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Volume 55, 2002

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Aust. J. Chem. **2002**, *55*, 565–576

Synthesis and Preliminary Pharmacological Evaluation of 4′-Arylmethyl Analogues of Clozapine. I. The Effect of Aromatic Substituents

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As part of a research program to develop compounds with mixed dopamine D_4 and serotonin 5-HT_{2A} antagonist activity with potential for the treatment of schizophrenia, we report a family of compounds based on structural modification of the atypical antipsychotic, clozapine (2). The chemical synthesis, structural characterization and pharmacological evaluation of a series 4′-arylmethyl analogues of clozapine are described. Preliminary receptor binding data are presented, examining primarily the electronic and positional effects of substituents on the introduced arylmethyl group, and secondarily the nature of the aryl ring.

Manuscript received: 30 April 2002.
Final version: 17 June 2002.

Introduction

Schizophrenia is a mental disorder characterized by fragmented thought processes manifested in the form of two distinct symptomatic categories: positive symptoms (delusions and hallucinations) and negative symptoms (emotional and social withdrawal).[1] Despite intensive research over the last 50 years, neither the biological basis of schizophrenia nor the mechanism of action of antipsychotic drugs is fully understood. However, several hypotheses have been proposed, such as the dopamine hypothesis which links positive psychotic symptoms with hyperactivity of dopaminergic neurons in the mesolimbic region of the brain.[2–8] There is also strong evidence to support the involvement of the neurotransmitter serotonin 5-HT in schizophrenia, particularly in negative symptomatology.

Amongst the many themes of antipsychotic drug action,[2] a high affinity at D_4 receptors relative to D_2 receptors has been proposed to rationalize efficacy against positive symptoms and low potential for extrapyramidal symptoms (EPS); Parkinsonian movement disorders resulting from dopamine receptor blockade in the nigrostriatal brain region.[9,10] Similarly, a high affinity at 5-HT_{2A} receptors relative to D_2 receptors may explain improvement in negative symptoms and reduced EPS liability.[11,12] A selection of currently used antipsychotic agents is depicted in Figure 1. Table 1 shows inhibition constants for these therapeutics at specific dopamine and serotonin receptors, in addition to ratios of affinities at receptor pairs.[13,14]

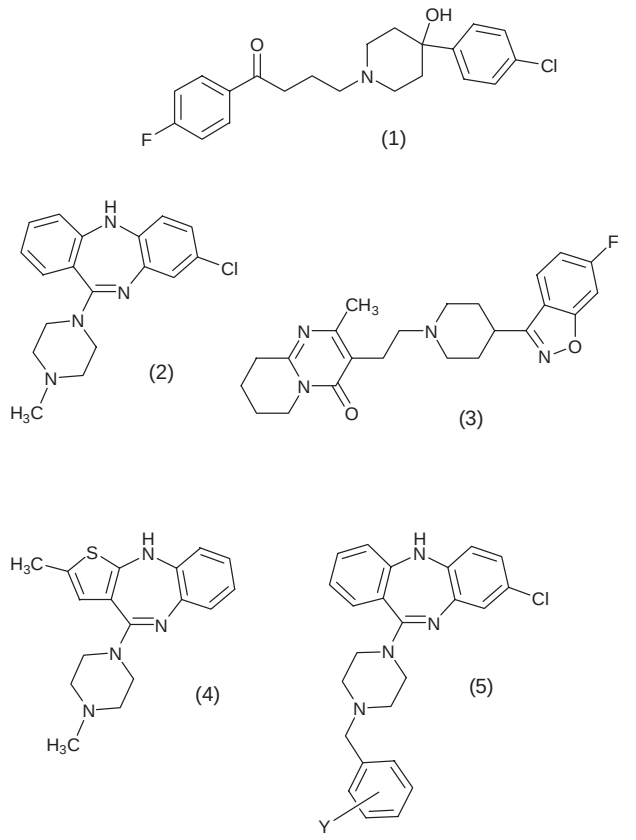


Fig. 1. The chemical structures of some currently prescribed antipsychotics; haloperidol (1), clozapine (2), risperidone (3), olanzapine (4), and proposed clozapine analogues (5).

 10.1071/CH02093 0004-9425/02/050565

Table 1. Binding affinities of selected antipsychotic agents for dopamine and serotonin receptors and relative affinities for receptor pairs[13,14]

Agent	K_i (nM)			Selectivity		
	D_2	D_4	5-HT_{2A}	$\frac{Ki(D_2)}{Ki(D_4)}$	$\frac{Ki(D_2)}{Ki(5\text{-}HT_{2A})}$	$\frac{Ki(D_4)}{Ki(5\text{-}HT_{2A})}$
Haloperidol (1)	2.2	11	200	0.2	0.011	0.055
Clozapine (2)	190	40	9.6	4.75	19.8	4.2
Risperidone (3)	5.9	16	0.52	0.37	11.3	31
Olanzapine (4)	31	28	2.5	1.11	12.4	11

The introduction of the butyrophenone haloperidol (1) into the clinic represented a significant advance in the treatment of schizophrenia, due to its efficacy in treating the positive symptoms of the disease.[15] However, haloperidol is ineffective in the treatment of negative symptoms,[16,17] a therapeutic profile that could be rationalized by the relatively high affinity for D_4 receptors compared with 5-HT_{2A} receptors. Based on its propensity to produce EPS,[18] accounted for by the relatively high affinity for D_2 receptors compared with D_4 and 5-HT_{2A} receptors, haloperidol is classified as a typical antipsychotic.

The dibenzodiazepine clozapine (2) has proven to be effective in ameliorating both positive and negative symptoms of schizophrenia,[19–22] and is virtually devoid of movement disorders.[23,24] This may be attributed to its low affinity for D_2 receptors compared with D_4 and 5-HT_{2A} receptors. However the potentially fatal blood disorder agranulocytosis,[25,26] detected in 1–2% of patients, requires its clinical use to be accompanied by monitoring of white blood cells count. Clozapine earns its title as the prototypic atypical antipsychotic[27] through its ability to provide antipsychotic efficacy free from EPS.

The benzisoxazole risperidone (3) has been shown to be more effective than haloperidol in improving both the negative and positive symptoms of schizophrenia, with a low incidence of EPS.[28,29] Doses above 6 mg/day produce negligible therapeutic improvement but worsening EPS in a dose-dependant manner,[30,31] highlighting risperidone's narrow therapeutic window and raising questions about its classification as atypical. The documented EPS at the higher dose may be due to risperidone's greater affinity for D_2 receptors compared with D_4 receptors.

The thienobenzodiazepine, olanzapine (4), a close analogue of clozapine, displays pronounced efficacy against both positive and negative symptoms, with a relatively low tendency to produce EPS at the medium dose range. Of interest is that at higher doses olanzapine produces an improvement in negative symptoms but with consequential EPS at 30–50% of the frequency evident in the haloperidol treatment group.[32] The observed motor side effects at higher doses may be a result of olanzapine's comparable affinity for D_2 and D_4 receptors. Recent findings also link olanzapine with convulsions, neuroleptic malignant syndrome and, more significantly, the white blood cell disorder, neutropenia.[33,34]

From the above overview of these established and recently introduced antipsychotic drugs there is, clearly, still a need to develop novel antipsychotics devoid of the many and disparate clinically limiting side effects but with greater efficacy in treatment-resistant schizophrenia. The clinical model for antipsychotic activity we have selected is directed towards compounds with a potential dual action. Primarily, the profile of high D_4 and 5-HT_{2A} receptor affinity is postulated for the improvement of positive and negative symptoms, respectively. Low D_2 affinity is also important to minimize EPS liability.

Based on previous modelling work, we have developed a structural model for antipsychotic activity for use in devising new synthetic targets.[35–37] This model, of which structure (5) (Fig. 1) is a representative, combines structural features from a diverse range of current therapeutic antipsychotics. Structure (5) consists of clozapine with an additional substituted aryl group attached to the distal nitrogen atom, separated by a methylene spacer. Here we report the synthesis and preliminary pharmacological evaluation of this novel series of clozapine analogues.

Results and Discussion

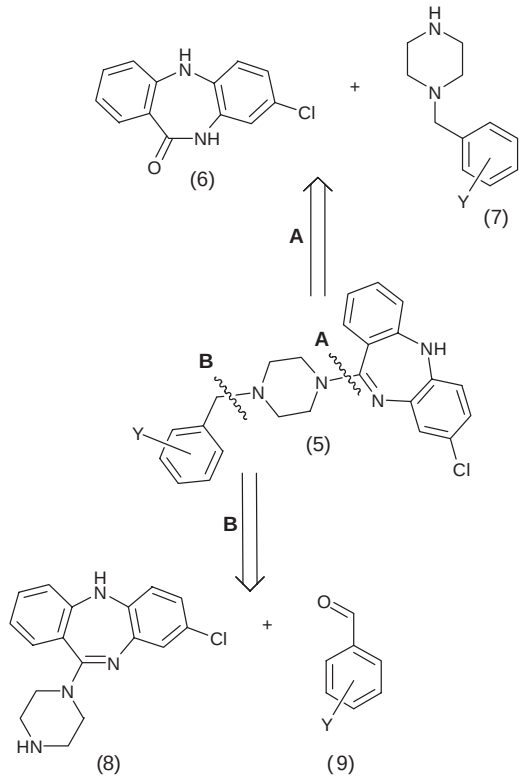
Chemistry

The compounds described herein are based on structural modifications of the atypical antipsychotic, clozapine (2), and are represented by the general structure (5) (Fig. 1). The resulting template essentially contains the tricyclic nucleus characteristic of clozapine in addition to a substituted aromatic ring attached to the distal nitrogen (N4′) by a designated spacer. Of particular interest are the positional and electronic effects of substituted arylmethyl groups at the above-mentioned nitrogen atom, which have not been extensively explored.

The following two pathways were envisaged (Scheme 1) for the synthesis of the substituted arylmethyl analogues of clozapine. Retrosynthetically, disconnection at the highlighted bond **A** reveals a tricyclic lactam (6) and the appropriate monosubstituted piperazine (7) from which the target compounds could be furnished. Alternatively, by disconnection at bond **B**, we discover desmethylclozapine (8) and a substituted benzaldehyde (9) from which, under reductive amination conditions, compounds of interest could be synthesized.

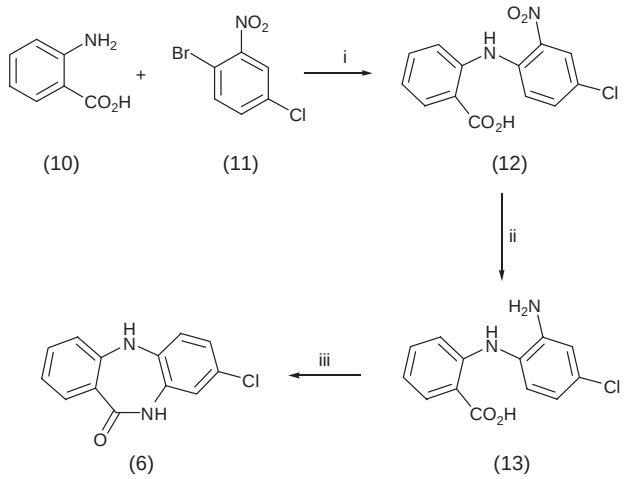
Scheme 2 depicts the synthesis of the known tricyclic lactam (6) using previously described literature procedures.[38,39] Coupling of anthranilic acid (10) and commercially available 2-bromo-5-chloronitrobenzene (11) under Ullmann conditions produced the nitro acid (12). Subsequent reduction using sodium dithionite afforded the amino compound (13). Thermal cyclization using Dean–Stark conditions furnished the key intermediate lactam (6) in respectable yield.

The monosubstituted piperazines (7a–r) were prepared by the direct alkylation of piperazine with a series of substituted benzyl halides (14a–r) (Scheme 3). All compounds were generated in reasonable to good yield. Of the monosubstituted piperazines, compounds (7c), (7f), (7p), and (7r) are novel.



