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Synthesis of the major metabolites of Paroxetine

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Abstract

Paroxetine is a well-known antidepressant, used worldwide in therapeutics. In comparison with other selective serotonin reuptake inhibitors, it exhibits the highest activity in serotonin reuptake inhibition. Paroxetine metabolism initially involves its demethylenation to the catechol intermediate, which is then *O*-methylated at positions C3 or C4. Herein, the chemistry resulting in the syntheses of these metabolites (3*S*,4*R*)-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine and (3*S*,4*R*)-4-(4-fluorophenyl)-3-(4-hydroxy-3-methoxyphenoxymethyl) piperidine is described starting from the common intermediate (3*S*,4*R*)-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine. Additionally, the common intermediate was used to synthesize paroxetine, which had the same structure and stereochemistry as commercial paroxetine, thereby confirming our synthetic route.
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1. Introduction

Paroxetine [(3*S*,4*R*)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine] is a well-known selective serotonin reuptake inhibitor (SSRI) antidepressant, used worldwide in therapeutics. In comparison with other SSRIs, it exhibits the

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highest activity in serotonin reuptake inhibition [1]. Paroxetine (**1**) metabolism (Fig. 1) initially involves its demethylenation to the catechol intermediate (**2**), followed by *O*-methylation at position 3 or 4. The catechol intermediate can be also metabolized to afford (3*S*,4*R*)-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine (metabolite III). These metabolites undergo rapid and extensive conjugation to form glucuronides and sulfate esters [2–5].

Pharmacokinetic data for paroxetine metabolites in humans are limited. Non-linear pharmacokinetics of paroxetine after repeated doses have been reported [2,3,5,6]. Mechanisms resulting in this non-linearity are not clear. The methylenedioxyphenyl moiety present in the paroxetine chemical structure, strongly suggests that a carbene formed in the *O*-demethylenation reaction may interact with cytochrome P450 (CYP2D6) and lead to the formation of an intermediate enzyme metabolite complex. This resulting complex may be responsible for a quasi-irreversible inhibition of the enzymatic activity and thereby explain the non-linear kinetic behavior. Similar mechanisms of enzyme metabolite complex formation have been proposed for other compounds bearing the methylendioxyphenyl grouping such as pesticide synergists [7,8]. To verify this hypothesis, it is necessary to determine paroxetine and its metabolites in biological fluids from patients and healthy volunteers, who had been administered the drug.

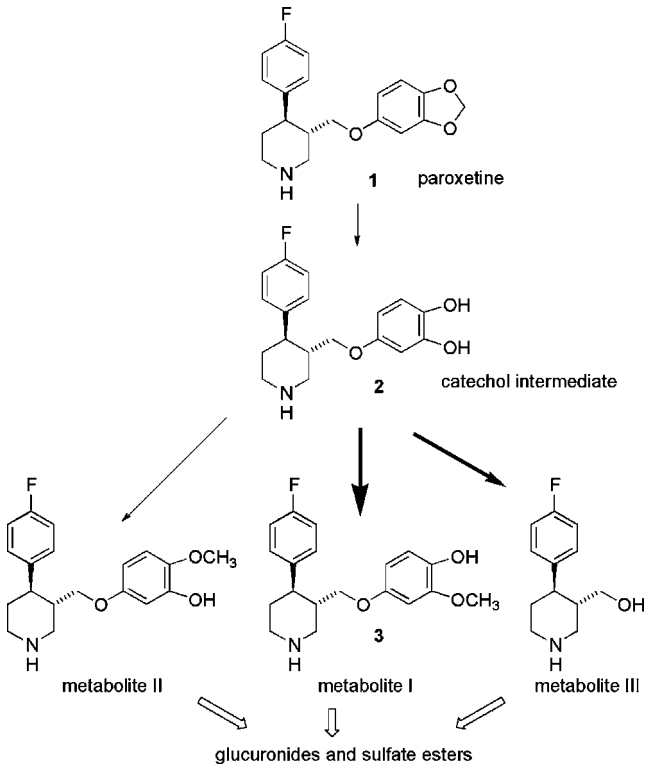

Fig. 1. Metabolic pathway of paroxetine.

We are particularly interested in the two main metabolites that appear after the *O*-demethylenation of the 3,4-methylenedioxybenzene ring, namely the catechol (**2**) and its methoxy derivative (**3**) (Fig. 1). Such compounds have been described in very preliminary drug development reports, but to our knowledge the synthesis and pharmacokinetics in humans have not been described in the general literature. In order to conduct detailed pharmokinetics, it is necessary to synthesize **2** and **3** because these two metabolites are not commercially available. In the present manuscript, the synthetic chemistry leading to these standards is described starting from the common intermediate (3*S*,4*R*)-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine (**4**). The synthetic route was validated by the synthesis of paroxetine, whose stucture and stereochemistry were identical to that of commercially available paroxetine.

