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Synthesis and Preliminary Pharmacological Evaluation of 4′-Arylalkyl Analogues of Clozapine. II.* Effect of the Nature and Length of the Linker

Ben Capuano,[A,C] *Ian T. Crosby*,[A] *Edward J. Lloyd*,[A] *Anna Podloucka*[A] *and David A. Taylor*[B]

[A] Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University, Parkville, 3052, Australia.

[B] Department of Pharmaceutical Biology and Pharmacology, Victorian College of Pharmacy, Monash University, Parkville, 3052, Australia.

[C] Author to whom correspondence should be addressed (email: ben.capuano@vcp.monash.edu.au).

We report the synthesis of a second generation of tricyclic analogues of clozapine, investigating the length and nature of the chain between an ionizable nitrogen atom at physiological pH and the introduced aryl moiety. The chemistry, structural characterization, and pharmacological evaluation of this series of 4′-arylalkyl analogues of clozapine are described. Preliminary findings on the effects on activity of the nature and length of the linker, degree of unsaturation, and type of aryl moiety on blockade of dopamine D_4 and serotonin 5-HT_{2A} receptors are discussed and animal behavioural data for key compounds presented.

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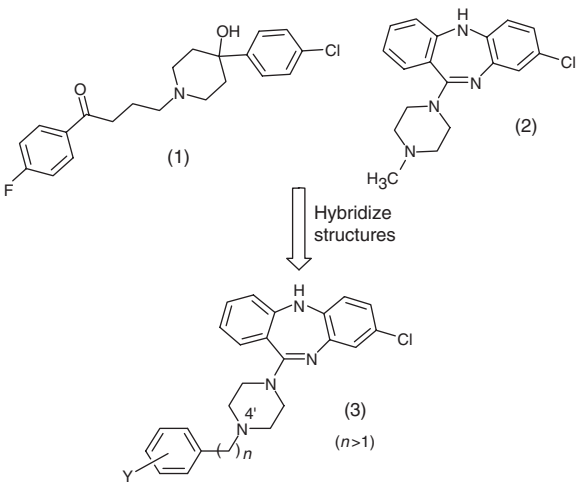
Introduction

Schizophrenia is a mental disorder characterized by chaotic jumbling and fragmentation of sensations and thought processes. This debilitating psychosis, often inaccurately referred to as a 'split mind', is identified by a gross distortion of reality affecting approximately 1% of the world population.[1–3] Our current research interests involve the development of compounds with mixed D_4 and 5-HT_{2A} antagonist activity for the treatment of schizophrenia. The 4′-arylmethyl analogues described previously,[4] which investigated the positional and electronic effects of substituents on the introduced aryl ring, generally proved to be less potent than clozapine in binding to the selected dopaminergic ($D_{4.4}$) and serotonergic (5-HT_{2A}) receptors. From these data and our revised structural model (Scheme 1), conceived from a structural hybridization of the antipsychotics, haloperidol (1) and clozapine (2), we embarked on the synthesis and pharmacological evaluation of second generation clozapine analogues (3), exploring the length and nature of the link between the distal nitrogen atom N4′ and the introduced aryl moiety. The profile of potent D_4 and 5-HT_{2A} receptor affinity is hypothesized for the improvement of positive and negative symptoms of schizophrenia, respectively, and relatively low striatal D_2 receptor affinity to diminish EPS (extra pyramidal symptoms) liability.



Scheme 1. Structural hybridization of clozapine (1) and haloperidol (2) yielding a tricyclic template (3).

Results and Discussion

Chemistry

Biochemical data for the *N*-benzyl analogue of clozapine,[4] where $n = 1$, described previously, provided the catalyst to assess the effect of modifying the length of the saturated spacer, on the affinity for the $D_{4.4}$ and 5-HT_{2A} receptors.