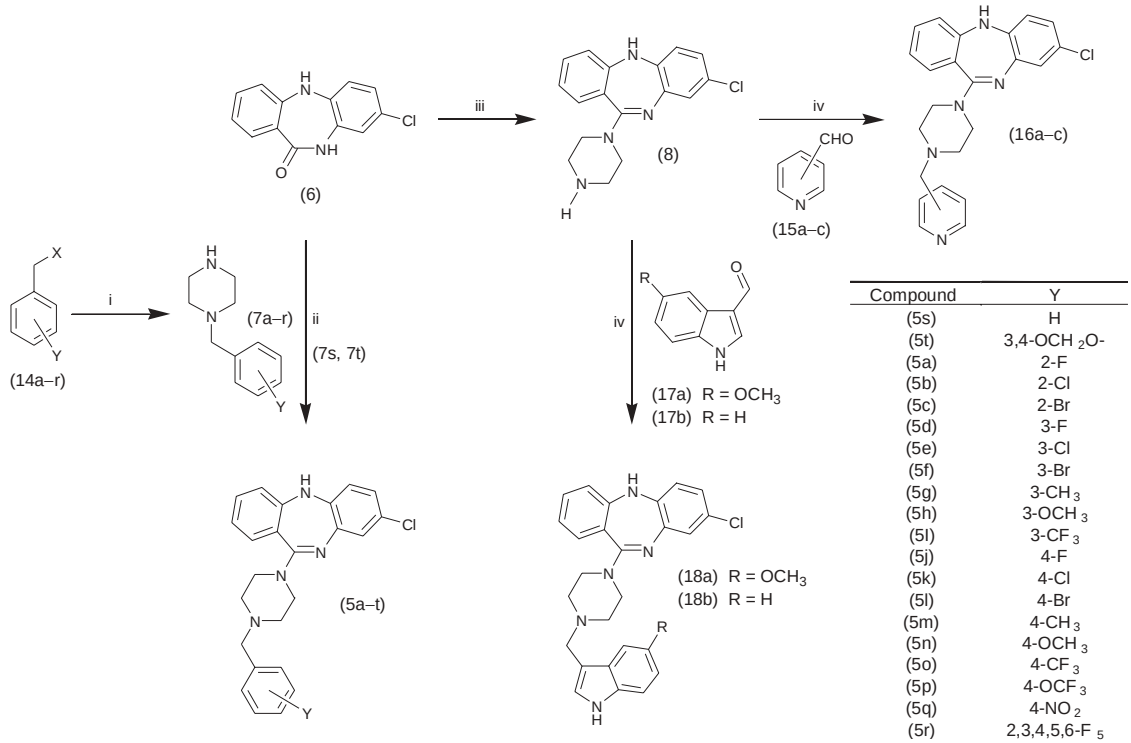
Scheme 1. Retrosynthetic analysis of clozapine analogues.

These monosubstituted piperazines (7a–r), in addition to the commercially available reagents 1-benzylpiperazine (7s) and 1-piperonylpiperazine (7t), were coupled to the tricyclic lactam (6) in the presence of the Lewis acid, titanium tetrachloride. This method afforded a series of substituted benzyl analogues of clozapine (5a–t) as shown in Scheme 3. All yields were essentially above 50% with the exception of the 4-nitrobenzyl analogue (5q), the low yield of 21% being attributed to the poor solubility of 1-(4-nitrobenzyl)piperazine in anisole.



Scheme 2. Reagents and conditions: (i) Cu powder, K_2CO_3, 3-methyl-1-butanol, reflux; (ii) $Na_2S_2O_4$, 2M aqueous NH_3, 80°C; (iii) xylenes, reflux.

The commercial availability of synthetically useful aldehydes prompted investigations on the synthesis of clozapine analogues using desmethylclozapine (8) under



Compound	Y
(5s)	H
(5t)	3,4-OCH_2O-
(5a)	2-F
(5b)	2-Cl
(5c)	2-Br
(5d)	3-F
(5e)	3-Cl
(5f)	3-Br
(5g)	3-CH_3
(5h)	3-OCH_3
(5i)	3-CF_3
(5j)	4-F
(5k)	4-Cl
(5l)	4-Br
(5m)	4-CH_3
(5n)	4-OCH_3
(5o)	4-CF_3
(5p)	4-OCF_3
(5q)	4-NO_2
(5r)	2,3,4,5,6-F_5

Scheme 3. Reagents and conditions: (i) piperazine, toluene, 85°C; (ii) $TiCl_4$, anisole, 25 to 55°C, reflux; (iii) piperazine, $TiCl_4$, 1,4-dioxan, 25 to 55°C, reflux; (iv) $NaBH(OAc)_3$, 1,2-dichloroethane.

reductive amination conditions. The synthesis of desmethylclozapine (8) (Scheme 3), entailed reaction of (6) with piperazine in the presence of titanium tetrachloride. The product was isolated after flash chromatography as a bright yellow foam in 69% yield.

The syntheses of pyridinylmethyl (16a–c) and 3-indolylmethyl (18a–b) analogues of clozapine are outlined in Scheme 3. Treatment of (8) with the appropriate pyridine-carboxaldehydes (15a–c) and indole-3-carboxaldehydes (17a–b) in the presence of sodium triacetoxyborohydride afforded the target compounds. The pyridine and indole moieties were selected to examine the effect on activity of the nature of the aryl group.

Compounds (5t) and (18a) were further treated with boron tribromide affording the corresponding catechol (19) and indolol (20) analogues of clozapine (Fig. 2), respectively. These compounds were of interest due to their structural similarities to the neurotransmitters, dopamine and serotonin.

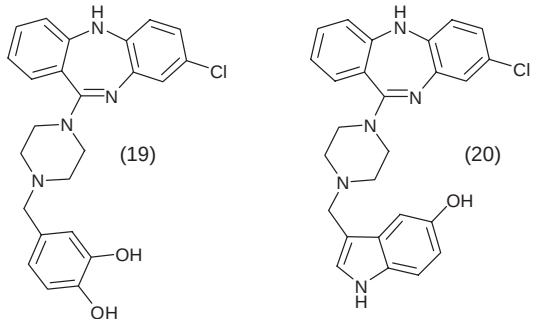


Fig. 2. The chemical structures of the catechol (19) and indolol (20) analogues.

In Vitro Studies

Compounds were evaluated in vitro in a series of preliminary receptor binding screens, assayed at a final concentration of 1 μM. Their affinities for cloned human dopamine $D_{4.4}$ receptors,[40] rat cortical serotonin 5-HT_{2A} receptors[41–43] (both of which represent the primary receptors of interest) and rat striatal dopamine D_2 receptors[40] were assessed by measuring the displacement of the designated radioligand in terms of percentage inhibition (% I). The results are displayed in Table 2 along with the reference compound clozapine. The *N*-piperonyl analogue (5t) (Y = 3,4–OCH_2O–) demonstrated the most promising affinity for the $D_{4.4}$ and 5-HT_{2A} receptors, showing 84 and 90% I, respectively. These values compare well with clozapine's values of 93 and 94% I at $D_{4.4}$ and 5-HT_{2A} receptors, respectively. Compound (5t) also displayed D_2 affinity comparable to that of clozapine. The *N*-benzyl analogue (5s) (Y = H) displayed respectable receptor affinity for $D_{4.4}$ (78% I) and 5-HT_{2A} (90% I) receptors. The electron-deficient aryl systems (5q) (Y = 4-NO_2) and (5r) (Y = 2,3,4,5,6-F_5) exhibited reduced affinity for both primary receptor types compared with (5s) and (5t), which contained an electron-rich aryl moiety. Thus, introduction of the electron-withdrawing nitro group at the *para* position of the benzene ring (5q) lead to diminished affinity (41% I) for the $D_{4.4}$ receptor but with reasonable retention of serotonergic affinity (73% I) compared with (5s). The pentafluorobenzyl analogue of clozapine (5r), exhibited a similar profile to that of (5q).

Amongst the halo-substituted analogues (5a–f, 5j–l), placement of fluorine at the *para* position of the introduced benzene ring (5j) (Y = 4-F) resulted in greatest affinity for the $D_{4.4}$ receptor (86% I). Within this series, the 4-chlorobenzyl analogue (5k) (Y = 4-Cl) showed greatest affinity for the 5-HT_{2A} receptor (89% I). These values were comparable to those obtained for the *N*-benzyl analogue (5s). The 2-bromobenzyl compound (5c) (Y = 2-Br) exhibited intermediate affinity for both receptors whereas substitution by bromine at the 3-position (5f) (Y = 3-Br) displayed minimal affinity for the receptors of interest compared with (5s) (Y = H) and clozapine. The 2-halosubstituted clozapine analogues showed greatest affinity for the D_2 receptor, comparable to (5s) and clozapine. The 3-halosubstituted compounds showed a generally lower affinity for D_2 receptors with the 3-bromo compound (5f) (Y = 3-Br) exhibiting 30% I compared with clozapine, 76% I.

Replacement of hydrogen with methoxy at the *para* position, (5n) (Y = 4-OCH_3), produced favourable $D_{4.4}$

Table 2. Preliminary binding studies[A]

Compound	Percentage inhibition (% I) at 1 μM		
	$D_{4.4}$ [^{3}H]spiperone	5-HT_{2A} [^{3}H]ketanserin	D_2 [^{3}H]spiperone
clozapine	93 ± 3	94 ± 1	76 ± 3
(5s)	78 ± 6	90 ± 8	81 ± 2
(5t)	84 ± 7	90 ± 4	66 ± 14
(5a)	64 ± 4	80 ± 6	82 ± 4
(5b)	69 ± 5	86 ± 12	92 ± 3
(5c)	75 ± 1	86 ± 5	78 ± 6
(5d)	72 ± 3	80 ±6	64 ± 28
(5e)	60 ± 2	83 ± 14	48 ± 19
(5f)	55 ± 2	76 ± 9	30 ± 20
(5g)	63 ± 6	83 ± 16	40 ± 7
(5h)	50 ± 8	87 ± 5	67 ± 9
(5i)	25 ± 11	81 ± 7	38 ±5
(5j)	86 ± 3	85 ± 7	75 ± 4
(5k)	72 ± 14	89 ± 2	75 ± 3
(5l)	70 ± 3	79 ± 12	50 ± 3
(5m)	70 ± 1	80 ± 10	82 ± 9
(5n)	84 ± 8	74 ± 18	79 ± 4
(5o)	21 ± 1	62 ± 3	87 ± 8
(5p)	34 ± 4	81 ± 15	37 ± 15
(5q)	41 ± 7	73 ± 5	63 ± 21
(5r)	34 ± 6	73 ± 5	53 ± 24
(16a)	57 ± 22	75 ± 13	65 ± 1
(16b)	44 ± 2	69 ± 5	54 ± 6
(16c)	58 ± 4	80 ± 7	45 ± 9
(18a)	69 ± 7	63 ± 8	27 ± 19
(18b)	51 ± 3	72 ± 6	20 ± 10
(19)	49 ± 5	70 ± 7	62 ± 5
(20)	54 ± 4	81 ± 7	40 ± 9

[A] All compounds were tested as their hydrochloride salts. Clozapine was assayed in triplicate (mean ± SEM) and test compounds were assayed in duplicate.

affinity (84% I) whilst the 3-methoxybenzyl analogue (5h) (Y = 3-OCH_3) displayed very good affinity (87% I) for 5-HT_{2A} receptors. These values compared favourably to those observed for (5s). Placing a 4-trifluoromethoxy substituent on the introduced benzene ring (5p) (Y = 4-OCF_3) produced moderate affinity for 5-HT_{2A} receptors (81% I) but the compound displayed reduced $D_{4.4}$ receptor affinity (34% I). Interestingly, placing the inductively electron-withdrawing trifluoromethyl substituent at either the *meta* or *para* position of the benzene ring [(5i) (Y = 3-CF_3) and (5o) (Y = 4-CF_3), respectively] showed a dramatic reduction in $D_{4.4}$ receptor affinity (25 and 21% I, respectively) compared with (5s) and clozapine (78 and 93% I, respectively). Introduction of the weakly ring-activating methyl group at either the *meta* or *para* position of the benzyl moiety as in (5g) (Y = 3-CH_3) and (5m) (Y = 4-CH_3), respectively, produced moderate affinity for both primary receptors assayed compared with (5s). All compounds of the methoxy and methyl substituted series displayed moderate affinity for 5-HT_{2A} receptors and mixed $D_{4.4}$ receptor affinity relative to (5s), but diminished overall receptor affinity compared with clozapine.

The pyridinylmethyl analogues of clozapine (16a–c) were assayed to examine the effects of incorporating a pyridine moiety in place of the previously described benzene ring system. Isosteric replacement of carbon with nitrogen yielded analogues with electron-deficient aryl groups, that displayed comparable affinity for 5-HT_{2A} receptors yet reduced affinity for $D_{4.4}$ receptors when compared with the carbocyclic system of (5s) (Y = H). Overall, compounds (16a–c) exhibited diminished affinity compared with clozapine for D_4 and 5-HT_{2A} receptors. The indolylmethyl (18a–b) analogues, with their larger and more electron-rich aryl systems, displayed moderate affinity for the 5-HT_{2A} and $D_{4.4}$ receptors, compared with (5s), but diminished affinities relative to clozapine.

The catecholmethyl analogue (19) displayed good affinity for the 5-HT_{2A} receptor (70% I) but this result was only moderate when compared with (5s) (90% I) and clozapine (94% I). The indolol analogue (20) showed promising 5-HT_{2A} receptor affinity (81% I) but significantly reduced $D_{4.4}$ receptor affinity (54% I) compared with clozapine. Both compounds exhibited reduced affinity for the D_2 receptor compared with (5s) and clozapine. The moieties attached to the distal nitrogen atom in (19) and (20) are structurally similar to the neurotransmitters dopamine and serotonin, and may thus have intrinsic drug-receptor interactions involved in potential antagonist activity.

Conclusions

A series of 4′-arylmethyl analogues of clozapine was synthesized and assessed in a variety of preliminary receptor binding screens to ascertain their affinities for the D_4, 5-HT_{2A}, and D_2 receptors. Although exhibiting moderate affinity, particularly with compounds (5s) and 5(t), it is evident that the introduction of an *N*-arylmethyl group into the structure of clozapine appears not to have a significant effect on binding at the receptors studied in these preliminary experiments. However, these findings may be of some interest to medicinal chemists dealing with clozapine related chemistry, since on these data alone, it excludes the introduction of an arylmethyl group in the development of clozapine analogues. To further probe the effect of substituents attached to the distal nitrogen on activity at receptors of interest, it is planned to modify the length and nature of the chain between the ionizable nitrogen atom and the introduced aryl moiety.