2. Material and methods

2.1. General methods

(3*S*,4*R*)-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine (**4**) was a gift of a pharmaceutical company. All other chemicals and reagents were purchased from Sigma-Aldrich Química, S.A. (Alcobendas, Spain). Solvents were obtained from Panreac Química, S.A. (Barcelona, Spain). Reactions sensitive to moisture were carried out under argon atmosphere. Commercial grade reagents were used directly without further purification (unless otherwise indicated). Solvents were dried by standard methods and distilled before use. Purification of products by column chromatography was performed on Merck silica gel 60. TLC was carried out on precoated silica gel Merck 60 F_{254} (0.25 mm) sheets. FT-IR spectra were recorded on a Michelson Bomem MB-120 and are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions (unless otherwise indicated) on a Varian Gemini XL200 or a Varian Unity 300 spectrometer, operating at 200 and 300 MHz for ^{1}H and 50 and 75 MHz for ^{13}C, respectively. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from $(CH_3)_4Si$, or in ppm relative to the singlet at 7.26 ppm of CDC_3 for ^{1}H, in ppm relative to the central line of a triplet at 77.0 ppm of $CDCl_3$ for ^{13}C, and in ppm relative to the singlet at 0 ppm of the Cl_3CF for ^{19}F. ^{13}C NMR multiplicities were determined by DEPT (Distortionless Enhancement by Polarization Transfer) experiments using standard pulse sequences. A Perkin–Elmer polarimeter was used for optical rotatory measures. Gas chromatography-mass spectrometry (GC-MS) was performed on a Fisons gas chromatograph (8000 series) coupled to a Fisons MD-800 quadrupole mass selective detector. The system was equipped with a non-polar DB-5 (J&W) capillary column (25 m × 0.25 μm × 0.22 mm I.D.) using helium as carrier gas at a flow rate of 1 mL/min. The oven was heated starting at 80 °C at a rate of 5 °C/min up to 200 °C, then it was maintained for 1 min and then heated again at 10 °C/min up to 280 °C. Samples were injected in the splitless mode although the split valve was closed for 48 s. Injector and interface were set at 250 °C. The mass spectrometer was operated by electron ionization (EI, 70 eV) and in the scan mode (working range 40–600 amu).

2.2. Synthesis of paroxetine metabolites **2** and **3**

2.2.1. p-Toluenesulfonate derivative of **4** [9]

In a 25 mL round bottom flask were placed 2 g (8.9 mmol) of (3*S*,4*R*)-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine (**4**) and 855 mg (8.9 mmol) of trimethylamine hydrochloride in 30 mL of anhydrous methylene chloride under an argon atmosphere. The flask was placed in an ice bath and 2.5 g (13.5 mmol) of *p*-toluenesulfonyl chloride were added and the solution was stirred for 4 h. Then the mixture was adjusted to pH 7.0 with 1 N HCl aqueous solution, and water (100 mL) was added to the mixture, which was extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with brine (3×25 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum and the crude product obtained was purified by silica-gel column chromatography using ethyl acetate/methanol/ammonia (20:2:1) as the eluent yielding 2.98 g (7.90 mmol, 89%) of compound **5** as the free amine which was converted to its hydrochloride salt with an ethanolic solution of hydrogen chloride. m.p.: 121–122 °C. IR (neat, ν_{max}): 2939, 2897, 2791, 1598, 1509, 1362, 840, 820, 670. ^{1}H-NMR (200 MHz): 7.63–7.57 (m, 2H), 7.28–7.20 (m, 2H), 7.05–6.78 (m, 4H), 3.71 (dd, $J = 2.5$ and 10.0 Hz, 1H), 3.54 (dd, $J = 6.0$ and 10.0 Hz, 1H), 3.02–2.81 (m, 2H), 2.42 (s, 3H), 2.29 (s, 3H), 2.15–1.69 (m, 6H). ^{13}C-NMR (75 MHz): 163.5, 160.3, 145.5, 135.4, 131.6, 130.0, 129.1, 128.9, 127.8, 115.9, 115.7, 68.3, 56.2, 54.7, 43.8, 40.2, 38.6, 30.1, 21.6. ^{19}F-NMR (282 MHz): −116.7 to −116.6 (m, 1F). GC-MS (*m*/*z*): 58, 91,192, 206, 222, 377. *Anal.* Calcd. for $C_{20}H_{24}FNO_3S$: C: 63.64; H: 6.41; F: 5.03; N: 3.71; O: 12.72; S: 8.49. Found: C: 63.52; H: 6.47; N: 3.70. $[\alpha]_D^{20} = -42.9$ ($c = 0.01$, methanol).

2.2.2. (3S,4R)-3-(3,4-dibenzyloxyphenoxymethyl)-4-(4-fluorophenyl)-1-methylpiperidine (**6**)

