Supplementary Material

Synthesis of Florbetapir aza-analogues using chemistry of pyridinium N-aminides

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1. Table S1. Optimization of the alkylation of aminides 3 and synthesis of acetamides 4

Table S1. Optimization of the alkylation of aminides 3 and synthesis of acetamides 4

<table>
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<th>Entry</th>
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<th>n</th>
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*Carbonization of the mixture
2. Numbering employed in NMR analysis

![Structural diagrams of compounds with numbering](image)

**Figure S1.** Numbering employed in NMR analysis.
3. Synthesis of alkylation agents

2-[2-[Benzylxy]ethoxy]ethoxy]ethanol (20). Benzyl bromide (6.5 mL, 55 mmol) was added dropwise to a solution of triethylene glycol (7.51 g, 50 mmol) and freshly prepared Ag₂O (17.4 g, 75 mmol) in CH₂Cl₂ (20 mL) at room temperature. The suspension was stirred for 24 h then filtered through Celite. The filtrate was evaporated and the resulting residue was purified by flash chromatography (hexane/ethyl acetate 1:1), to give 2-[2-[Benzylxy]ethoxy]ethoxy]ethanol 20 (10.5 g, 88 %, 44 mmol) as a colourless oil. ¹H NMR (300 MHz, CDCl₃): δ 7.34-7.26 (5H, m, ArH), 4.56 (2H, s, CH₂Ar), 3.72-3.58 (12H, m, CH₂O), 2.50 (1H, br s, OH) ppm.

1,12-diphenyl-2,5,8,11-tetraoxadodecane 21 was obtained as a secondary product. Colourless oil (0.82 g, 5 %, 2.5 mmol). ¹H NMR (500 MHz, CDCl₃): δ 7.34-7.25 (10H, m, ArH), 4.57 (4H, s, CH₂Ar), 3.69-3.63 (12H, m, CH₂O) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 138.3 (C1), 128.3 (C3(5)), 127.7 (C2(6)), 127.6 (C4), 73.2 (CH₂Ph), 70.7 (2CH₂O), 69.4 (4CH₂O) ppm.

Tosylation of poly (ethylene glycol) derivatives

General procedure. Tosyl chloride (10.5 g, 55 mmol) in dry CH₂Cl₂ (250 mL) at 0 °C, and the mixture was stirred for 2 h at room temperature. After washing with 1 M HCl, then with a saturated aqueous solution of NaHCO₃ and finally with brine, the organic layer was dried (Na₂SO₄) and the solvent evaporated to dryness, to obtain the desired product, which was used in the next step without further purification. Experimental data were consistent with previously reported literature values.

2-[2-[Benzylxy]ethoxy]ethoxy]ethyl-4-methylbenzenesulfonate (22a). Tosylate 22a was obtained as a yellow oil (14.9 g, 85 %, 42.5 mmol). ¹H NMR (300 MHz, CDCl₃): δ 7.79 (2H, d, J 8.4, H2(6)), 7.29 (7H, m, H3(5) and ArH), 4.53 (2H, s, CH₂Ar), 3.56 (6H, m, CH₂B, CH₂C and CH₂D), 2.40 (3H, s, CH₃) ppm.

2-[2-[Benzylxy]ethoxy]ethoxy]ethyl-4-methylbenzenesulfonate (22b). Tosylate 22b was obtained as an yellow oil (12.0 g, 72 %, 36 mmol). ¹H NMR (300 MHz, CDCl₃): δ 7.77 (2H, d, J 8.4, H2(6)), 7.33-7.26 (7H, m, H3(5) and ArH), 4.54 (2H, s, CH₂-Ph), 4.14 (2H, m, CH₂A), 3.67 (2H, m, CH₂B), 3.62-3.57 (8H, m, CH₂C, CH₂D, CH₂E and CH₂F), 2.41 (3H, s, CH₃) ppm.

Obtaining of the polyethylene glycol bromides

General procedure. LiBr (24.5 g, 280 mmol) was added to a solution of the corresponding tosylate 22 (28 mmol) in acetone (80 mL) and the mixture refluxed for 6 h. The solution was then cooled and the solvent removed. The resulting residue was suspended in H₂O (80 mL), extracted four times with CH₂Cl₂ (4 x 80 mL) and the layers separated. The combined organic extracts were then dried (Na₂SO₄), filtered and the solvent evaporated to obtain the desired product 7. Experimental data were consistent with previously reported literature values.

