lerner, D., Berger-Paskin, T. and Yellin, F. (1995) *US Patent US 5453446*.
[8] Guillon, J., Lelong, V., Renault, O., Boulouard, M., Dallemagne, P., Rault, S. and Robba, M. (1998) *Chem. Pharm. Bull.* **46**, 711–714.
[9] Guillon, J., Alsaidi, A., Dallemagne, P. and Rault, S. (1998) *Pharm. Pharmacol. Commun.* **4**, 231–235.
[10] Guillon, J., Boulouard, M., Lelong, V., Dallemagne, P., Rault, S. and Jarry, C. (2001) *J. Pharm. Pharmacol.* **53**, 1561–1568.
[11] Mennicken, F., Savasta, M., Peretti-Renucci, R. and Feuerstein, C. (1992) *J. Neural. Transm. Gen. Sect.* **87**, 1–14.
[12] Rault, S., Tembo, O.N., Dallemagne, P. and Robba, M. (1991) *Heterocycles* **32**, 1301–1305.
[13] Rault, S., Dallemagne, P. and Robba, M. (1987) *Bull. Soc. Chim. Fr.* **6**, 1079–1083.
[14] Rodionow, W.M. and Malewinskaja, E.T. (1926) *Chem. Ber.* **59**, 2952–2958.
[15] Johnson, T.B. and Livak, J.E. (1936) *J. Am. Chem. Soc.* **58**, 299–303.
[16] Dallemagne, P., Boustre, M., Rault, S. and Robba, M. (1993) *J. Heterocyclic Chem.* **30**, 799–802.
[17] Renault, O., Dallemagne, P. and Rault, S. (1998) *Pharm. Pharmacol. Commun.* **4**, 3–7.
[18] Clauson-Kaas, N. and Tyle, Z. (1952) *Acta Chem. Scand.* **6**, 667–670.
[19] Elming, N. and Clauson-Kaas, N. (1952) *Acta Chem. Scand.* **6**, 867–874.
[20] Khanh, L.P., Dallemagne, P., Alsaïdi, A. and Rault, S. (1997) *Heterocycles* **45**, 527–535.
[21] Takahashi, T., Fujimura, H. and Okamura, K. (1962) *Yakugaku Zasshi* **82**, 1597–1603.
[22] Supplementary X-ray crystallographic data of compound **10a** (CCDC-187302): Cambridge Crystallographic Data Centre, University Chemical Lab, 12 Union Road, Cambridge, CB2 1EZ, U.K., E-mail: deposit@ccdc.cam.ac.uk.
[23] Castagnoli, K., Palmer, S. and Castagnoli, N. (1999) *Neurobiology* **7**, 135–149.