0.48 g (1.6 mmol) of 3,4-dibenzyloxyphenol [10] dissolved in 10 mL of anhydrous DMF were slowly added to a stirred suspension of NaH (2.12 mmol) in 10 mL of DMF. The mixture was refluxed for 3 h, left to reach room temperature and then the flask was placed in an ice bath. To this solution, were added 0.5 g (1.32 mmol) of tosylate **5** dissolved in 10 mL of DMF and then heated to reflux for 4 h. Once it was at room temperature, water was slowly added in order to eliminate the remaining NaH and the mixture was adjusted to pH 7 with the addition of 1N HCl solution. Water (250 mL) was added to the mixture which was extracted with ethyl acetate (10×50 mL). The organic layer was washed with water (4×25 mL), brine (2×25 mL), dried over anhydrous $MgSO_4$, and filtered. The solvent was evaporated under vacuum and the crude product was purified by flash chromatography (hexane/EtOAc 3:1; then EtOAc/MeOH/NH_3 20:3:1) to give 0.54 g (1.06 mmol, 80%) of the free amine **6** as a reddish solid. IR (neat, ν_{max}): 3033, 2936, 2785, 1604, 1510, 1466, 1221, 1173, 1026, 832, 755, 697. ^{1}H-NMR (300 MHz): 7.48–7.24 (m, 10H), 7.20–7.11 (m, 2H), 7.10–6.93 (m, 2H), 6.80 (d, $J = 9.0$ Hz, 1H), 6.47 (d, $J = 3.0$ Hz, 1H), 6.20 (dd, $J = 3.0$ and 8.5 Hz, 1H), 5.10 (s, 2H), 5.06 (s, 2H), 3.58 (dd, $J = 3.0$ and 9.0 Hz, 1H), 3.46 (dd, $J = 7.0$ and 9.5 Hz, 1H), 3.23 (dd, $J = 2.5$ and 11.0 Hz, 1H), 3.01 (d, $J = 11.0$ Hz, 1H), 2.46 (dt, $J = 4.5$ and 11.5 Hz, 1H), 2.40 (s, 3H),

2.35–2.20 (m, 1H), 2.15–1.80 (m, 4H). ^{13}C-NMR (75 MHz): 161.4 ($J_{C-F} = 244$ Hz), 154.0, 150.0, 142.9, 139.4, 137.5, 136.9, 128.8, 128.7, 128.4, 128.3, 127.7, 127.6, 127.4, 127.2, 116.9, 115.5, 115.2, 105.1, 103.2, 72.5, 71.0, 68.8, 59.3, 56.0, 46.3, 43.3, 41.9, 34.1. *Anal.* Calcd. for $C_{33}H_{34}FNO_3$: C: 77.47; H: 6.70; F: 3.71; N: 2.74; O: 9.38. Found: C: 77.32; H: 6.79; N: 2.77. $[\alpha]_D^{20} = -38.2$ ($c = 0.01$, methanol).

2.2.3. (3S,4R)-4-(4-fluorophenyl)-3-(3-methoxy-4-benzyloxyphenoxymethyl)-1-methylpiperidine (7)

By following the above procedure, treatment of 0.55 g (2.41 mmol) of 3-methoxy-4-benzyloxyphenol (synthesized according to [10]) with NaH (2.41 mmol) and 0.76 g (2.01 mmol) of tosylate **5** yielded **7** as the free amine, after column chromatography purification (hexane/AcOEt 3:1) (0.47 g, 1.07 mmol, 53%). IR (neat, ν_{max}): 2937, 2785, 1510, 1222, 1199. ^{1}H-NMR (300 MHz): 7.41–7.19 (m, 5H), 7.18–7.10 (m, 2H), 6.99–6.90 (m, 2H), 6.67 (d, $J = 8.5$ Hz, 1H), 6.37 (d, $J = 2.5$ Hz, 1H), 6.08 (dd, $J = 2.5$ and 8.5 Hz, 1H), 5.02 (s, 2H), 3.57 (dd, $J = 3.0$ and 9.5 Hz, 1H), 3.45 (dd, $J = 7.0$, and 9.5 Hz, 1H), 3.20 (m, 1H), 3.08 (s, 3H), 2.98 (d, $J = 10.8$ Hz, 1H), 2.44 (dt, $J = 4.5$ and 11.5 Hz, 1H), 2.36 (s, 3H), 2.30–2.18 (m, 1H), 2.13–1.76 (m, 4H). ^{13}C-NMR (75 MHz): 161.5 ($J_{C-F} = 244$ Hz), 154.0, 150.7, 142.3, 139.5, 137.4, 128.8, 128.7, 128.4, 127.7, 127.4, 115.5, 115.4, 115.2, 103.7, 100.9, 72.0, 68.9, 59.5, 56.1, 55.8, 46.4, 43.4, 42.0, 34.2. ^{19}F-NMR (282 MHz): −117.1 to −116.9 (m, 1F). GC/MS (m/z): 109, 140, 153, 218, 262, 358, 401. *Anal.* Calcd. for $C_{27}H_{30}FNO_3$: C: 74.46; H: 6.94; F: 4.36; N: 3.22; O: 11.02. Found: C: 74.34; H: 6.97; N: 3.20. $[\alpha]_D^{20} = -59.5$ ($c = 0.01$, methanol).