Experimental

Chemistry

Melting points were determined on a Reichert Micro-melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 270-30 Infra-Red spectrophotometer as KBr discs unless indicated otherwise. Ultraviolet–visible spectra were recorded as ethanolic solutions on a Pharmacia Biotech Ultraspec 2000 UV-VIS spectrophotometer utilizing Swift II software. Wavelengths of maximum absorbance and points of inflexions (denoted by *inf*) are quoted with accompanying molar absorptivity data ($\log_{10}\varepsilon$). ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75.4 MHz, respectively, using a Bruker Avance DPX 300 spectrometer equipped with a Silicon Graphics workstation. Chemical shifts for all ^1H spectra are reported in parts per million (ppm), using tetramethylsilane (TMS) as the internal reference. Proton assignments were based upon coupling constants and two-dimensional homonuclear ($^1H/^1H$) correlation spectroscopy. Chemical shifts for all ^{13}C spectra are reported in parts per million (ppm), using the solvent chemical shift as the reference.[44] Fast atom bombardment (FAB) mass spectra were determined using a JEOL JMS-DX300 Mass Spectrometer. The thioglycerol/glycerol matrix was used for samples analysed by FAB. Electrospray ionization (ESI) mass spectra were determined in positive ion mode using a Micromass Platform II Mass Spectrometer. High-resolution mass spectra were determined using a Bruker BioApex II FTICR Mass Spectrometer. In reporting spectroscopic data, the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; br, broad; app, apparent. Analytical reverse-phase HPLC was performed on a Waters HPLC system fitted with a Nova-Pak HR C_{18} column (6 μm, 60 Å, 8 mm × 100 mm) using a binary solvent system; solvent A: 0.1% TFA/H_2O; solvent B: 0.1% TFA/90% CH_3CN/H_2O. Analyses were conducted using isocratic (60% A/40% B, flow rate 1.5 mL/min, UV detection at 264 nm) and gradient (100% A to 100% B over 30 minutes, flow rate 1.5 mL/min, UV detection at 264 nm) elution modes. Thin-layer chromatography (TLC) was carried out on silica gel 60 F_{254} pre-coated plates (0.25 mm, Merck, ART. 5554). Preparative TLC was performed on glass plates (20 cm × 20 cm × 2 mm, Merck, ART 5717). Flash column chromatography[45] was carried out routinely using Merck Silica gel 60, 230–400 mesh ASTM. Elemental analyses were carried out on samples dried under vacuum over phosphorus pentoxide at 30°C for 24 h, by Chemical & Micro Analytical Services Pty Ltd, Melbourne, or Microanalytical Service, Chemistry Department, University of Queensland, Brisbane, Queensland. All solvents used were redistilled prior to use. Tetrahydrofuran was distilled from sodium metal/benzophenone ketyl under nitrogen immediately prior to use. Dry dichloromethane and 1,2-dichloroethane were obtained by distillation from phosphorus pentoxide followed by storage over Type 3A molecular sieves. Dry ethanol and methanol were distilled from their respective magnesium alkanolates and stored over Type 4A and Type 3A molecular sieves, respectively.

2-(4-Chloro-2-nitroanilino)benzoic acid (12)

A mixture of anthranilic acid (10) (13.8 g, 101 mmol), 2-bromo-5-chloronitrobenzene (11) (25.0 g, 106 mmol), anhydrous potassium carbonate (13.9 g, 101 mmol), 3-methylbutan-1-ol (200 mL) and copper powder (500 mg) was heated under reflux for 4 h. The steam volatile components were removed by steam distillation and

acidification of the aqueous residue with aqueous hydrochloric acid (2 M) gave a precipitate that was collected by filtration. Recrystallization from aqueous ethanol gave (12) as red/brown needles (21.8 g, 74%), m.p. 246–248°C (lit.[39] 245–248°C). ν_{max} 3480, 1678, 1612 cm^{-1}. ^1H NMR [(D_6)acetone] δ 7.14, ddd, *J* 8, 6, 2 Hz, 1H, H5; 7.52–7.63, m, 3H, H3, H4, H5′; 7.74, d, *J* 9 Hz, 1H, H6′; 8.11, dd, *J* 8, 1 Hz, 1H, H6; 8.15, d, *J* 3 Hz, 1H, H3′; 11.11, s, 1H, NH. ^{13}C NMR [(D_6)DMSO] δ 118.8, 118.9, 120.8, 122.1, 123.3, 125.3, 131.8, 133.5, 135.1, 137.0, 137.3, 141.5, 168.6. FAB mass spectrum *m/z* 293.1.

2-(2-Amino-4-chloroanilino)benzoic acid (13)

A mixture of 2-(4-chloro-2-nitroanilino)benzoic acid (12) (1.00 g, 3.42 mmol) and aqueous ammonia (2 M, 25 mL) was warmed to 80°C. Sodium dithionite (3.57 g, 20.5 mmol) was then added portion-wise to the red/crimson solution and a colour change to pale yellow was observed. Decolourising charcoal was added and the mixture filtered whilst hot. The filtrate was adjusted to pH 4.5 with glacial acetic acid and the product collected by filtration. Recrystallization from methanol/water afforded (13) as pale yellow needles (0.575 g, 64%), m.p. 198–200°C (lit.[39] 200–203°C). ν_{max} 3484, 3384, 3356, 3300, 1668, 1622, 1600 cm^{-1}. ^1H NMR [(D_6)DMSO] δ 5.22, br s, 2H, NH_2; 6.54–6.63, m, 2H, H3, H5′; 6.69, ddd, *J* 8, 7, 1 Hz, 1H, H5; 6.84, d, *J* 2 Hz, 1H, H3′; 7.03, d, *J* 8 Hz, 1H, H6′; 7.30, ddd, *J* 9, 7, 2 Hz, 1H, H4; 7.87, dd, *J* 8, 2 Hz, 1H, H6; 8.98, s, 1H, NH; 12.91, br s, 1H, CO_2H. ^{13}C NMR [(D_6)DMSO] δ 111.7, 113.3, 114.3, 115.8, 116.2, 123.8, 127.6, 130.2, 131.6, 134.1, 145.9, 148.9, 170.0. FAB mass spectrum *m/z* 261.9.

*8-Chloro-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-one (6)*

A mixture of 2-(2-amino-4-chloroanilino)benzoic acid (13) (10.0 g, 38.1 mmol) and xylenes (250 mL) was heated under Dean–Stark conditions for 96 h. The reaction mixture was then cooled, evaporated to dryness under vacuum and the resulting residue washed with hot aqueous ammonia (2 M, 2 × 50 mL). The product was recrystallized from acetone/water to give (6) as pale yellow platelets (7.40 g, 79%), m.p. 232–233°C (lit.[39] 231–232°C). ν_{max} 3476, 3384, 1664, 1612 cm^{-1}. ^1H NMR [(D_6)acetone] δ 6.95, ddd, *J* 8, 7, 1 Hz, 1H, H2; 6.98, dd, *J* 8, 2 Hz, 1H, H7; 7.02, dd, *J* 8, 1 Hz, 1H, H4; 7.06, d, *J* 8 Hz, 1H, H6; 7.15, d, *J* 2 Hz, 1H, H9; 7.29, s, 1H, H5; 7.36, ddd, *J* 8, 7, 2 Hz, 1H, H3; 7.84, dd, *J* 8, 2 Hz, 1H, H1; 9.01, s, 1H, H10. ^{13}C NMR [(D_6)acetone] δ 120.1, 121.7, 122.1, 122.3, 123.7, 125.2, 128.4, 132.5, 133.5, 134.5, 139.7, 150.8, 168.7. FAB mass spectrum *m/z* 245.0.

General Procedure for the Preparation of Monosubstituted Piperazines

To a solution of a substituted benzyl bromide [(14c), (14f), (14l), (14o–p), or (14r)] or substituted benzyl chloride [(14a–b), (14d–e), (14g–k), (14m–n), or (14q)] (10.0 g) in toluene (250 mL) was added piperazine (4 equivalents). The solution was heated at 85°C for 2 h after which it was cooled, filtered and the filtrate evaporated to dryness under vacuum. The resulting residue was then partitioned between aqueous hydrochloric acid (2 M, 50 mL) and dichloromethane (50 mL) and the aqueous phase washed with dichloromethane (2 × 50 mL). The aqueous phase was adjusted to pH 14 with solid sodium hydroxide, the resulting oil removed and the aqueous phase extracted with dichloromethane (2 × 100 mL). The oil and organic fractions were combined, washed with water (2 × 50 mL), brine (50 mL), dried over anhydrous sodium sulfate, filtered and then concentrated under vacuum to yield an oil. Vacuum distillation afforded the title compound as a colorless liquid, unless otherwise indicated.

The following monosubstituted (7a–r) piperazines were prepared in this manner.

1-(2-Fluorobenzyl)piperazine (7a).[46] (10.7 g, 80%), b.p. 93–96°C (0.2 mmHg). ^1H NMR ($CDCl_3$) δ 1.41, s, 1H, H4; 2.43, m, 4H, H2, H6; 2.86, m, 4H, H3, H5; 3.56, d, *J* 1 Hz, 2H, H1′; 7.00, ddd, *J* 10, 8, 1 Hz, 1H, H3′′; 7.08, app td, *J* 7.5, 1 Hz, 1H, H5′′; 7.20, m, 1H, H4′′; 7.37, app td, *J* 7.5, 2 Hz, 1H, H6′′. ^{13}C NMR ($CDCl_3$) δ 46.1, 54.3, 55.8 (d, *J* 2 Hz, CH_2), 115.1 (d, *J* 22 Hz, CH), 123.7 (d, *J* 4 Hz, CH), 124.6 (d, *J* 15 Hz, C), 128.6 (d, *J* 8 Hz, CH), 131.5 (d, *J* 5 Hz, CH), 161.4 (d, *J* 246 Hz, CF). ESI mass spectrum *m/z* 195.3.

1-(2-Chlorobenzyl)piperazine (7b). (8.39 g, 64%), b.p. 108–110°C (0.9 mmHg), [lit.[47] 92–98°C (0.13 mmHg)]. ^1H NMR ($CDCl_3$) δ 1.43, s, 1H, H4; 2.46, m, 4H, H2, H6; 2.87, m, 4H, H3, H5; 3.58, s, 2H, H1′; 7.14, app td, *J* 7.5, 2 Hz, 1H, H4′′; 7.21, app td, *J* 7.5, 1.5 Hz, 1H, H5′′; 7.32, dd, *J* 7.5, 1.5 Hz, 1H, H3′′; 7.47, dd, *J* 7.5, 2 Hz, 1H, H6′′. ^{13}C NMR ($CDCl_3$) δ 46.2, 54.6, 59.8, 126.5, 128.0, 129.3, 130.6, 134.3, 135.9. ESI mass spectrum *m/z* 211.2.

1-(2-Bromobenzyl)piperazine (7c). (7.68 g, 75%), b.p. 108–112°C (0.4 mmHg). ^1H NMR ($CDCl_3$) δ 1.40, s, 1H, H4; 2.43, m, 4H, H2, H6; 2.84, m, 4H, H3, H5; 3.53, s, 2H, H1′; 7.04, app td, *J* 7.5, 2 Hz, 1H, H4′′; 7.22, app td, *J* 7.5, 1 Hz, 1H, H5′′; 7.45, dd, *J* 7.5, 2 Hz, 1H, H6′′; 7.49, dd, *J* 8, 1.5 Hz, 1H, H3′′. ^{13}C NMR ($CDCl_3$) δ 45.9, 54.3, 62.0, 124.3, 126.8, 127.9, 130.3, 132.3, 137.3. ESI mass spectrum *m/z* 255.2.

1-(3-Fluorobenzyl)piperazine (7d).[48] (9.96 g, 74%), b.p. 110–115°C (0.25 mmHg). ^1H NMR ($CDCl_3$) δ 1.71, s, 1H, H4; 2.40, m, 4H, H2, H6; 2.88, m, 4H, H3, H5; 3.47, s, 2H, H1′; 6.92, m, 1H, H6′′; 7.03–7.14, m, 2H, H2′′, H4′′; 7.25, m, 1H, H5′′. ^{13}C NMR ($CDCl_3$) δ 46.1, 54.5, 63.1, 113.9 (d, *J* 21 Hz, CH), 115.7 (d, *J* 21 Hz, CH), 124.6, 129.6 (d, *J* 8 Hz, CH), 141.2 (d, *J* 8 Hz, C), 163.0 (d, *J* 246 Hz, CF). ESI mass spectrum *m/z* 195.2.

