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Synthesis of Benzyl 2-(4-(8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)piperazin-1-yl)acetate

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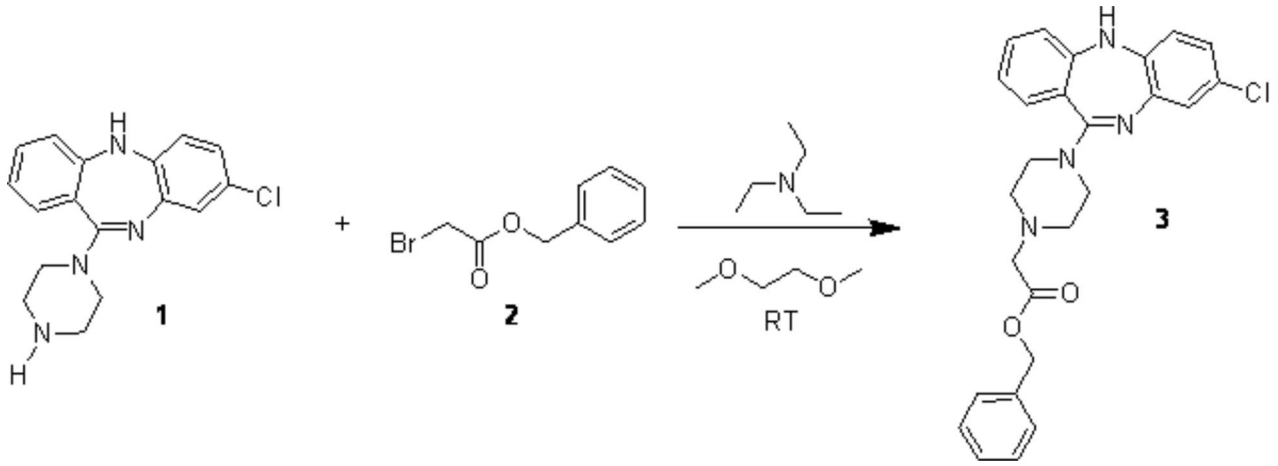
As part of our research programme, we have synthesized the title compound as an intermediate for the preparation of a zwitterionic analogue of the atypical antipsychotic, clozapine. The starting material, desmethylclozaine, **1** was synthesized in accordance with a previously reported literature procedure [1]. Subsequent treatment of **1** with benzyl 2-bromoacetate (**2**) afforded the title compound **3** in very good yield.



To a solution of desmethylclozapine (**1**, 503 mg, 1.61 mmol) and anhydrous triethylamine (0.451 mL, 3.23 mmol) in anhydrous 1,2-dimethoxyethane (25 mL) was added benzyl 2-bromoacetate (**2**, 0.287 mL, 1.81 mmol) *via* syringe. The reaction mixture was stirred at room temperature for 3 hours, filtered and then evaporated to dryness. The residue was treated with distilled water (10 mL) and extracted with dichloromethane (4 ´ 50 mL). The combined organic fractions were dried with anhydrous sodium sulfate, filtered, then evaporated to dryness. The resulting residue was purified using flash chromatography (silica gel 230-400 mesh, ethyl acetate:hexane, 1:1). The fractions containing product were combined and evaporated to dryness affording a yellow oil that solidified on standing. Recrystallisation from dichloromethane-hexane gave the title compound **3** as bright yellow prisms (536 mg, 72%).

Melting Point: 182-183˚C

TLC: R_f (silica; ethyl acetate:hexane, 1:1) 0.35.

Elemental Analysis: Calculated for $C_{26}H_{25}ClN_4O_2$: C, 67.75%; H, 5.47%; N, 12.15%. Found: C, 67.62%; H, 5.51%; N, 12.17%.

IR (KBr, cm^{-1}): 3320, 1728, 1600, 1558.

UV ((EtOH; λ_{max} nm; $log_{10}e$): 209 (4.55), 228 (4.43), 260 (4.28), 297 (4.09).

^{1}H-NMR (300 MHz, CD_2Cl_2): d= 7.39-7.25 (m, 7 H, H1", H3", H2"", H3"", H4"", H5"", H6""); 7.05-7.00 (m, 2 H, H2", H4"); 6.87-6.81 (m, 2 H, H7", H9"); 6.65 (d, *J* = 8.5 Hz, 1 H, H6"); 5.17 (s, 2 H, H1'"); 5.05 (s, 1 H, H5"); 3.46 (m, 4 H, H3', H5'); 3.33 (s, 2 H, H2); 2.67 (m, 4 H, H2', H6').

^{13}C-NMR (75 MHz, CD_2Cl_2): d= 170.6 (C=O); 163.4 (C_q); 153.4 (C_q); 142.6 (C_q); 141.2 (C_q); 136.6 (C_q); 132.5 (CH); 130.8 (CH); 129.3 (C_q); 129.1 (CH); 128.8 (CH); 127.0 (CH); 124.0 (C_q); 123.6 (CH); 123.4 (CH); 120.7 (CH); 120.7 (CH); 120.6 (CH); 66.8 (CH_2); 59.8 (CH_2); 53.2 (CH_2); 47.8 (CH_2).

MS ESI (*m/z*, %): 463.2 (M[^{37}Cl]H^{+}, 32%); 461.2 (M[^{35}Cl]H^{+}, 100%).

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References:
1. Capuano, B.; Crosby, I. T.; Lloyd, E. J.; Taylor D. A. *Aust. J. Chem.* **2002**, *55*, 565.

Sample Availability: Available from the author.