2-[2-Bromoethoxy]ethoxy)methylbenzene (7a). Derivative 7a was obtained as a yellow liquid (6.89 g, 95 %, 26.6 mmol). ¹H NMR (300 MHz, CDCl₃): δ 7.31 (5H, m, ArH), 4.55 (2H, s, CH₂Ar), 3.78 (2H, t, J 6.3 Hz, CH₂B), 3.66 (2H, m, CH₂C or CH₂D), 3.60 (2H, m, CH₂D or CH₂C), 3.45 (2H, t, J 6.3 Hz, CH₂A) ppm.

2-[2-[2-Bromoethoxy]ethoxy]ethoxy)methylbenzene (7b). Derivative 7b was obtained as a yellow liquid (7.89 g, 93 %, 26.0 mmol). ¹H NMR (300 MHz, CDCl₃): δ 7.35-7.26 (5H, m, ArH), 4.57 (2H, s, CH₂Ar), 3.81 (2H, t, J 7.0 Hz, CH₂B), 3.70-3.63 (8H, m, CH₂C, CH₂D, CH₂E and CH₂F), 3.46 (2H, t, J 7.0 Hz, CH₂A) ppm.

4. $^1$H, $^{13}$C and $^{19}$F NMR of new compounds synthesized.

Figure S2. $^1$H-NMR of product 3.

Figure S3. $^{13}$C-NMR of product 3.
Figure S4. $^1$H-NMR of product 4a.

Figure S5. $^{13}$C-NMR of product 4a.
Figure S6. $^1$H-NMR of product 4b.

Figure S7. $^{13}$C-NMR of product 4b.
Figure S8. $^1$H-NMR of product 6.

Figure S9. $^{13}$C-NMR of product 6.
Figure S10. $^1$H-NMR of mixture of salts 8b and 9b.
Figure S11. $^1$H-NMR of product 10a.

Figure S12. $^{13}$C-NMR of product 10a.
Figure S13. $^1$H-NMR of product 10b.

Figure S14. $^{13}$C-NMR of product 10b.
Figure S15. $^1$H-NMR of product 11a.

Figure S16. $^{13}$C-NMR of product 11a.
Figure S17. $^1$H-NMR of product 11b.

Figure S18. $^{13}$C-NMR of product 11b.
Figure S19. $^1$H-NMR of product 12a.

Figure S20. $^{13}$C-NMR of product 12a.
Figure S21. $^{19}$F-NMR of product 12a.

Figure S22. $^{19}$F-NMR of product 12b.
Figure S23. $^1$H-NMR of product 12b.

Figure S24. $^{13}$C-NMR of product 12b.
Figure S25. $^1$H-NMR of product 13.

Figure S26. $^{13}$C-NMR of product 13.
Figure S27. $^1$H-NMR of product 14a.

Figure S28. $^{13}$C-NMR of product 14a.
Figure S29. $^1$H-NMR of product 14b.

Figure S30. $^{13}$C-NMR of product 14b.
Figure S31. $^1$H-NMR of product 15a.

Figure S32. $^{13}$C-NMR of product 15a.
Figure S33. $^1\text{H}$-NMR of product 15b.

Figure S34. $^{13}\text{C}$-NMR of product 15b.
Figure S35. $^1$H-NMR of product 16a.

Figure S36. $^{13}$C-NMR of product 16a.
Figure S37. $^1$H-NMR of product 16b.

Figure S38. $^{13}$C-NMR of product 16b.
Figure S39. $^1$H-NMR of product 18.

Figure S40. $^{13}$C-NMR of product 16b.
Figure S41. $^1$H-NMR of product 1a.

Figure S42. $^{13}$C-NMR of product 1a.
Figure S43. $^{19}$F-NMR of product 1a.

Figure S44. $^{19}$F-NMR of product 1b.
Figure S45. $^1$H-NMR of product 1b.

Figure S46. $^{13}$C-NMR of product 1a.
Figure S47. $^1$H-NMR of product 19.

Figure S48. $^{13}$C-NMR of product 19.