1-(3-Chlorobenzyl)piperazine (7e). (9.58 g, 73%), b.p. 115–120°C (0.05 mmHg), [lit.[49,50] 120–123ºC (1.5 mmHg) and 123–127°C (2 mmHg), respectively]. ^1H NMR ($CDCl_3$) δ 1.54, s, 1H, H4; 2.37, m, 4H, H2, H6; 2.85, m, 4H, H3, H5; 3.42, s, 2H, H1′; 7.16–7.22, m, 3H, H4′′, H5′′, H6′′; 7.32, m, 1H, H2′′. ^{13}C NMR [(D_4)methanol] δ 46.4, 54.9, 63.9, 128.5, 128.9, 130.4, 130.9, 135.3, 141.4. ESI mass spectrum *m/z* 211.1.

1-(3-Bromobenzyl)piperazine (7f). (8.07 g, 79%), b.p. 110–115°C (0.04 mmHg). ^1H NMR ($CDCl_3$) δ 1.53, s, 1H, H4; 2.38, m, 4H, H2, H6; 2.86, m, 4H, H3, H5; 3.42, s, 2H, H1′; 7.15, app t, *J* 7.5 Hz, 1H, H5′′; 7.23, app br d, *J* 7.5 Hz, 1H, H6′′; 7.35, app br td, *J* 7.5, 1.5 Hz, 1H, H4′′; 7.48, m, 1H, H2′′. ^{13}C NMR ($CDCl_3$) δ 46.0, 54.4, 62.9, 122.4, 127.6, 129.7, 123.0, 131.9, 140.8. ESI mass spectrum *m/z* 255.2.

1-(3-Methylbenzyl)piperazine (7g). (4.05 g, 30%), b.p. 108–110°C (0.2 mmHg), [lit.[51] 100–105°C (0.2 mmHg)]. ^1H NMR ($CDCl_3$) δ 1.98, s, 1H, H4; 2.34, s, 3H, CH_3; 2.41, m, 4H, H2, H6; 2.88, m, 4H, H3, H5; 3.45, s, 2H, H1′; 7.02–7.15, m, 3H, H2′′, H4′′, H6′′; 7.19, app t, *J* 7.5 Hz, 1H, H5′′. ^{13}C NMR ($CDCl_3$) δ 21.4, 46.0, 54.5, 63.8, 126.4, 127.8, 128.1, 130.0, 137.8, 138.0. ESI mass spectrum *m/z* 191.2.

1-(3-Methoxybenzyl)piperazine (7h). (10.6 g, 80%), b.p. 125–130°C (0.5 mmHg), [lit.[52] 107°C (0.4 mmHg)]. ^1H NMR ($CDCl_3$) δ 1.56, s, 1H, H4; 2.39, m, 4H, H2, H6; 2.86, m, 4H, H3, H5; 3.44, s, 2H, H1′; 3.78, s, 3H, OCH_3; 6.77, dd, *J* 8, 2 Hz, 1H, H4′′; 6.88, m, 2H, H2′′, H6′′; 7.20, app t, *J* 8 Hz, 1H, H5′′. ^{13}C NMR ($CDCl_3$) δ 45.8, 54.3, 54.8, 63.3, 112.1, 114.3, 121.2, 128.8, 139.6, 159.3. ESI mass spectrum *m/z* 207.3.

1-(3-Trifluoromethylbenzyl)piperazine (7i).[48,53] (9.41 g, 75%), b.p. 100–104°C (0.09 mmHg). ^1H NMR ($CDCl_3$) δ 1.59, s, 1H, H4; 2.41, m, 4H, H2, H6; 2.88, m, 4H, H3, H5; 3.52, s, 2H, H1′; 7.41, app t, *J* 7.5 Hz, 1H, H5′′; 7.47–7.55, m, 2H, H4′′, H6′′; 7.60, app br s, 1H, H2′′. ^{13}C NMR ($CDCl_3$) δ 45.9, 54.3, 62.9, 123.8 (q, *J* 3.8 Hz, CH), 124.1 (q, *J* 272 Hz, CF), 125.6 (q, *J* 4 Hz, CH), 128.4, 130.4 (q, *J* 32 Hz, C), 132.2, 139.3. ESI mass spectrum *m/z* 245.2.

1-(4-Fluorobenzyl)piperazine (7j). (5.90 g, 44%), b.p. 80–84°C (0.2 mmHg), [lit.[54] 108°C (2.3 mmHg)], crystallized on standing. ^1H NMR ($CDCl_3$) δ 2.03, s, 1H, H4; 2.38, m, 4H, H2, H6; 2.86, m, 4H, H3, H5; 3.43, s, 2H, H1′; 6.98, app t, *J* 8.5 Hz, 2H, H3′′, H5′′; 7.27, dd, *J* 8.5, 5.5 Hz, 2H, H2′′, H6′′. ^{13}C NMR ($CDCl_3$) δ 46.1, 54.4, 62.9, 114.9 (d, *J* 22 Hz, CH), 130.7 (d, *J* 8 Hz, CH), 133.9, 162.0 (d, *J* 245 Hz, CF). ESI mass spectrum *m/z* 195.2.

1-(4-Chlorobenzyl)piperazine (7k). (3.85 g, 38%), b.p. 114–116°C (0.2 mmHg), [lit.[49,51] 132–135°C (2 mmHg), and 132–134°C (1.4 mmHg), respectively]. ^1H NMR ($CDCl_3$) δ 1.62, s, 1H, H4; 2.37, m, 4H, H2, H6; 2.85, m, 4H, H3, H5; 3.42, s, 2H, H1′; 7.25, app br s, 4H, H2′′, H3′′, H5′′, H6′′. ^{13}C NMR ($CDCl_3$) δ 46.0, 54.4, 62.8, 120.7, 130.8, 131.2, 137.3. ESI mass spectrum *m/z* 211.2.

1-(4-Bromobenzyl)piperazine (7l). (3.85 g, 38%), b.p. 122–124°C (0.4 mmHg), [lit.[47] 112–116°C (0.25 mmHg)]. ^1H NMR ($CDCl_3$) δ

1.90, s, 1H, H4; 2.37, m, 4H, H2, H6; 2.85, m, 4H, H3, H5; 3.62, s, 2H, H1′; 7.19, d, *J* 8 Hz, 2H, H2′′, H6′′; 7.41, d, *J* 8 Hz, 2H, H3′′, H5′′. ^{13}C NMR ($CDCl_3$) δ 46.0, 54.4, 62.8, 120.7, 130.7, 131.2, 137.3. ESI mass spectrum *m/z* 255.2.

1-(4-Methylbenzyl)piperazine (7m). (4.82 g, 36%), b.p. 97–98°C (0.3 mmHg), [lit.[49] 118–120°C (2 mmHg)], crystallized on standing. ^{1}H NMR ($CDCl_3$) δ 1.55, s, 1H, H4; 2.30, s, 3H, CH_3; 2.36, m, 4H, H2, H6; 2.88, m, 4H, H3, H5; 3.41, s, 2H, H1′; 7.10, d, *J* 7.5 Hz, 2H, H3′′, H5′′; 7.20, d, *J* 7.5 Hz, 2H, H2′′, H6′′. ^{13}C NMR ($CDCl_3$) δ 21.2, 45.8, 54.3, 63.5, 126.2, 127.6, 127.9, 129.8, 137.6, 137.8. ESI mass spectrum *m/z* 191.2.

1-(4-Methoxybenzyl)piperazine (7n). (4.90 g, 37%), b.p. 122–124°C (0.7 mmHg), [lit.[47,49] 134–138°C (2 mmHg), and 147–148°C (3 mmHg), respectively], crystallized on standing. ^{1}H NMR ($CDCl_3$) δ 1.50, s, 1H, H4; 2.37, m, 4H, H2, H6; 2.86, m, 4H, H3, H5; 3.41, s, 2H, H1′; 3.77, s, 3H, OCH_3; 6.84, d, *J* 8.5 Hz, 2H, H3′′, H5′′; 7.22, d, *J* 8.5 Hz, 2H, H2′′, H6′′. ^{13}C NMR ($CDCl_3$) δ 46.1, 54.4, 55.1, 63.0, 113.5, 130.1, 130.3, 158.7. ESI mass spectrum *m/z* 207.3.

1-(4-Trifluoromethylbenzyl)piperazine (7o).[55] (8.14 g, 80%), b.p. 98–100°C (0.05 mmHg). ^{1}H NMR ($CDCl_3$) δ 1.62, s, 1H, H4; 2.41, m, 4H, H2, H6; 2.88, m, 4H, H3, H5; 3.52, s, 2H, H1′; 7.45, d, *J* 8 Hz, 2H, H2′′, H6′′; 7.56, d, *J* 8 Hz, 2H, H3′′, H5′′. ^{13}C NMR ($CDCl_3$) δ 46.1, 54.5, 63.0, 124.3 (q, *J* 272 Hz, CF), 125.1 (app t, *J* 5 Hz, CH), 129.2, 129.3 (q, *J* 33 Hz, C), 142.7. ESI mass spectrum *m/z* 245.2.

1-(4-Trifluoromethoxybenzyl)piperazine (7p). (7.94 g, 78%), b.p. 100–105°C (0.05 mmHg). ^{1}H NMR ($CDCl_3$) δ 1.77, s, 1H, H4; 2.40, m, 4H, H2, H6; 2.88, m, 4H, H3, H5; 3.48, s, 2H, H1′; 7.15, d, *J* 8 Hz, 2H, H3′′, H5′′; 7.34, d, *J* 8 Hz, 2H, H2′′, H6′′. ^{13}C NMR ($CDCl_3$) δ 46.1, 54.5, 63.8, 120.6 (q, *J* 257 Hz, CF), 120.7, 130.3, 137.1, 148.3. ESI mass spectrum *m/z* 261.2.

1-(4-Nitrobenzyl)piperazine (7q).[46] The product was obtained as pale yellow platelets, recrystallized from dichloromethane/hexane (7.88 g, 61%), m.p. 250–255°C (dec.). ^{1}H NMR ($CDCl_3$) δ 2.31, s, 1H, H4; 2.44, m, 4H, H2, H6; 2.92, m, 4H, H3, H5; 3.58, s, 2H, H1′; 7.51, d, *J* 9 Hz, 2H, H2′′, H6′′; 8.17, d, *J* 9 Hz, 2H, H3′′, H5′′. ^{13}C NMR [(D_6)DMSO] δ 45.3, 53.8, 61.7, 123.1, 129.5, 146.4, 146.7. ESI mass spectrum *m/z* 222.3.

1-(2,3,4,5,6-Pentafluorobenzyl)piperazine (7r). (6.05 g, 59%), b.p. 75–80°C (0.35 mmHg), crystallized on standing, m.p. 135°C (softens), 216–217°C (melts). ^{1}H NMR ($CDCl_3$) δ 1.91, s, 1H, H4; 2.47, m, 4H, H2, H6; 2.88, m, 4H, H3, H5; 3.72, s, 2H, H1′. ^{13}C NMR ($CDCl_3$) δ 45.9, 49.1, 53.2, 110.3 (t, *J* 20 Hz, C), 137.2 (m, 2 × CF), 140.4 (m, CF), 145.6 (m, 2 × CF). ESI mass spectrum *m/z* 267.2.

General Procedure for the Preparation of 4′-Substituted Benzyl Analogues of Clozapine

To a solution of the monosubstituted piperazine (7a–t) (4.09 mmol, 5 equivalents) in anhydrous anisole (5 mL) under nitrogen was added a solution of titanium tetrachloride in toluene (1.0 M, 0.90 mL, 0.900 mmol, 1.1 equivalents). 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 (6) (200 mg, 0.817 mmol) in anhydrous anisole (10 mL) was then added. The mixture was heated at reflux for 4 h after which time it was cooled and then evaporated to dryness under vacuum. The brown coloured residue was partitioned between ethyl acetate (50 mL) and aqueous sodium hydroxide (2 M, 30 mL), the mixture was filtered under vacuum and the residue was washed with ethyl acetate (20 mL). The organic layer was separated and the aqueous phase was 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. The major product was evaporated to dryness, and where appropriate, the residual solid recrystallized from a suitable solvent system.

The following compounds (5a–t) were prepared in this manner.

*8-Chloro-11-(4-benzylpiperazino)-5*H*-dibenzo[*b,e*][1,4]diazepine (5s)*. Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from ethyl acetate/hexane as bright yellow microneedles (77%), m.p. 200–201°C (Found: C, 71.4; H, 5.6; N, 13.8%. $C_{24}H_{23}ClN_4$ requires C, 71.5; H, 5.8; N, 13.9%). ν_{max} 3300, 1604, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 229 (4.43), 260 (4.25), 296 (4.05) nm. ^{1}H NMR [(D6)acetone] δ 2.51, m, 4H, H3′, H5′; 3.42, m, 4H, H2′, H6′; 3.54, s, 2H, H1′′; 6.49, s, 1H, H5; 6.80, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.87, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.00, app td, *J* 7.5, 1 Hz, 1H, H2; 7.06, dd, *J* 7, 1 Hz, 1H, H4; 7.20–7.38, m, 7H, H1, H3, H2′′′, H3′′′, H4′′′, H5′′′, H6′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.8, 63.6, 121.2, 121.4, 123.4, 123.5, 124.7, 127.1, 127.9, 128.6, 129.1, 129.9, 131.8, 132.8, 139.5, 142.9, 143.5, 155.0, 164.1. FAB mass spectrum *m/z* 403.2.