*2.2.4. (3S,4R)-3-(3,4-dibenzyloxyphenoxymethyl)-4-(4-fluorophenyl)-1-vinyloxycarbonylpiperidine (**8**)*

To a stirred solution of **6** (553 mg, 1.08 mmol) and anhydrous potassium carbonate (2.1 g, 15.3 mmol) in anhydrous 1,2-dichloroethane (15 mL) was added vinyl chloroformate (1.1 mL, 11.5 mmol). The reaction mixture was refluxed for 4 h, the solvent was evaporated and the residue partitioned between ethyl acetate and brine (200 mL, 1:1). The organic layer was decanted and the aqueous layer extracted with ethyl acetate (5×25 mL). The combined organic layer was washed with brine (2×10 mL), dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under vacuum to give a crude brown oil which was purified by column chromatography (hexane and then hexane/EtOAc 3:1) yielding 0.32 g (0.56 mmol, 52%) of **8** as colorless oil. IR (neat, ν_{max}): 3033, 2921, 2865, 1716, 1509, 1435, 1220, 1149. ^{1}H-NMR (200 MHz): 7.52–7.20 (m, 11H), 7.15–9.90 (m, 4H), 6.79 (d, $J = 8.5$ Hz, 1H), 6.48 (d, $J = 3.0$ Hz, 1H), 6.19 (dd, $J = 2.5$ and 6.5 Hz, 1H), 5.11 (s, 2H), 5.06 (s, 2H), 4.82 (dd, $J = 1.5$ and 13.5 Hz, 1H), 4.54 (d, $J = 13.5$ Hz, 1H), 4.50 (dd, $J = 1.5$ and 6.5 Hz, 1H), 4.35 (d, $J = 13.5$ Hz, 1H), 3.61 (dd, $J = 3.0$ and 9.5 Hz, 1H), 3.45 (dd, $J = 6.0$ and 9.5 Hz, 1H), 2.95 (m, 2H), 2.72 (dt, $J = 4.0$ and 11.5 Hz, 1H), 2.15–1.94 (m, 1H), 1.90–1.61 (m, 2H). ^{13}C-NMR (75 MHz): 161.9 ($J_{C-F} = 244$ Hz), 153.4, 150.1, 143.5, 139.7, 137.4, 136.9, 128.9, 128.5, 128.4, 127.9, 127.7, 127.5, 127.3, 115.9, 115.8, 115.7, 105.2, 103.4, 72.4, 71.1, 66.9, 41.6, 39.4,

30.9, 30.0. *Anal.* Calcd. for $C_{35}H_{34}FNO_5$: C: 74.06; H: 6.04; F: 3.35; N: 2.47; O: 14.09. Found: C: 74.22; H: 6.21; N: 2.44. $[\alpha]_D^{20} = -38.5$ ($c = 0.01$, methanol).

*2.2.5. (3S,4R)-4-(4-fluorophenyl)-3-(3-methoxy-4-benzyloxyphenoxymethyl)-1-vinyloxycarbonylpiperidine (**9**)*

Following the above procedure, treatment of a solution **7** (426 mg, 0.98 mmol) and anhydrous potassium carbonate (1.27 g, 9.2 mmol) in 1,2-dichloroethane (12 mL) with vinyl chloroformate (0.62 mL, 6.92 mmol) gave 0.27 g (0.55 mmol, 56%) of **9**, after purification by flash silica-gel column chromatography. IR (neat, ν_{max}): 2919, 1717, 1647, 1509, 1450, 1437, 1221, 1197, 1150, 844. ^{1}H-NMR (300 MHz): 7.42–7.21 (m, 6H), 7.16–7.09 (m, 2H), 7.01–6.91 (m, 2H), 6.70 (d, $J = 8.5$ Hz, 1H), 6.42 (d, $J = 3.0$ Hz, 1H), 6.12 (bs, 1H), 5.04 (s, 2H), 4.78 (dd, $J = 3.0$ and 14.0 Hz, 1H), 4.55 (br, 1H), 4.48 (dd, $J = 1.5$ and 6.5 Hz, 1H), 4.34 (br, 1H), 3.82 (s, 3H), 3.63 (dd, $J = 2.5$ and 9.5 Hz, 1H), 3.49 (t, 1H), 3.04–2.80 (m, 2H), 2.73 (dt, $J = 4.0$ and 11.5 Hz, 1H), 2.15–1.96 (m, 1H), 1.90–1.66 (m, 2H). ^{13}C-NMR (75 MHz): 161.6 ($J_{C-F} = 245$ Hz), 153.7, 152.4, 150.7, 142.5, 138.7, 138.6, 137.4, 128.8, 128.7, 128.4, 127.7, 127.3, 115.7, 115.4, 115.3, 103.6, 101.0, 95.4, 71.9, 68.0, 55.9, 47.3, 44.5, 43.8, 42.0, 41.7, 33.9, 33.5, 30.9. ^{19}F-NMR (282 MHz): −116.4 to −116.3 (m, 1F). *Anal.* Calcd. for $C_{29}H_{30}FNO_5$: C: 70.86; H: 6.15; F: 3.86; N: 2.85; O: 16.27. Found: C: 70.75; H: 6.17; N: 2.83. $[\alpha]_D^{20} = -16.8$ ($c = 0.01$, methanol).

