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Synthesis of 8-chloro-11-(4-(3-(*p*-tolyloxy)propyl)piperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepine

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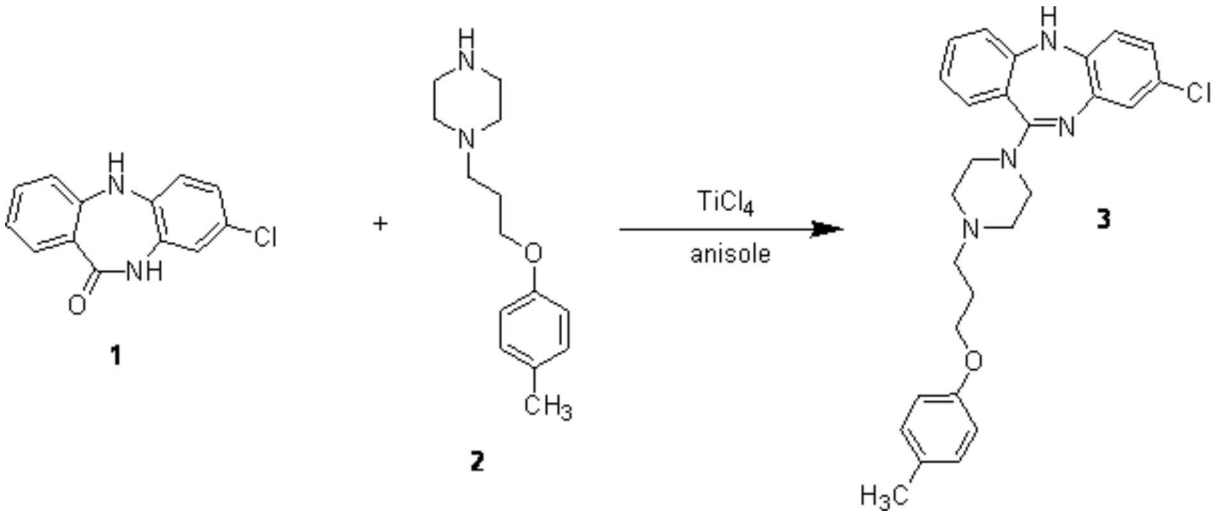
As part of our ongoing research programme in the area of anti-schizophrenia therapeutics, we have synthesized the title compound based on the structural hybridization of the two prominent antipsychotic drugs, clozapine and haloperidol. The starting tricyclic lactam, **1**, was synthesized according to previously described literature procedures [1, 2, 3]. Subsequent treatment of **1** with the titanium-amine complex [4] formed from the addition of titanium tetrachloride to the monosubstituted piperazine, **2**, furnished the title compound **3** in respectable yield.



To a solution of 1-(3-(*p*-tolyloxy)propyl)piperazine (**2**) (1.20 g, 5.14 mmol) in anhydrous anisole (5 mL) under nitrogen was added a solution of titanium tetrachloride in toluene (1.0 M, 1.10 mL, 1.10 mmol). The mixture was warmed to 50-55°C and a hot solution of 8-chloro-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-one (**1**) (250 mg, 1.02 mmol) in anhydrous anisole (10 mL) was then added *via* syringe. The mixture was heated at reflux for 4 h after which time it was cooled and then evaporated to dryness *in vacuo*. The brown coloured residue was partitioned between ethyl acetate (50 mL) and aqueous sodium hydroxide (2 M, 30 mL), the mixture filtered under vacuum and the residue washed with ethyl acetate (20 mL). The organic layer was separated and the aqueous phase extracted with ethyl acetate (2 ´ 50 mL). The organic fractions were combined, washed with water (2 ´ 30 mL), dried (anhydrous sodium sulfate), evaporated to dryness and the resulting residue purified using flash column chromatography (silica gel 230-400 mesh, ethyl acetate:hexane, 4:1). The fractions corresponding to the major product were pooled and evaporated to dryness producing a yellow oily residue. Recrystallisation from a methanol-water gave the title compound **3** as bright yellow prisms (252 mg, 53%).

Melting Point: 154.4–156.8ºC

TLC: R_f (silica; ethyl acetate:hexane, 4:1) 0.30.

Elemental Analysis: Calculated for $C_{27}H_{29}ClN_4O$: C, 70.34%; H, 6.34%; N, 12.15%. Found: C, 70.36%; H, 6.36%; N, 12.24%.

IR (KBr, cm^{-1}): 3292, 2920, 2852, 1598, 1558.

UV ((EtOH; λ_{max} nm; $log_{10}e$): 217 (4.54), 225 (4.55), 261 (4.26), 297 (4.08).

^{1}H-NMR (300 MHz, d_6-acetone): *d*= 7.36–7.26 (m, 2 H); 7.08–6.99 (m, 4 H); 6.96 (m, 1 H); 6.88–6.75 (m, 4 H); 6.52 (s, 1 H, H5); 4.02 (t, *J* = 6.5 Hz, 2 H, H3''); 3.41 (m, 4 H, H2', H6'); 2.60–2.50 (m, 6 H, H1'', H3', H5'); 2.23 (s, 3 H, C*H*$_3$); 1.93 (m, *J* = 6.5 Hz, 2 H, H2'').

^{13}C-NMR (75 MHz, d_6-acetone): *d*= 164.0 (C_q); 158.1 (C_q); 154.9 (C_q); 143.4 (C_q); 142.9 (C_q); 132.7 (CH); 130.9 (CH); 130.6 (CH); 130.1 (C_q); 128.5 (C_q); 126.9 (CH); 124.6 (C_q); 123.40 (CH); 123.35 (CH); 121.3 (CH); 121.1 (CH); 115.2 (CH); 66.8 (CH_2); 55.7 (CH_2); 53.8 (CH_2); 48.2 (CH_2); 27.6 (CH_2); 20.5 (CH_3).

MS ESI (*m/z*, %): 463.3 (M[^{37}Cl]H$^+$, 36%); 461.3 (M[^{35}Cl]H$^+$, 100%).

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Sample Availability: Available from the author.