*11-[4-(1,3-Benzodioxol-5-ylmethyl)piperazino]-8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepine (5t)*. Column chromatography (ethyl acetate/hexane; 1 : 1) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (50%), m.p. 156–157°C (Found: C, 66.9; H, 5.0; N, 12.3%. $C_{25}H_{23}ClN_4O_2$ requires C, 67.2; H, 5.2; N, 12.5%). ν_{max} 3368, 1600, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 230 (4.53), 260 (4.31), 290 (4.23) nm. ^{1}H NMR [(D_6)acetone] δ 2.51, m, 4H, H3′, H5′; 3.42, m, 4H, H2′, H6′; 3.47, s, 2H, H1′′; 5.97, s, 2H, H2′′′; 6.55, s, 1H, H5; 6.77, dd, *J* 8, 0.5 Hz, 1H, H7′′′; 6.78–6.83, m, 2H, H7, H6′′′; 6.86–6.90, m, 2H, H6, H4′′′; 6.93, d, *J* 2.5 Hz, 1H, H9; 7.02, app td, *J* 7.5, 1 Hz, 1H, H2; 7.07, dd, *J* 8, 1 Hz, 1H, H4; 7.29, dd, *J* 8, 1.5 Hz, 1H, H1; 7.33, ddd, *J* 8, 7.5, 1.5 Hz, 1H, H3. ^{13}C NMR [(D_3)acetonitrile] δ 48.7, 54.1, 63.6, 102.6, 109.2, 110.6, 121.6, 121.9, 123.6, 124.1, 124.3, 124.9, 127.3, 129.4, 131.6, 133.5, 133.9, 143.1, 143.8, 148.1, 149.2, 155.0, 164.5. ESI mass spectrum *m/z* 447.3.

*8-Chloro-11-(4-(2-fluorobenzyl)piperazino)-5H-dibenzo[*b,e*][1,4]-diazepine (5a)*. Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow microcrystals (53%), m.p. 213–216°C (Found: C, 68.3; H, 5.3; N, 13.3%. $C_{24}H_{22}ClFN_4$ requires C, 68.5; H, 5.3; N, 13.3%). ν_{max} 3292, 1604, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 229 (4.36), 263 (4.21), 295 (4.04) nm. ^{1}H NMR [(D_6)acetone] δ 2.57, m, 4H, H3′, H5′; 3.43, m, 4H, H2′, H6′; 3.64, d, *J* 1 Hz, 2H, H1′′; 6.51, s, 1H, H5; 6.81, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.87, d, *J* 8.5 Hz, 1H, H6; 6.93, d, *J* 2.5 Hz, 1H, H9; 7.02, app td, *J* 8, 1 Hz, 1H, H2; 7.06, m, 1H, H4; 7.10, ddd, *J* 10, 8, 1 Hz, 1H, H3′′′; 7.17, app td, *J* 7, 1 Hz, 1H, H5′′′; 7.27–7.36, m, 3H, H1, H3, H4′′′; 7.49, app td, *J* 8, 2 Hz, 1H, H6′′′. ^{13}C NMR (CD_2Cl_2) δ 47.9, 53.4, 55.8 (d, *J* 2 Hz, CH_2), 115.7 (d, *J* 22 Hz, CH), 120.66, 120.68, 123.4, 123.6, 124.1, 124.5 (d, *J* 4 Hz, CH), 125.4 (d, *J* 15 Hz, C), 127.0, 129.3, 129.4 (d, *J* 8 Hz, CH), 130.8, 132.2 (d, *J* 5 Hz, CH), 132.5, 141.0, 142.7, 153.4, 162.1 (d, *J* 246 Hz, CF), 163.4. ESI mass spectrum *m/z* 421.3.

*8-Chloro-11-(4-(2-chlorobenzyl)piperazino)-5*H*-dibenzo[*b,e*][1,4]-diazepine (5b)*. Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow platelets (73%) m.p. 234–236°C (Found: C, 65.8; H, 5.1; N, 12.8%. $C_{24}H_{22}Cl_2N_4$ requires C, 65.9; H, 5.1; N, 12.8%). ν_{max} 3284, 1604, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 229 *inf* (4.35), 261 (4.16), 297 (3.97) nm. ^{1}H NMR [(D_6)acetone]δ 2.61, m, 4H, H3′, H5′; 3.45, m, 4H, H2′, H6′; 3.68, s, 2H, H1′′; 6.56, s, 1H, H5; 6.82, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.88, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.03, m, 1H, H2; 7.07, m, 1H, H4; 7.27, app td, *J* 7.5, 2 Hz, 1H, H4′′′; 7.29–7.36, m, 3H, H1, H3, H5′′′; 7.39, app td, *J* 8, 2 Hz, 1H, H3′′′; 7.58, dd, *J* 7.5, 2 Hz, 1H, H6′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.8, 59.9, 121.2, 121.4, 123.48, 123.54, 124.6, 127.0, 127.8, 128.6, 129.4, 130.3, 131.0, 131.9, 132.9, 134.9, 136.9, 143.0, 143.4, 155.1, 164.0. ESI mass spectrum *m/z* 437.3.

*8-Chloro-11-(4-(2-bromobenzyl)piperazino)-5*H*-dibenzo[*b,e*][1,4]-diazepine (5c)*. Column chromatography (acetone/hexane; 1 : 1) gave the title compound, which recrystallized from acetone/hexane as bright yellow prisms (66%), m.p. 243–246°C (Found: C, 60.0; H, 4.6; N, 11.6%. $C_{24}H_{22}BrClN_4$ requires C, 59.8; H, 4.6; N, 11.6%). ν_{max} 3276, 1604, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 227 *inf* (4.46), 260 (4.23), 296 (4.04) nm. ^{1}H NMR [(D_6)acetone] δ 2.62, m, 4H, H3′, H5′; 3.45, m, 4H, H2′, H6′; 3.66, s, 2H, H1′′; 6.56, s, 1H, H5; 6.82, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.89, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.03, m, 1H, H2; 7.07, m, 1H, H4; 7.20, app td, *J* 7.5, 2 Hz, 1H, H4′′′; 7.30–7.35, m, 2H, H1, H3; 7.37, m, 1H, H5′′′; 7.58, dd, *J* 7.5, 1.5 Hz, 1H, H6′′′; 7.59, dd, *J* 8, 1 Hz,

1H, H3′′′. ^{13}C NMR (CD_2Cl_2) δ 48.3, 53.8, 59.9, 121.2, 121.4, 123.48, 123.54, 124.6, 127.0, 127.8, 128.6, 129.4, 130.3, 131.0, 131.9, 132.9, 134.9, 136.9, 143.0, 143.4, 155.1, 164.0. ESI mass spectrum *m/z* 481.3.

*8-Chloro-11-(4-(3-fluorobenzyl)piperazino)-5*H-*dibenzo[*b,e*][1,4]-diazepine (5d).* Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (79%), m.p. 213.5–215°C (Found: C, 68.6; H, 5.3; N, 13.2%. $C_{24}H_{22}ClFN_4$ requires C, 68.5; H, 5.3; N, 13.3%). ν_{max} 3292, 1604, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 227 (4.38), 261 (4.21), 297 (4.00) nm. ^{1}H NMR [(D_6)acetone] δ 2.53, m, 4H, H3′, H5′; 3.43, m, 4H, H2′, H6′; 3.57, s, 2H, H1′′; 6.50, s, 1H, H5; 6.80, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.87, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 6.97–7.10, m, 3H, H2, H4, H6′′′; 7.13–7.23, m, 2H, H2′′′, H4′′′; 7.27–7.41, m, 3H, H1, H3, H5′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.8, 62.9, 114.6 (*J* 22 Hz, CH), 116.3 (*J* 22 Hz, CH), 121.3, 121.4, 123.5, 123.6, 124.7, 125.6, 127.1, 128.7, 130.9 (d, *J* 8 Hz, CH), 131.0, 132.9, 142.7 (d, *J* 7 Hz, C), 143.0, 143.5, 155.1, 164.0 (d, *J* 244 Hz, CF), 164.1. ESI mass spectrum *m/z* 421.3.

*8-Chloro-11-(4-(3-chlorobenzyl)piperazino)-5*H-*dibenzo[*b,e*][1,4]-diazepine (5e).* Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow platelets (59%), m.p. 222–223°C (Found: C, 66.0; H, 5.1; N, 13.1%. $C_{24}H_{22}Cl_2N_4$ requires C, 65.9; H, 5.1; N, 12.8%). ν_{max} 3292, 1604, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 228 *inf* (4.42), 261 (4.22), 297 (4.02) nm. ^{1}H NMR [(D_6)acetone] δ 2.54, m, 4H, H3′, H5′; 3.44, m, 4H, H2′, H6′; 3.57, s, 2H, H1′′; 6.51, s, 1H, H5; 6.81, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.88, d, *J* 8.5 Hz, 1H, H6; 6.93, d, *J* 2.5 Hz, 1H, H9; 7.02, ddd, *J* 8, 7.5, 1 Hz, 1H, H2; 7.07, dd, *J* 8, 1 Hz, 1H, H4; 7.24–7.37, m, 5H, H1, H3, H4′′′, H5′′′, H6′′′; 7.41, m, 1H, H2′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.8, 62.8, 121.3, 121.4, 123.5, 123.6, 124.7, 127.1, 128.0, 128.3, 128.6, 129.7, 130.8, 131.1, 132.9, 134.7, 142.3, 143.0, 143.5, 155.1, 164.1. ESI mass spectrum *m/z* 437.3.

*8-Chloro-11-(4-(3-bromobenzyl)piperazino)-5*H-*dibenzo[*b,e*][1,4]-diazepine (5f).* Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow platelets (48%), m.p. 223–225°C (Found: C, 60.1; H, 4.5; N, 11.5%. $C_{24}H_{22}BrClN_4$ requires C, 59.8; H, 4.6; N, 11.6%). ν_{max} 3288, 1602, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 225 *inf* (4.49), 261 (4.25), 297 (4.05) nm. ^{1}H NMR [(D_6)acetone] δ 2.54, m, 4H, H3′, H5′; 3.44, m, 4H, H2′, H6′; 3.57, s, 2H, H1′′; 6.50, s, 1H, H5; 6.81, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.87, d, *J* 8.5 Hz, 1H, H6; 6.93, d, *J* 2.5 Hz, 1H, H9; 7.02, ddd, *J* 8, 7.5, 1 Hz, 1H, H2; 7.07, dd, *J* 8, 1 Hz, 1H, H4; 7.23–7.46, m, 5H, H1, H3, H4′′′, H5′′′, H6′′′; 7.57, br s, 1H, H2′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.8, 62.8, 121.3, 121.4, 123.0, 123.5, 123.6, 124.7, 127.1, 128.7, 128.8, 131.0, 131.07, 131.14, 132.7, 132.9, 142.6, 143.0, 143.5, 155.1, 164.1. ESI mass spectrum *m/z* 481.2.

*8-Chloro-11-(4-(3-methylbenzyl)piperazino)-5*H-*dibenzo[*b,e*][1,4]-diazepine (5g).* Column chromatography (ethyl acetate/hexane; 1 : 1) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (72%), m.p. 202.5–204°C (Found: C, 72.2; H, 6.1; N, 13.5%. $C_{25}H_{25}ClN_4$ requires C, 72.0; H, 6.0; N, 13.4%). ν_{max} 3304, 1604, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 228 *inf* (4.41), 261 (4.22), 297 (4.02) nm. ^{1}H NMR [(D_6)acetone] δ 2.31, s, 3H, CH_3; 2.51, m, 4H, H3′, H5′; 3.42, m, 4H, H2′, H6′; 3.50, s, 2H, H1′′; 6.51, s, 1H, H5; 6.80, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.90, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.01, app td, *J* 7.5, 1 Hz, 1H, H2; 7.04–7.09, m, 2H, H4, H2′′′; 7.10–7.23, m, 3H, H4′′′, H5′′′, H6′′′; 7.25–7.36, m, 2H, H1, H3. ^{13}C NMR [(D_6)acetone] δ 21.5, 48.3, 53.8, 63.6, 121.2, 121.4, 123.45, 123.52, 124.7, 127.1 (2 × CH), 128.6, 129.0, 130.6, 131.0, 132.8, 133.9, 138.5, 139.4, 142.9, 143.5, 155.0, 164.1. ESI mass spectrum *m/z* 417.3.

*8-Chloro-11-(4-(3-methoxybenzyl)piperazino)-5*H-*dibenzo[*b,e*]-[1,4]diazepine (5h).* Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (81%), m.p. 156.5–158°C (Found: C, 69.4; H, 5.8; N, 13.0%. $C_{25}H_{25}ClN_4O$ requires C, 69.4; H, 5.8; N, 12.9%). ν_{max} 3276, 1602, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 226 *inf* (4.49), 262 (4.19), 298 (3.99) nm. ^{1}H NMR [(D_6)acetone] δ 2.53, m, 4H, H3′, H5′; 3.43, m, 4H, H2′, H6′; 3.53, s, 2H, H1′′; 3.78, s, 3H, OCH_3; 6.51, s, 1H, H5; 6.80, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.81, m, 1H, H2′′′; 6.87, d, *J* 8 Hz, 1H, H6; 6.91–6.97, m, 2H, H4′′′, H6′′′; 6.93, d, *J* 2 Hz, 1H, H9; 7.02, ddd, *J* 8, 7.5, 1 Hz, 1H, H2; 7.06, dd, *J* 8, 1 Hz, 1H, H4; 7.22, app t, *J* 8 Hz, 1H, H5′′′; 7.29, dd, *J* 7.5, 1.5 Hz, 1H, H1; 7.33, ddd, *J* 7.5, 7, 2 Hz, 1H, H3. ^{13}C NMR [(D_6)acetone] δ 48.4, 53.8, 55.5, 63.5, 113.4, 115.4, 121.2, 121.4, 122.1, 123.45, 123.50, 124.7, 127.1, 128.6, 130.1, 131.0, 132.8, 141.1, 142.9, 143.5, 155.0, 160.9, 164.1. ESI mass spectrum *m/z* 433.4.