*2.2.6. (3S,4R)-3-(3,4-dibenzyloxyphenoxymethyl)-4-(4-fluorophenyl)-piperidine (**10**)*

Anhydrous hydrogen chloride was bubbled through a stirred solution of **8** (0.21 g, 0.37 mmol) in anhydrous 1,2-dichloroethane (5 mL) for 45 min. After the solvent was evaporated, 2 mL of 1,2-dichloroethane were added, and the solvent was removed by evaporation. The resulting orange residue was dried under vacuum for 3 h, then it was taken up in absolute ethanol (10 mL) and refluxed for 1.5 h. Ethanol was evaporated to yield **10** (0.21 g, 0.44 mmol, 73%) as a pink solid. IR (neat, ν_{max}): 2929, 2356, 1607, 1515, 1461, 1226, 1177. ^{1}H-NMR (200 MHz): 9.82 (brs, 1H), 7.41–7.20 (m, 10H), 7.14 (t, 2H), 6.94 (t, 2H), 6.73 (d, $J = 9.0$ Hz, 1H), 6.42 (d, $J = 2.0$ Hz, 1H), 6.12 (dd, $J = 2.0$, and 9.0 Hz, 1H), 5.07 (s, 2H), 5.01 (s, 2H), 3.73–3.50 (m, 3H), 3.49–3.42 (m, 1H), 3.25–2.70 (m, 3H), 2.70–2.50 (m, 1H), 2.50–2.23 (m, 1H), 2.10–1.90 (m, 1H). ^{13}C-NMR (75 MHz): 162.0 ($J_{C-F} = 246$ Hz), 153.4, 150.1, 143.5, 139.7, 137.4, 136.9, 128.9, 128.5, 128.4, 127.8, 127.7, 127.4, 127.3, 116.8, 115.9, 115.6, 111.8, 105.2, 103.4, 72.4, 71.1, 66.9, 46.8, 44.5, 41.6, 39.4, 30.9, 30.0. ^{19}F-NMR (282 MHz): −115.5 to −115.3 (m, 1F). *Anal.* Calcd. for $C_{32}H_{32}FNO_3$: C: 77.24; H: 6.48; F: 3.82; N: 2.81; O: 9.65. Found: C: 77.12; H: 6.44; N: 2.85. $[\alpha]_D^{20} = -57$ ($c = 0.01$, methanol).

*2.2.7. (3S,4R)-4-(4-fluorophenyl)-3-(3-methoxy-4-benzyloxyphenoxymethyl)piperidine (**11**)*

Following the above procedure, treatment of a solution of **9** (220 mg, 0.45 mmol) in 1,2-dichloroethane (5 mL) with anhydrous hydrogen chloride, evaporation of solvent and subsequent heating of an ethanolic solution under reflux provided a yellow oil

which was purified by column chromatography (ethyl acetate/methanol/ammonia 20:3:1) to give 170 mg (87%) of the free amine **11** as colorless solid. m.p.: 66–67 °C. IR (neat, ν_{max}): 2932, 2796, 1598, 1511, 1222, 1199. ^{1}H-NMR (300 MHz): 7.42–7.22 (m, 5H), 7.20–7.09 (m, 2H), 7.00–6.90 (m, 2H), 6.66 (d, $J = 9.0$ Hz, 1H), 6.36 (d, $J = 3.0$ Hz, 1H), 6.07 (dd, $J = 3.0$ and 9.0 Hz, 1H), 5.02 (s, 2H), 3.80 (s, 3H), 3.56 (dd, $J = 3.0$ and 9.5 Hz, 1H), 3.45 (dd, $J = 7.0$ and 16.0 Hz, 1H), 3.44 (Br, 1H), 3.18 (d, $J = 11.0$ Hz, 1H), 2.80–2.50 (m, 2H), 2.40–2.20 (m, 1H), 2.14–2.00 (m, 1H), 1.90–1.70 (m, 2H). ^{13}C-NMR (75 MHz): 161.4 ($J_{C-F} = 243$ Hz), 154.0, 150.7, 142.3, 139.8, 137.4, 128.7, 128.4, 127.7, 127.4, 127.3, 115.5, 115.4, 115.2, 103.7, 100.9, 93.8, 88.3, 72.0, 68.9, 55.8, 44.4. ^{19}F-NMR (282 MHz): −115.5 to −115.3 (m, 1F). *Anal.* Calcd. for $C_{26}H_{28}FNO_3$: C: 74.09; H: 6.70; F: 4.51; N: 3.32; O: 11.39. Found: C: 73.96; H: 6.72; N: 3.35. $[\alpha]_D^{20} = -45.9$ ($c = 0.01$, methanol).

*2.2.8. (3S,4R)-3-(3,4-dihydroxyphenoxymethyl)-4-(4-fluorophenyl)-piperidine (**2**)*

In a pressure resistant glass reactor was dissolved 66 mg (0.13 mmol) of **10** in 15 mL of previously degassed methanol. To this solution was added a catalytic amount of Pd/C. Hydrogenation was performed at 3 bar pressure with continuous stirring at room temperature for 4 h. After filtration of the residue through Celite and concentration, **2** was obtained as a pink oil (38 mg, 0.12 mmol, 92%). IR (neat, ν_{max}): 3191, 1511, 1226, 1165. ^{1}H-NMR (300 MHz, CD_3OD): 7.34–7.22 (m, 2H), 7.12–7.02 (m, 2H), 6.59 (d, $J = 9.0$ Hz, 1H), 6.27 (d, $J = 3.0$ Hz, 1H), 6.08 (dd, $J = 3.0$ and 9.0 Hz, 1H), 3.72–3.42 (m, 4H), 3.22–3.07 (m, 2H), 3.02–2.82 (m, 1H), 2.37 (br, 1H), 2.03 (br, 2H). ^{13}C-NMR (75 MHz, CD_3OD): 163.3 ($J_{C-F} = 243$ Hz), 153.6, 147.0, 140.7, 139.2, 130.3, 130.2, 116.7, 116.5, 116.4, 105.9, 104.2, 68.6, 45.5, 42.7, 40.8, 31.6. ^{19}F-NMR (282 MHz): −115.8 to −115.7 (m, 1F). $[\alpha]_D^{20} = -69$ ($c = 0.01$, methanol).

