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

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Received: 24 November 2005 / Accepted: 7 December 2005 / Published: 12 December 2005

Keywords: clozapine, amidine, benzyl ester, N-alkylation, dibenzodiazepine.

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, desmethylclozapine, 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: Rf (silica; ethyl acetate:hexane, 1:1) 0.35.

Elemental Analysis: Calculated for C26H25ClN4O2: 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; \( \lambda_{\text{max}} \) nm; \( \log_{10} e \]): 209 (4.55), 228 (4.43), 260 (4.28), 297 (4.09).

\(^1\)H-NMR (300 MHz, CD\(_2\)Cl\(_2\)): \( \delta = 7.39\) - 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, \( J = 8.5 \text{ Hz} \), 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\(_2\)Cl\(_2\)): \( \delta = 170.6 \) (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); 120.6 (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}\text{Cl}]H^+\), 32%); 461.2 (M\[^{35}\text{Cl}]H^+\), 100%).

Acknowledgment

The authors gratefully acknowledge financial support from Monash University and the assistance of Ms Anna Podloucka and Mr James Shin.

References


Sample Availability: Available from the author.

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