*8-Chloro-11-(4-(3-trifluoromethylbenzyl)piperazino)-5*H-*dibenzo-[*b,e*][1,4]diazepine (5i).* Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (78%), m.p. 202–204°C (Found: C, 64.0; H, 4.7; N, 11.9%. $C_{25}H_{22}ClF_3N_4$ requires C, 63.8; H, 4.7; N, 11.9%). ν_{max} 3284, 1602, 1558 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 228 (4.48), 261 (4.29), 297 (4.09) nm. ^{1}H NMR [(D_6)acetone] δ 2.54, m, 4H, H3′, H5′; 3.44, m, 4H, H2′, H6′; 3.65, s, 2H, H1′′; 6.50, s, 1H, H5; 6.81, *J* 8.5, 2.5 Hz, 1H, H7; 6.88, d, *J* 8.5 Hz, 1H, H6; 6.95, d, *J* 2.5 Hz, 1H, H9; 7.01, app td, *J* 7.5, 1 Hz, 1H, H2; 7.06, br d, *J* 8 Hz, 1H, H4; 7.26–7.37, m, 2H, H1, H3; 7.51–7.75, m, 4H, H2′′′, H4′′′, H5′′′, H6′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.7, 62.8, 121.2, 121.4, 123.5, 123.6, 124.6, 124.7 (q, *J* 4 Hz, CH), 125.5 (q, *J* 271 Hz, CF), 126.3 (q, *J* 4 Hz, CH), 127.1, 128.7, 130.0, 130.98 (q, *J* 32 Hz, C), 131.02, 132.9, 133.7 (m, CH), 141.2, 142.9, 143.4, 155.0, 164.0. ESI mass spectrum *m/z* 471.3.

*8-Chloro-11-(4-(4-fluorobenzyl)piperazino)-5*H-*dibenzo[*b,e*][1,4]-diazepine (5j).* Column chromatography (ethyl acetate/hexane; 1 : 1) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (66%), m.p. 201–202°C (Found: C, 68.2; H, 5.1; N, 13.2%. $C_{24}H_{22}ClFN_4$ requires C, 68.5; H, 5.3; N, 13.3%). ν_{max} 3292, 1603, 1560 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 228 (4.39), 261 (4.21), 297 (4.01) nm. ^{1}H NMR [(D_6)acetone] δ 2.51, m, 4H, H3′, H5′; 3.42, m, 4H, H2′, H6′; 3.54, s, 2H, H1′′; 6.53, s, 1H, H5; 6.81, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.88, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 6.98–7.12, m, 4H, H2, H4, H3′′′, H5′′′; 7.26–7.43, m, 4H, H1, H3, H2′′′, H6′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.4, 62.7, 115.7 (d, *J* 21 Hz, CH), 121.2, 121.4, 123.4, 123.5, 124.7, 127.1, 128.7, 131.0, 131.6 (d, *J* 7.5 Hz, CH), 132.9, 135.6, 142.9, 143.5, 155.0, 163.0 (d, *J* 243 Hz, CF), 164.6. FAB Mass spectrum *m/z* 421.4.

*8-Chloro-11-(4-(4-chlorobenzyl)piperazino)-5*H-*dibenzo[*b,e*][1,4]-diazepine (5k).* Column chromatography (ethyl acetate/hexane; 1 : 1) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (76%), m.p. 201–203°C (Found: C, 65.8; H, 4.9; N, 12.7%. $C_{24}H_{22}Cl_2N_4$ requires C, 65.9; H, 5.1; N, 12.8%). ν_{max} 3368, 1604, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 232 *inf* (4.37), 261 (4.18), 298 (3.98) nm. ^{1}H NMR [(D_6)acetone] δ 2.52, m, 4H, H3′, H5′; 3.42, m, 4H, H2′, H6′; 3.54, s, 2H, H1′′; 6.50, s, 1H, H5; 6.80, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.87, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.01, app td, *J* 8, 1 Hz, 1H, H2; 7.06, app d, *J* 8 Hz, 1H, H4; 7.26–7.41, m, 6H, H1, H3, H2′′′, H3′′′, H5′′′, H6′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.7, 62.6, 121.2, 121.3, 123.4, 123.5, 124.6, 127.0, 128.6, 129.1, 131.0, 131.4, 132.8, 133.1, 138.5, 142.9, 143.4, 155.0, 164.0. ESI mass spectrum *m/z* 437.3.

*8-Chloro-11-(4-(4-bromobenzyl)piperazino)-5*H-*dibenzo[*b,e*][1,4]-diazepine (5l).* Column chromatography (ethyl acetate/hexane; 1 : 1) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (79%), m.p. 210–212°C (Found: C, 59.6; H, 4.5; N, 11.5%. $C_{24}H_{22}BrClN_4$ requires C, 59.8; H, 4.6; N, 11.6%). ν_{max} 3368, 1612, 1564 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 226 *inf* (4.55), 261 (4.24), 297 (4.05) nm. ^{1}H NMR [(D_6)acetone] δ 2.54, m, 4H, H3′, H5′; 3.44, m, 4H, H2′, H6′; 3.55, s, 2H, H1′′; 6.51, s, 1H, H5; 6.80, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.87, d, *J* 8.5 Hz, 1H, H6; 6.93, d, *J* 2.5 Hz, 1H, H9; 7.00, app td, *J* 7.5, 1 Hz, 1H, H2; 7.06, app d, *J* 8 Hz, 1H, H4; 7.25–7.37, m, 4H, H1, H3, H2′′′, H6′′′; 7.49, d, *J* 8.5 Hz, 2H, H3′′′, H5′′′. ^{13}C NMR ($CDCl_3$) δ 47.5, 53.2, 62.5, 120.2, 120.3, 121.2, 123.2, 123.3, 123.7, 127.0, 129.3, 130.5, 131.0, 131.6, 132.1, 137.3, 140.6, 142.1, 152.9, 163.0. ESI mass spectrum *m/z* 481.2.

*8-Chloro-11-(4-(4-methylbenzyl)piperazino)-5*H-*dibenzo[*b,e*][1,4]-diazepine (5m).* Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (74%), m.p. 195–197°C (Found: C, 71.6;

H, 5.9; N, 13.4%. $C_{25}H_{25}ClN_4$ requires C, 72.0; H, 6.0; N, 13.4%). ν_{max} 3364, 1602, 1560 cm^{-1}. λ_{max} ($log_{10}\varepsilon$) 228 *inf* (4.36), 261 (4.16), 299 (3.96) nm. ^{1}H NMR [(D_6)acetone] δ 2.29, s, 3H, CH_3; 2.49, m, 4H, H3′, H5′; 3.41, m, 4H, H2′, H6′; 3.49, s, 2H, H1′′; 6.50, s, 1H, H5; 6.80, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.87, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.00, app td, *J* 7.5, 1 Hz, 1H, H2; 7.06, app d, *J* 8 Hz, 1H, H4; 7.12, d, *J* 8 Hz, 2H, H3′′′, H5′′′; 7.22, d, *J* 8 Hz, 2H, H2′′′, H6′′′; 7.28, m, 1H, H1; 7.31, m, 1H, H3. ^{13}C NMR [(D_6)acetone] δ 21.2, 48.3, 53.7, 63.3, 121.2, 121.4, 123.45, 123.50, 124.7, 127.1, 128.6, 129.8, 129.9, 131.0, 132.8, 136.4, 137.3, 142.9, 143.5, 155.0, 164.0. ESI mass spectrum *m/z* 417.3.

*8-Chloro-11-(4-(4-methoxybenzyl)piperazino)-5*H*-dibenzo[*b,e*][1,4]-diazepine (5n).* Column chromatography (ethyl acetate/hexane; 3 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (80%), m.p. 176–178°C (Found: C, 69.4; H, 5.7; N, 12.9%. $C_{25}H_{25}ClN_4O$ requires C, 69.4; H, 5.8; N, 12.9%). ν_{max} 3360, 1600, 1558 cm^{-1}. λ_{max} ($log_{10}\varepsilon$) 227 (4.55), 262 (4.24), 297 (4.04) nm. ^{1}H NMR [(D_6)acetone] δ 2.50, m, 4H, H3′, H5′; 3.41, m, 4H, H2′, H6′; 3.49, s, 2H, H1′′; 3.78, s, 3H, OCH_3; 6.52, s, 1H, H5; 6.80, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.87, d, *J* 8.5 Hz, 1H, H6; 6.88, d, *J* 9, Hz, 2H, H3′′′, H5′′′; 6.93, d, *J* 2.5 Hz, 1H, H9; 7.02, ddd, *J* 8, 7.5, 1 Hz, 1H, H2; 7.06, dd, *J* 8, 1 Hz, 1H, H4; 7.26, d, *J* 9 Hz, 2H, H2′′′, H6′′′; 7.29, m, 1H, H1; 7.33, ddd, *J* 8, 7.5, 2 Hz, 1H, H3. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.7, 55.6, 63.0, 114.5, 121.2, 121.4, 123.4, 123.5, 124.7, 127.0, 128.6, 131.0, 131.1, 131.3, 132.8, 143.0, 143.5, 155.0, 160.0, 164.0. ESI mass spectrum *m/z* 433.4.

*8-Chloro-11-(4-(4-trifluoromethylbenzyl)piperazino)-5*H*-dibenzo-[*b,e*][1,4]diazepine (5o).* Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (82%), m.p. 184–186°C (Found: C, 63.7; H, 4.7; N, 11.7%. $C_{25}H_{22}ClF_3N_4$ requires C, 63.8; H, 4.7; N, 11.9%). ν_{max} 3370, 1599, 1560 cm^{-1}. λ_{max} ($log_{10}\varepsilon$) 229 (4.45), 261 (4.27), 297 (4.07) nm. ^{1}H NMR [(D_6)acetone] δ 2.55, m, 4H, H3′, H5′; 3.44, m, 4H, H2′, H6′; 3.66, s, 2H, H1′; 6.53, s, 1H, H5; 6.81, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.88, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.01, ddd, *J* 8, 7.5, 1 Hz, 1H, H2; 7.07, dd, *J* 8, 1 Hz, 1H, H4; 7.30, dd, *J* 7.5, 1.5 Hz, 1H, H1; 7.33, ddd, *J* 8, 7.5, 1.5 Hz, 1H, H3; 7.60, d, *J* 8 Hz, 2H, H2′′′, H6′′′; 7.67, d, *J* 8 Hz, 2H, H3′′′, H5′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.8, 62.9, 121.2, 121.4, 123.5, 123.6, 124.7, 125.6 (q, *J* 270 Hz, CF), 126.0 (q, *J* 4Hz, CH), 127.1, 128.6, 129.7 (q, *J* 32 Hz, C), 130.4, 131.0, 132.9, 143.0, 143.5, 144.5, 155.1, 164.1. ESI mass spectrum *m/z* 471.3.

*8-Chloro-11-(4-(4-trifluoromethoxybenzyl)piperazino)-5*H*-dibenzo-[*b,e*][1,4]diazepine (5p).* Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (78%), m.p. 163–164°C (Found: C, 61.7; H, 4.4; N, 11.3%. $C_{25}H_{22}ClF_3N_4O$ requires C, 61.7; H, 4.6; N, 11.5%). ν_{max} 3376, 1604, 1562 cm^{-1}. λ_{max} ($log_{10}\varepsilon$) 229 (4.34), 260 (4.15), 298 (3.96) nm. ^{1}H NMR [(D_6)acetone] δ 2.53, m, 4H, H3′, H5′; 3.42, m, 4H, H2′, H6′; 3.58, s, 2H, H1′′; 6.53, s, 1H, H5; 6.81, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.89, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.01, app td, *J* 7.5, 1 Hz, 1H, H2; 7.07, dd, *J* 8, 1 Hz, 1H, H4; 7.24–7.31, m, 3H, H1, H3′′′, H5′′′; 7.33, m, 1H, H3; 7.49, d, *J* 9 Hz, 2H, H2′′′, H6′′′. ^{13}C NMR [(D6)acetone]δ 48.3, 53.8, 62.6, 121.3, 121.4, 121.6 (q, *J* 255 Hz, CF), 121.7, 123.5, 123.6, 124.7, 127.1, 128.6, 131.1, 131.5, 132.9, 139.0, 143.0, 143.5, 149.1, 155.1, 164.1. ESI mass spectrum *m/z* 487.3.