*2.2.9. (3S,4R)-4-(4-fluorophenyl)-3-(3-methoxy-4-hydroxyphenoxymethyl)piperidine (**3**)*

Following the above procedure, treatment of 19 mg (0.045 mmol) of **11** provided 13 mg (0.040 mmol, 89%) of **3** as a pink oil. ^{1}H-NMR (300 MHz, CD_3 OD): 7.28–7.22 (m, 2H), 7.06–6.96 (m, 2H), 6.61 (d, $J = 9.0$ Hz, 1H), 6.37 (d, $J = 3.0$ Hz, 1H), 6.13 (dd, $J = 3.0$ and 9.0 Hz, 1H), 3.77 (s, 3H), 3.62–3.34 (m, 4H), 3.22–3.10 (m, 1H), 2.80–2.60 (m, 3H), 2.20 (br, 2H). ^{13}C-NMR (75 MHz, CD_3OD): 162.2 ($J_{C-F} = 243$ Hz), 153.9, 149.4, 141.4, 141.2, 130.1, 130.0, 116.3, 116.0, 106.3, 101.5, 82.9, 70.1, 47.2, 45.1, 43.3, 35.3. ^{19}F-NMR (282 MHz): −115.9 to −115.6 (m, 1F). $[\alpha]_D^{20} = -60.5$ ($c = 0.005$, methanol).

2.3. Synthesis of paroxetine

*2.3.1. (3S,4R)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-methylpiperidine (**12**)*

Following the same procedure as described for the preparation of **6**, treatment of 224 mg (1.59 mmol) of 3,4-methylenedioxyphenol with NaH and subsequent reaction with 500 mg (1.32 mmol) of tosylate **5** provided, after column chromatography purification, 370 mg (1.08 mmol, 80%) of **12** as free amine. IR (neat, ν_{max}): 2936, 2787,

1510, 1489, 1185, 1038, 832. ^{1}H-NMR (300 MHz): 7.18–7.10 (m, 2H), 7.01–6.90 (m, 2H), 6.60 (d, $J = 8.5$ Hz, 1H), 6.32 (d, $J = 2.5$ Hz, 1H), 6.11 (dd, $J = 2.5$ and 8.5 Hz, 1H), 5.85 (s, 2H), 3.55 (dd, $J = 3.0$ and 9.5 Hz, 1H), 3.42 (dd, $J = 7.0$ and 9.5 Hz, 1H), 3.20–3.15 (m, 1H), 3.00–2.90 (m, 1H), 2.42 (dt, $J = 5.5$ and 11.5 Hz, 1H), 2.34 (s, 3H), 2.26–2.11 (m, 1H), 2.10–1.75 (m, 4H). ^{13}C-NMR (75 MHz): 161.5 ($J_{C-F} = 244$ Hz), 154.3, 148.1, 141.5, 139.6, 128.8, 128.7, 115.5, 115.2, 107.8, 105.5, 101.0, 97.9, 69.5, 59.5, 56.1, 46.5, 43.5, 42.1, 34.3. ^{19}F-NMR (282 MHz): −117.2 to −117.0 (m, 1F). GC/MS (*m/z*): 58, 83, 109, 191, 206, 343. *Anal.* Calcd. for $C_{20}H_{22}FNO_3$: C: 69.95; H: 6.46; F: 5.53; N: 4.08; O: 13.98. Found: C: 70.04; H: 6.39; N: 4.12. $[\alpha]_D^{20} = -75.9$ ($c = 0.01$, methanol).

*2.3.2. (3S,4R)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-vinyloxycarbonylpiperidine (**13**)*

Following the same procedure as described for the preparation of **8**, treatment of a solution of **12** (300 mg, 0.87 mmol), and anhydrous potassium carbonate (1.23 g, 8.21 mmol) in 1,2-dichloroethane (5 mL) with vinyl chloroformate (0.55 mL, 6.18 mmol) gave, after purification by flash silica-gel column chromatography, 0.26 g (0.65 mmol, 75%) of (3*S*,4*R*)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1- vinyloxycarbonylpiperidine. IR (neat, ν_{max}): 2924, 2870, 1716, 1488, 1469, 1436, 1221, 1186, 1151. ^{1}H-NMR (300 MHz): 7.28–7.20 (m, 1H), 7.16–7.07 (m, 2H), 7.00–6.91 (m, 2H), 6.60 (d, $J = 8.5$ Hz, 1H), 6.34 (d, $J = 2.5$ Hz, 1H), 6.26 (dd, $J = 2.5$ and 8.5 Hz, 1H), 5.86 (s, 2H), 4.79 (dd $J = 1.5$ and 14.0 Hz, 1H), 4.50 (br, 1H), 4.46 (dd, J = 1.5 and 6.5 Hz, 1H), 4.33 (d, $J = 12.5$ Hz, 1H), 3.60 (dd, $J = 2.5$ and 9.5 Hz, 1H), 3.50–3.41 (m, 1H), 3.02–2.81 (m, 2H), 2.80–2.65 (m, 1H), 2.10–1.96 (m, 1H), 1.88–1.65 (m, 2H). ^{13}C-NMR (75 MHz): 161.6 ($J_{C-F} = 245$ Hz), 154.1, 152.4, 148.1, 142.5, 141.7, 138.6, 128.8, 128.7, 115.7, 115.4, 107.8, 105.5, 101.1, 98.0, 95.3, 68.5, 47.3, 44.5, 43.7, 41.8, 33.4. ^{19}F-NMR (282 MHz): −116.4 (s, 1F). GC/MS (*m/z*): 109, 151, 262, 356, 399. *Anal.* Calcd. for $C_{22}H_{22}FNO_5$: C: 66.16; H: 5.55; F: 4.76; N: 3.51; O: 20.03. Found: C: 66.04; H: 5.47; N: 3.62. $[\alpha]_D^{20} = -24.0$ ($c = 0.01$, methanol).

*2.3.3. (3S,4R)-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine, Paroxetine (**1**)*

Following the same procedure as described for the preparation of **10**, treatment of a solution of **13** (76 mg, 0.19 mmol) in 1,2-dichloroethane (3.5 mL) with anhydrous hydrogen chloride, evaporation of solvent and subsequent heating of an ethanolic solution under reflux provided an orange–yellow oil that was purified by column chromatography (ethyl acetate/methanol/ammonia 20:3:1) to give 60 mg (96%) of the free amine **1** as white solid. IR (neat, ν_{max}): 3403, 2921, 1509, 1488, 1470, 1186. ^{1}H-NMR (300 MHz, CD_3OD): 7.28–7.20 (m, 2H), 7.06–6.96 (m, 2H), 6.61 (d, $J = 9.0$ Hz, 1H), 6.33 (d, $J = 2.5$ Hz, 1H), 6.13 (dd, $J = 2.5$ and 9.0 Hz, 1H), 5.84 (s, 2H), 3.70–3.34 (m, 4H), 3.24–3.14 (m, 1H), 2.86–2.66 (m, 3H), 2.22–2.06 (m, 1H), 1.86–1.76 (m, 2H). ^{13}C-NMR (75 MHz, CD_3OD): 163.0 ($J_{C-F} = 242$ Hz), 155.7, 149.6, 143.1, 141.0, 140.9, 130.2, 130.1, 116.4, 116.1, 108.8, 106.5, 102.4, 98.7, 70.1, 46.9, 44.8, 43.0, 34.8. $[\alpha]_D^{20} = -66$ ($c = 0.01$, methanol).

3. Results and discussion

The preparation of both metabolites was planned following the synthesis described for paroxetine. Thus, commercially available 3,4-dibenzyloxybenzaldehyde and 4-benzyloxy-3-methoxybenzaldehyde were converted to the corresponding phenols [10]. (3*S*,4*R*)-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine, **4** [11] was converted to its tosylate derivative **5** [9] (Fig. 2) which by treatment with the sodium salt of the corresponding phenol was converted to the intermediates **6** and **7**.

N-demethylation of these compounds by reaction with vinyl chloroformate and subsequent heating with hydrogen chloride [12] in absolute ethanol provided both 3,4-disubstituted phenoxypiperidines **10** and **11** as their hydrochloride salts, which by hydrogenation in the presence of a catalytic amount of palladium on charcoal yielded the corresponding (3*S*,4*R*)-4-(4-fluorophenyl)-3-(3,4-dihydroxyphenoxymethyl)piperidine **2**, and (3*S*,4*R*)-4-(4-fluorophenyl)-3-(4-hydroxy-3-methoxyphenoxymethyl)piperidine **3**, respectively.

As it is known that the configuration of the C3 stereocenter could be inverted during the displacement of the corresponding sulfonate ester of *trans* 4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine with the sodium salt of 3,4-methylenedioxyphenol [13], the *trans* configuration of synthetic piperidines **2** and **3** was confirmed by NMR analysis of compound **7** (^{1}H-, ^{13}C-NMR, NOE, and heterocorrelation experiments). After assingment of all the signals, one may conclude that