*8-Chloro-11-(4-(4-nitrobenzyl)piperazino)-5*H*-dibenzo[*b,e*][1,4]-diazepine (5q).* Column chromatography (ethyl acetate/hexane; 1 : 2) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow microneedles (21%), m.p. 216–217.5°C (Found: C, 64.3; H, 4.9; N, 15.7%. $C_{24}H_{22}ClN_5O_2$ requires C, 64.4; H, 5.0; N, 15.6%). ν_{max} 3300, 1600, 1558 cm^{-1}. λ_{max} ($log_{10}\varepsilon$) 228 *inf* (4.40), 264 (4.34), 293 (4.15) nm. ^{1}H NMR [(D_6)acetone] δ 2.57, m, 4H, H3′, H5′; 3.45, m, 4H, H2′, H6′; 3.71, s, 2H, H1′′; 6.54, s, 1H, H5; 6.82, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.88, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.02, app td, *J* 7.5, 1 Hz, H2; 7.07, app d, *J* 8 Hz, 1H, H4; 7.30, dd, *J* 8, 1.5 Hz, 1H, H1; 7.33, ddd, *J* 8, 7.5, 1.5 Hz, 1H, H3; 7.67, d, *J* 9 Hz, 2H, H2′′′, H6′′′; 8.20, d, *J* 9 Hz, 2H, H3′′′, H5′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.8, 62.6, 121.2, 121.4, 123.5, 123.6, 124.3, 124.6, 127.1, 128.6, 130.7, 131.0, 132.9, 143.0, 143.4, 147.8, 148.2, 155.1, 164.1. ESI mass spectrum *m/z* 448.3.

*8-Chloro-11-(4-(2,3,4,5,6-pentafluorobenzyl)piperazino)-5*H*-dibenzo[*b,e*][1,4]-diazepine (5r).* Column chromatography (ethyl acetate/hexane; 2 : 3) gave the title compound, which recrystallized from dichloromethane/hexane as bright yellow prisms (82%), m.p. 218.5–220°C (Found: C, 58.4; H, 3.7; N, 11.1%. $C_{24}H_{18}ClF_5N_4$ requires C, 58.5; H, 3.7; N, 11.4%). ν_{max} 3296, 1604, 1562 cm^{-1}. λ_{max} ($log_{10}\varepsilon$) 227 (4.41), 261 (4.22), 296 (4.00) nm. ^{1}H NMR [(D_6)acetone] δ 2.59, m, 4H, H3′, H5′; 3.40, m, 4H, H2′, H6′; 3.78, t, *J* 2 Hz, 2H, H1′′; 6.51, s, 1H, H5; 6.80, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.88, d, *J* 8.5 Hz, 1H, H6; 6.92, d, *J* 2.5 Hz, 1H, H9; 7.00, app td, *J* 7.5, 1 Hz, H2; 7.06, dd, *J* 8, 1 Hz, 1H, H4; 7.27, dd, *J* 7.5, 1.5 Hz, 1H, H1; 7.32, ddd, *J* 8, 7.5, 1.5 Hz, 1H, H3. ^{13}C NMR [(D_6)acetone] δ 48.2, 49.4, 53.0, 112.2 (m, C), 121.2, 121.4, 123.5, 123.6, 124.6, 127.1, 128.7, 131.0, 132.9, 138.3 (m, 2 × CF), 141.6 (m, CF), 142.9, 143.3, 146.7 (m, 2 × CF), 155.0, 164.1. ESI mass spectrum *m/z* 493.3.

*8-Chloro-11-piperazino-5*H*-dibenzo[*b,e*][1,4]diazepine (8)*

To a solution of piperazine (5.28 g, 61.3 mmol) in anhydrous 1,4-dioxan (30 mL) under nitrogen was added a solution of titanium tetrachloride in dry toluene (1.0 M, 13.5 mL, 13.5 mmol). The mixture was warmed to 50–55°C and a solution of 8-chloro-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-one (6) (3.00 g, 12.3 mmol) in anhydrous 1,4-dioxan (50 mL) was added. The mixture was heated at reflux for 24 h after which time it was evaporated to dryness under vacuum. The residue was partitioned between ethyl acetate (100 mL) and aqueous hydrochloric acid (2 M, 100 mL) then filtered under vacuum. The aqueous phase was washed with ethyl acetate (2 × 50 mL) to remove any unreacted lactam (ca. 170 mg crude starting material recovered). The aqueous layer was basified with solid sodium hydroxide to a pH of 14 then extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water (2 × 30 mL), dried over anhydrous sodium sulfate then evaporated to dryness. The product was purified using flash chromatography (ethyl acetate/methanol; 1 : 1) and the major product evaporated to dryness. The residue was taken up in dichloromethane, filtered to remove any previously dissolved silica gel then evaporated to dryness affording a bright yellow foam (2.17 g, 69%). The product (8) was used in subsequent reactions without further purification [mp 104–110°C, dichloromethane/hexane (lit.[56] 105–116°C)]. ^{1}H NMR (CD_2Cl_2) δ 2.36, s, 1H, H4′; 2.94, m, 4H, H3′, H5′; 3.41, m, 4H, H2′, H6′; 5.03, s, 1H, H5; 6.60, d, *J* 8.5 Hz, 1H, H6; 6.75–6.86, m, 2H, H4, H7; 7.00, app t, *J* 7.5 Hz, 1H, H2; 7.06, br s, 1H, H9; 7.19–7.35, m, 2H, H1, H3. ^{13}C NMR (CD_2Cl_2) δ 46.0, 48.7, 120.18, 120.24, 123.2 (2 × CH), 123.6, 126.8, 129.1, 130.4, 132.0, 140.7, 142.0, 152.9, 163.2. ESI mass spectrum *m/z* 313.2.

General Procedure for the Preparation of 4′-(Pyridinylmethyl) Analogues of Clozapine

To a stirred solution of 8-chloro-11-piperazino-5*H*-dibenzo[*b,e*][1,4]-diazepine (6) (200 mg, 0.639 mmol) in dry 1,2-dichloroethane (20 mL) under N_2 was added the pyridinecarboxaldehyde (15a–c) (0.703 mmol). Sodium triacetoxyborohydride (190 mg, 0.895 mmol) was subsequently added and stirring continued overnight. Aqueous hydrochloric acid (2 M, 25 mL) was added to the reaction mixture and the entire contents transferred into a separatory funnel. The organic layer was separated and the aqueous phase was washed with dichloromethane (2 × 30 mL). The aqueous layer was basified with solid potassium hydroxide to a pH of 14 then extracted with dichloromethane (3 × 30 mL). The organic fractions were pooled, washed with water (30 mL), dried over dried magnesium sulfate, evaporated to dryness and the resulting residue was purified using flash column chromatography. The major product was concentrated under vacuum and the residual solid recrystallized from a suitable solvent system.

The following compounds (16a–c) were prepared in this manner.

*8-Chloro-11-[4-(2-pyridinylmethyl)piperazino]-5*H*-dibenzo[*b,e*]-[1,4]diazepine (16a).* Column chromatography (ethyl acetate/

methanol; 20 : 1) gave the title compound, which recrystallized from dichloromethane/hexane as pale yellow microprisms (68%), m.p. 196–198°C (Found: C, 68.3; H, 5.5; N, 17.4%. $C_{23}H_{22}ClN_5$ requires C, 68.4; H, 5.5; N, 17.3%). ν_{max} 3276, 1608, 1568 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 229 (4.40), 261 (4.27), 297 (4.02) nm. ^1H NMR [(D_6)acetone] δ 2.60, m, 4H, H3′, H5′; 3.44, m, 4H, H2′, H6′; 3.70, s, 2H, H1′′; 6.53, s, 1H, H5; 6.81, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.88, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.02, ddd, *J* 8, 7, 1 Hz, 1H, H2; 7.07, m, 1H, H4; 7.22, ddd, *J* 7.5, 5, 1 Hz, 1H, H5′′′; 7.28–7.36, m, 2H, H1, H3; 7.53, app d, *J* 7.5 Hz, 1H, H3′′′; 7.74, app td, *J* 7.5, 2 Hz, 1H, H4′′′; 8.49, ddd, *J* 5, 2, 1 Hz, 1H, H6′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.9, 65.2, 121.2, 121.4, 122.9, 123.46, 123.53, 123.7, 124.6, 127.0, 128.6, 131.0, 132.9, 137.1, 143.0, 143.4, 149.9, 155.0, 159.8, 164.1. ESI mass spectrum *m/z* 404.4.

*8-Chloro-11-[4-(3-pyridinylmethyl)piperazino]-5*H*-dibenzo[*b,e*]-[1,4]diazepine (16b)*. Column chromatography (ethyl acetate/methanol; 10 : 1) gave the title compound, which recrystallized from methanol/water as bright yellow prisms (74%), mp 171–173°C (Found: C, 68.2; H, 5.6; N, 17.1%. $C_{23}H_{22}ClN_5$ requires C, 68.4; H, 5.5; N, 17.3%). ν_{max} 3296, 1600, 1558 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 229 (4.42), 262 (4.29), 296 (4.03) nm. ^1H NMR [(D_6)acetone] δ 2.54, m, 4H, H3′, H5′; 3.43, m, 4H, H2′, H6′; 3.59, s, 2H, H1′′; 6.58, s, 1H, H5; 6.82, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.90, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.02, ddd, *J* 8, 7.5, 1 Hz, 1H, H2; 7.07, dd, *J* 8, 1 Hz, 1H, H4; 7.28–7.37, m, 3H, H1, H3, H5′′′; 7.76, m, 1H, H4′′′; 8.47, dd, *J* 5, 1.5 Hz, 1H, H6′′′; 8.56, app d, *J* 1.5 Hz, 1H, H2′′′. ^{13}C NMR [(D_6)acetone] δ 48.3, 53.6, 60.6, 121.2, 121.4, 123.45, 123.54, 124.2, 124.6, 127.0, 128.6, 131.0, 132.9, 134.7, 137.3, 143.0, 143.4, 149.9, 151.4, 155.0, 164.0. ESI mass spectrum *m/z* 404.4.

*8-Chloro-11-[4-(4-pyridinylmethyl)piperazino]-5*H*-dibenzo[*b,e*]-[1,4]diazepine (16c)*. Column chromatography (ethyl acetate/methanol; 20 : 1) gave the title compound, which recrystallized from methanol/water as bright yellow prisms (68%), m.p. 181.5–183°C (Found: C, 68.3; H, 5.5; N, 17.4%. $C_{23}H_{22}ClN_5$ requires C, 68.4; H, 5.5; N, 17.3%). ν_{max} 3268, 1600, 1559 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 229 (4.38), 260 (4.23), 297 (3.99) nm. ^1H NMR [(D_6)acetone] δ 2.56, m, 4H, H3′, H5′; 3.45, m, 4H, H2′, H6′; 3.61, s, 2H, H1′′; 6.54, s, 1H, H5; 6.81, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.88, d, *J* 8.5 Hz, 1H, H6; 6.93, d, *J* 2.5 Hz, 1H, H9; 7.02, ddd, *J* 8, 7.5, 1 Hz, 1H, H2; 7.07, dd, *J* 8, 1 Hz, 1H, H4; 7.30, dd, *J* 8, 1.5 Hz, 1H, H1; 7.33, m, 1H, H3; 7.36, m, 2H, H3′′′, H5′′′; 8.51, dd, *J* 4.5, 1.5 Hz, 2H, H2′′′, H6′′′. ^{13}C NMR [(D_6)acetone] δ 48.2, 53.7, 62.1, 121.2, 121.4, 123.4, 123.6, 124.6, 124.7, 127.0, 128.5, 131.0, 132.9, 143.0, 143.4, 148.5, 150.7, 155.0, 164.1. ESI mass spectrum *m/z* 404.4.

*8-Chloro-11-{4-[(5-methoxy-1*H*-3-indolyl)methyl]piperazino)-5*H*-dibenzo[*b,e*][1,4]diazepine (18a)*

To a stirred solution of 8-chloro-11-piperazino-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (400 mg, 1.28 mmol) in dry 1,2-dichloroethane (25 mL) under N_2 was added 5-methoxyindole-3-carboxaldehyde (17a) (204 mg, 1.16 mmol). The mixture was stirred and warmed to dissolve the aldehyde, then cooled to room temperature. Sodium triacetoxyborohydride (345 mg, 1.63 mmol) was added and stirring continued overnight. The reaction mixture was evaporated to dryness and the resulting oily residue acidified with aqueous hydrochloric acid (2 M, 50 mL) producing a pale yellow precipitate. The aqueous mixture was warmed and stirred until complete dissolution and then washed with dichloromethane (2 × 50 mL). The aqueous layer was basified with solid sodium hydroxide to a pH of 14, then extracted with dichloromethane (3 × 50 mL). The organic fractions were pooled, washed with water (25 mL), dried over anhydrous sodium sulfate then evaporated to dryness. The resulting residue was purified using flash chromatography (ethyl acetate/methanol; 25 : 1). The column fractions were pooled, evaporated to dryness furnishing a pale yellow/brown solid. The product (18a) was recrystallized from methanol/water as pale yellow prisms (436 mg, 79%), mp 150–156°C (Found: C, 67.0; H, 5.9; N, 13.8%. $C_{27}H_{26}ClN_5O{\cdot}CH_3OH$ requires C, 66.7; H, 6.0; N, 13.9%). ν_{max} 3432, 3296, 1602, 1560 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 223 *inf* (4.40), 264 (4.32), 298 (4.21) nm. ^1H NMR [(D_6)acetone] δ 2.56, m, 4H, H3′, H5′; 3.42, m, 4H, H2′, H6′; 3.72, s, 2H, H1′′; 3.80, s, 3H, OCH_3; 6.50, s, 1H, H5; 6.76, dd, *J* 9, 2.5 Hz, 1H, H6′′′; 6.80, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.86, d, *J* 8.5 Hz, 1H, H6; 6.94, d, *J* 2.5 Hz, 1H, H9; 7.00, app td, *J* 7.5, 1 Hz, 1H, H2; 7.06, br d, *J* 8 Hz, 1H, H4; 7.21, br s, 1H, H2′′′; 7.25–7.30, m, 3H, H1, H4′′′, H7′′′; 7.31(m, 1H, H3; 9.93, br s, 1H, H1′′′. ^{13}C NMR (CD_2Cl_2) δ 48.0, 53.5, 54.3, 56.4, 102.1, 112.3, 112.6, 112.7, 120.7 (2 × CH), 123.3, 123.6, 124.1, 125.2, 127.0, 129.0, 129.3, 130.9, 132.2, 132.4, 141.3, 142.8, 153.4, 154.4, 163.5. ESI mass spectrum *m/z* 472.3.

*8-Chloro-11-{4-[(1*H*-indol-3-yl)methyl]piperazino)-5*H*-dibenzo[*b,e*][1,4]diazepine (18b)*

8-Chloro-11-piperazino-5*H*-dibenzo[*b*,*e*][1,4]diazepine (200 mg, 0.639 mmol) in dry 1,2-dichloroethane (20 mL) was treated with indole-3-carboxaldehyde (17b) (102 mg, 0.703 mmol) followed by sodium triacetoxyborohydride (203 mg, 0.959 mmol) and worked up as described in the preparation of (18a). The residue was purified using flash chromatography (ethyl acetate) and the product (18b) recrystallized from methanol/water as yellow prisms (199 mg, 70%), mp 122°C (softens), 135°C (melts) (Found: C, 68.6; H, 6.0; N, 15.0%. $C_{26}H_{24}ClN_5{\cdot}CH_3OH$ requires C, 68.4; H, 6.0; N, 14.8%). ν_{max} 3448, 3356, 1600, 1562 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 220 (4.79), 263 (4.31), 291 (4.20) nm. ^1H NMR [(D_6)acetone] δ 2.54, m, 4H, H3′, H5′; 3.42, m, 4H, H2′, H6′; 3.73, s, 2H, H1′′; 6.46, s, 1H, H5; 6.79, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.85, d, *J* 8.5 Hz, 1H, H6; 6.95, d, *J* 2.5 Hz, 1H, H9; 6.98–7.06, m, 3H, H2, H4, H5′′′; 7.10, app td, *J* 7, 1 Hz, 1H, H6′′′; 7.23, d, *J* 2.5 Hz, 1H, H2′′′; 7.24–7.33, m, 2H, H1, H3; 7.37, br d, *J* 8 Hz, 1H, H7′′′; 7.74, br d, *J* 8 Hz, 1H, H4′′′; 10.05, br s, 1H, H1′′′. ^{13}C NMR [(D_6)acetone] δ 48.4, 53.7, 54.6, 112.2, 112.6, 119.7, 120.3, 121.2, 121.3, 122.2, 123.39, 123.40, 124.7, 125.2, 127.0, 128.6, 129.0, 131.0, 132.8, 137.9, 142.9, 143.5, 154.9, 164.0. ESI mass spectrum *m/z* 442.3.

*4-{[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)piperazino]methyl}benzene-1,2-diol (19)*

To a solution of 11-[4-(1,3-benzodioxol-5-ylmethyl)piperazino]-8-chloro-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (5t) (242 mg, 0.541 mmol) in anhydrous dichloromethane (20 mL) at room temperature was added a solution of boron tribromide in dichloromethane (1.0 M, 5.4 mL, 5.41 mmol). A precipitate was observed and the mixture was stirred at ambient temperature for 5 h. After this time, methanol (10 mL) was added to the mixture and the resulting solution evaporated to dryness. The residue was partitioned between saturated sodium bicarbonate solution (50 mL) and ethyl acetate (50 mL) and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The organic fractions were pooled, washed with water (50 mL), brine (50 mL), dried over dried magnesium sulfate then evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate). The column fractions were combined, evaporated to dryness affording the title compound (19) as a bright yellow foam (184 mg, 78%). ν_{max} 3600–3000, 3268, 1600, 1560 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 225 (4.49), 262 (4.23), 291 (4.11) nm. ^1H NMR [(D_4)methanol] δ 2.55, m, 4H, H3′′, H5′′; 3.40, m, 4H, H2′′, H6′′; 3.44, s, 2H, H1′; 6.65, dd, *J* 8, 2 Hz, 1H, H5; 6.72, d, *J* 8 Hz, 1H, H6; 6.78, d, *J* 8.5, Hz, 1H, H6′′′; 6.80, d, *J* 2 Hz, 1H, H3; 6.83, dd, *J* 8.5, 2.5 Hz, 1H, H7′′′; 6.93, d, *J* 2.5 Hz, 1H, H9′′′; 6.98, dd, *J* 8, 1 Hz, 1H, H4′′′; 7.01, app td, *J* 8, 1 Hz, 1H, H2′′′; 7.26, dd, *J* 8, 1.5 Hz, 1H, H1′′′; 7.32, app td, *J* 8, 1.5 Hz, 1H, H3′′′. ^{13}C NMR [(D_4)methanol] δ 48.3, 53.8, 63.7, 116.2, 118.1, 121.3, 121.6, 122.6, 123.9, 124.4, 124.5, 127.3, 129.5, 129.6, 131.5, 133.4, 143.1, 143.6, 145.9, 146.3, 155.4, 165.4. ESI high-resolution mass spectrum (Found: *m/z*, 435.1586. Calc. for $C_{24}H_{24}ClN_4O_2$: *m/z*, 435.1588). The title compound was converted into the hydrochloride salt by treatment with 3 M hydrogen chloride in ethyl acetate, evaporated to dryness, dissolved in water then lyophilized (Found: C, 53.3; H, 5.0; N, 9.9%. $C_{24}H_{23}ClN_4O_2{\cdot}2HCl{\cdot}2H_2O$ requires C, 53.0; H, 5.4; N, 10.3%).

*8-Chloro-11-{4-[(5-hydroxy-1*H*-3-indolyl)methyl]piperazino)-5*H*-dibenzo[*b,e*][1,4]diazepine (20)*

8-Chloro-11-{4-[(5-methoxy–1*H*-3-indolyl)methyl]piperazino)-5*H*-dibenzo[b,e][1,4]diazepine (18a) (180 mg, 0.381 mmol) in anhydrous dichloromethane (20 mL) was treated with a solution of boron

tribromide in dichloromethane (1.0 M, 3.8 mL, 3.81 mmol) and worked up as described in the preparation of (19). The residue was purified using flash chromatography (dichloromethane/methanol, 20 : 1) and the product (20) evaporated to dryness to yield a tan foam (135 mg, 77%). ν_{max} 3452, 3352, 1600, 1560 cm^{-1}. λ_{max} ($\log_{10}\varepsilon$) 226 *inf* (4.57), 264 (4.24), 298 (4.11) nm. ^{1}H NMR [(D_4)methanol] δ 2.65, m, 4H, H3′, H5′; 3.41, m, 4H, H2′, H6′; 3.74, s, 2H, H1′′; 6.69, dd, *J* 8.5, 2.5 Hz, 1H, H6′′′; 6.77, d, *J* 8.5 Hz, 1H, H6; 6.82, dd, *J* 8.5, 2.5 Hz, 1H, H7; 6.94, d, *J* 2.5 Hz, 1H, H4′′′; 6.94–7.02, m, 2H, H2, H4; 7.05, d, *J* 2.5 Hz, 1H, H4′′′; 7.17, br s, 1H, H2′′′; 7.19, d, *J* 8.5 Hz, 1H, H7′′′; 7.22, dd, *J* 7.5, 1.5 Hz, 1H, H1; 7.30, app td, *J* 7.5, 1.5 Hz, 1H, H3. ^{13}C NMR [(D_4)methanol] δ 48.3, 53.7, 54.3, 104.1, 110.0, 112.8, 112.9, 121.4, 121.6, 124.0, 124.5, 124.6, 127.2, 127.3, 129.6, 130.2, 131.5, 133.0, 133.5, 143.2, 143.7, 151.7, 155.5, 165.4. ESI high-resolution mass spectrum (Found: *m/z*, 458.1732. Calc. for $C_{26}H_{25}ClN_5O$: *m/z*, 458.1748). The title compound was converted into the hydrochloride salt by treatment with 3 M hydrogen chloride in ethyl acetate, evaporated to dryness, and then analysed chromatographically. High performances liquid chromatography t_R 2.39 min (isocratic), t_R 18.24 min (gradient).

Pharmacology Procedures

Test Compounds

The synthetic targets were tested in preliminary in-vitro assays as their hydrochloride salts. The compounds were dissolved in anhydrous ethyl acetate as their free base. A solution of 3 M hydrogen chloride in dry ethyl acetate was added precipitating the compound as the hydrochloride salt. The solvent was removed under reduced pressure and the resulting oil dissolved in anhydrous methanol. The solvent was again concentrated under vacuum to remove all traces of hydrogen chloride. The remaining residue was taken up in 1 mL methanol to which 9 mL of ethyl acetate was added. The resulting suspension was concentrated under reduced pressure, dried under vacuum overnight to afford the hydrochloride salt as a fine pale yellow powder in quantitative yield.

In Vitro Studies

Striatal and Cortical Tissue Preparation. Adult male Sprague–Dawley rats weighing 200–250 g were killed by decapitation and the brains removed rapidly and placed on ice. The striatum and cortex were dissected and samples were placed in microcentrifuge tubes and stored frozen at –80°C until the day of the receptor binding assays.

Rat Radioligand Binding Assays. Frozen tissue samples from rat striatum were homogenized gently in ice-cold assay buffer (50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 nM $CaCl_2$ and 1 mM $MgCl_2$; pH 7.4) in an Ultra-Turrax homogenizer. Tissue was pelleted by centrifugation at 1000 × *g* for 10 min at 0°C in a Beckman Avanti™ J-25 Centrifuge. The pellet was discarded, and the supernatant centrifuged for 15 min at 40000 × *g* at 0°C. The resulting supernatant was then discarded, and the remaining pellet re-suspended in buffer and re-centrifuged for 15 min at 40000 × *g* at 0°C. The supernatant was discarded and the remaining pellet re-suspended in assay buffer to a final concentration of 2.0 mg/mL (estimated protein concentration of 0.07 mg of protein/assay tube), frozen and stored at –80°C until the day of the binding experiment.

Tissue-protein levels were estimated using the Lowry method. The assays were carried out using the following: (i) for 5-HT_{2A}; rat cortical membranes, [^{3}H]ketanserin (0.5 nM) as radioligand and methysergide (1 μM) as reference compound for non-specific binding; and (ii) for D_2; rat striatal membranes, [^{3}H]spiperone (0.3 nM) and haloperidol (10 μM). All compounds were assayed as their hydrochloride salts dissolved in 30% ethanol/water to a stock concentration of 3 mM, then diluted with assay buffer to a final concentration of 1 μM. Following incubation at 37°C for 15 min, 96 tube plates were filtered rapidly through a Packard 96 GF/C filter and rinsed four times with 5 mL of ice-cold buffer (50 mM Tris, 140 mM NaCl, 5 mM $MgCl_2$; pH 7.4) using a Packard microcell harvester (Packard Instruments, Downers Grove, IL). Filters were allowed to dry, and then 40 μL of Microscint-20 scintillation cocktail was added to each filter well. Each plate was sealed using a microplate heat-sealing film on a microplate sealer then counted on a Packard topcount microplate scintillation counter (Packard Instruments, Downers Grove, IL). In the preliminary binding assay, the results are expressed as percentage inhibition compared with results in the absence of drug and represent the mean of duplicate tubes at the tested concentration of 1 μM in a single experiment.

Cloned Radioligand Binding Assays. The assay for the determination of dopamine $D_{4.4}$ receptor affinity was carried out using human recombinant (mammalian CHO-K_1 cells) $D_{4.4}$ receptors, [^{3}H]spiperone (0.3 nM) as radioligand and L-754,870 (1 μM) as reference compound for non-specific binding. All compounds were assayed as their hydrochloride salts dissolved in 30% ethanol/water to a stock concentration of 3 mM, and then diluted with assay buffer to a final concentration of 1 μM. The incubation, filtration and counting procedures were equivalent to those described for the rat radioreceptor assay. The results are expressed as percent inhibition and represent the mean of duplicate tubes at the tested concentration of 1 μM in a single experiment.

Acknowledgments

The authors gratefully acknowledge W. Lau for the in vitro pharmacology testing and S. Thomson for NMR and mass spectra of the compounds described. Funding for this work was provided by the Victorian College of Pharmacy (Monash University).

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