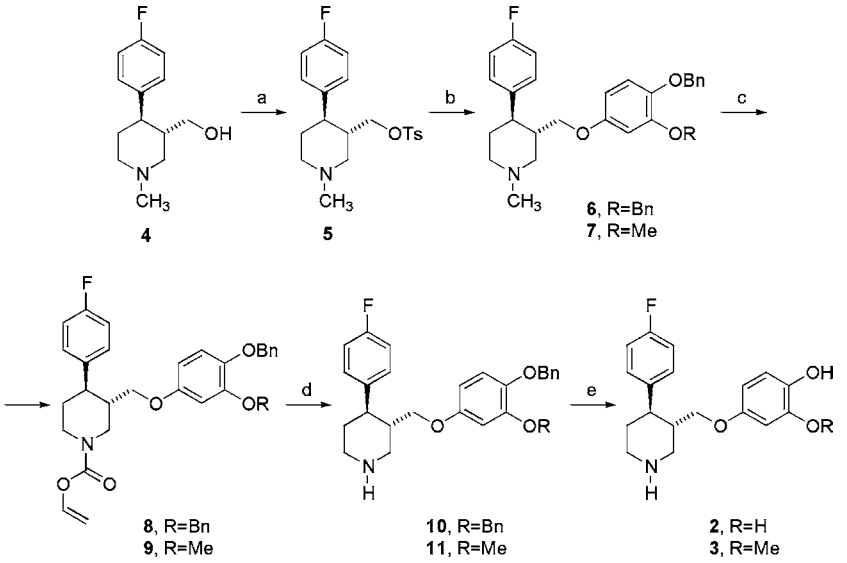

Fig. 2. Synthesis of paroxetine main metabolites **2** and **3**. Reagents and conditions. (a) TsCl, Et_3N, $Me_3N{\cdot}HCl$, CH_2Cl_2, 0 °C, 1.5 h, 90%; (b) NaH, DMF, add a solution of corresponding phenol in DMF, reflux, 3 h, cool to RT and add a solution of **5** in DMF, reflux, 4 h, then cool to RT; (c) $CH_2{=}CHOCOCl$, K_2CO_3, $ClCH_2CH_2Cl$, reflux, 4 h, evaporation to dryness; (d) HCl(g) in absolute EtOH, reflux, 1.5 h; (e) H_2, Pd–C, MeOH, 4 h.

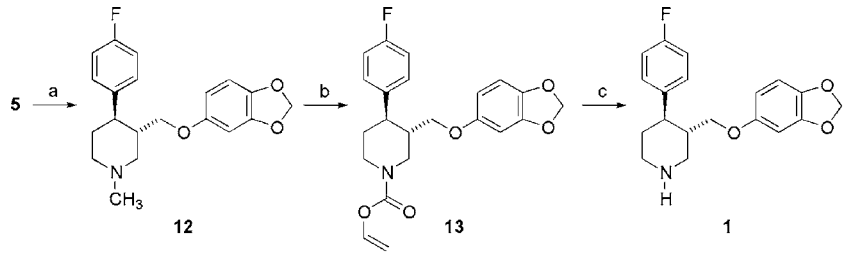

Fig. 3. Chemical synthesis of paroxetine **1**. Reagents and conditions. (a) NaH, DMF, then add a solution of 3,4-methylenedioxyphenol in DMF, reflux, 3 h, cool to Rt and add a solution of **5** in DMF, reflux, 4 h, then cool to RT; (b) CH_2=CHOCOCl, K_2CO_3, $ClCH_2CH_2Cl$, reflux, 4 h, evaporation to dryness; (c) HCl(g) in absolute EtOH, reflux, 1.5 h.

hydrogen attached to C4 displays three vicinal coupling constants (11.5, 11.0, and 4.5 Hz). The first two correspond typically to 1,2-*trans*-diaxial system and the third one to a vicinal axial-equatorial which would only be possible if substituents at C3 and C4 are in a 1,2-*trans*-diaxial disposition. This confirms that no inversion at C3 had occurred during the displacement reaction.

This stereochemistry was also confirmed by comparison of synthetic and commercial samples of paroxetine. Accordingly, treatment of tosylate derivative **5** (Fig. 3) with the sodium salt of 3,4-methylenedioxyphenol resulted in the *N*-methylpiperidine intermediate **12**, which by demethylation following the same procedure as described above, yielded a product whose structure and stereochemistry was confirmed as paroxetine **1** by comparison of its analytical data with those of an authentic sample.

4. Conclusion

This is the first report describing the synthesis of paroxetine main metabolites (3*S*,4*R*)-4-(4-fluorophenyl)-3-(3,4-dihydroxyphenoxymethyl)piperidine **2** and (3*S*, 4*R*)-4-(4-fluorophenyl)-3-(4-hydroxy-3-methoxyphenoxymethyl)piperidine **3**, that are crucial for our future in vivo studies on the metabolism of paroxetine.

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[13] Christensen et al. reported the conversion of the (±)-*trans* isomer of the methane sulfonic ester derivative of **4** into a mixture of (±)-*trans* and mainly (±)-*cis* of compound **10** by reaction with the sodium salt of 3,4-methylenedioxyphenol (see reference [11b]). In this regard, the same authors [see Christensen, J.A.; Engelstoft, M.; Schaumburg, K.; Schou, H.; Wätjen, F. (1983) Tetrahedron Lett., 24, 5151–5152.] published work on the preparation of a similarly substituted piperidine (Femoxetine) stating that a mixture of *cis* and *trans* (85:15) benzenesulphonyl ester was converted, by treatment with the sodium salt of *p*-methoxyphenol, into a *cis*/*trans* (15/85) of Femoxetine, but if pure (±)-*trans* sulphoester is used as the starting material pure (±)-*trans* Femoxetine is the product, indicating in this case a clean S_N2 reaction. This contradiction led us to investigate the relative stereochemical outcome of our reaction.