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

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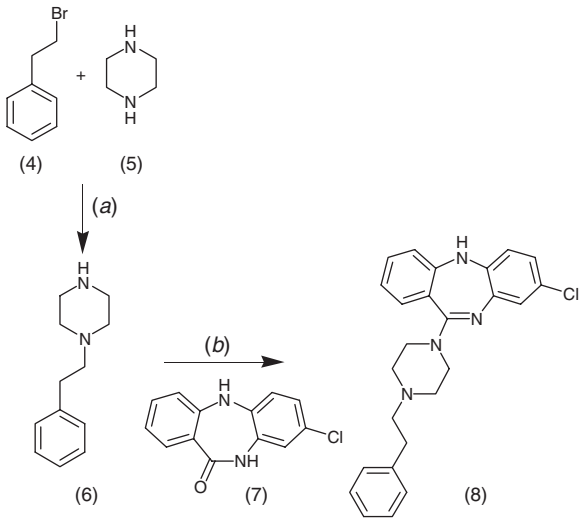
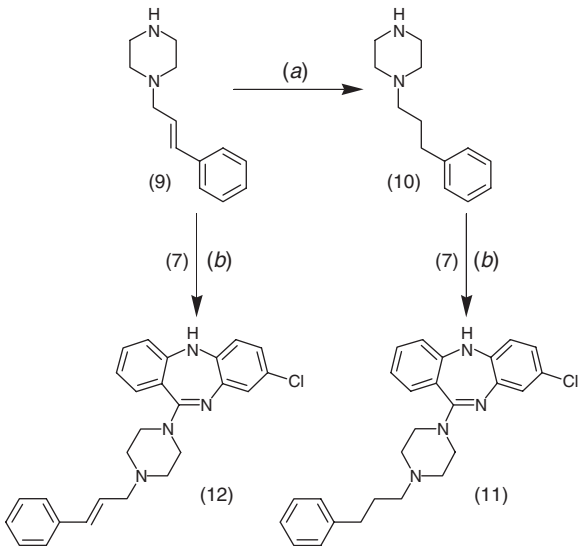
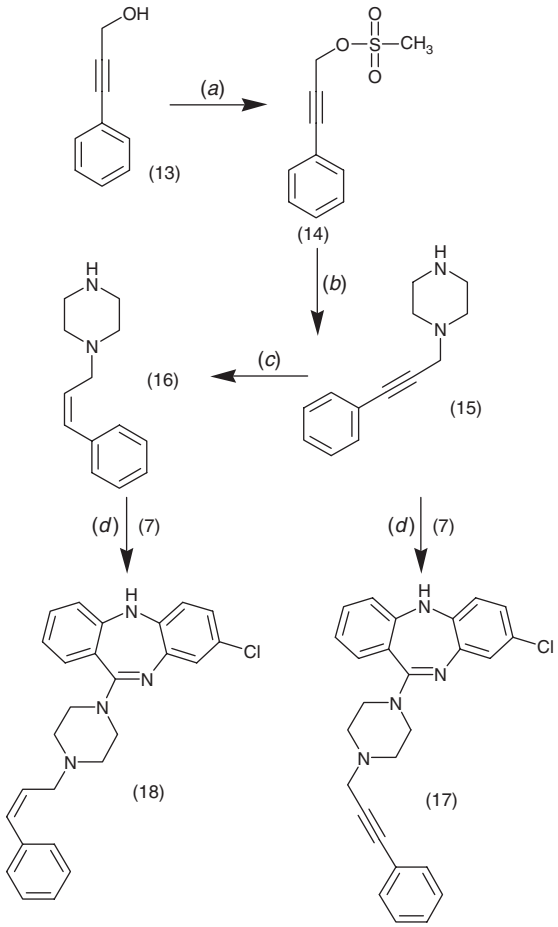


Scheme 2. Reagents and conditions: (*a*) toluene, 85°C; (*b*) $TiCl_4$, anisole, 25 to 55°C, reflux.



Scheme 3. Reagents and conditions: (*a*) 10% Pd/C, H_2, absolute ethanol; (*b*) $TiCl_4$, anisole, 25 to 55°C, reflux.

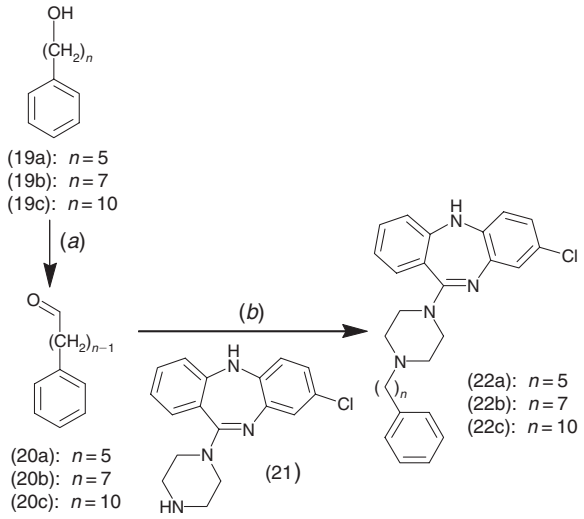
For $n = 2$, the monosubstituted piperazine of interest, 1-(2-phenylethyl)piperazine (6), was prepared by the alkylation of piperazine (5) with (2-bromoethyl)benzene (4), as presented in Scheme 2. Subsequent treatment of the titanium–amine complex[5] of (6) with the tricyclic lactam (7) afforded the *N*-phenylethyl analogue (8) as bright yellow prisms. The synthesis of the homologue corresponding to the *N*-phenylpropyl analogue of clozapine (11) ($n = 3$) is outlined in Scheme 3. The intermediate 1-(3-phenylpropyl)piperazine (10) was obtained by hydrogenation of commercially available (*E*)-1-cinnamylpiperazine (9). Subsequent treatment with titanium tetrachloride followed by the lactam (7) afforded (11) in excellent yield (87%). Our efforts were also focussed on incorporating unsaturation, in the form of double (*E* and *Z*) and triple bonds, into the link between N4′ and the introduced aryl moiety, and examining the effect of these conformational restrictions on biological activity. The



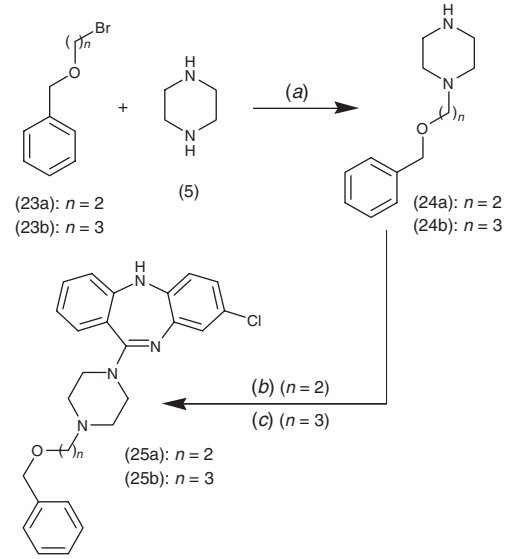
Scheme 4. Reagents and conditions: (*a*) *N*-ethyldiisopropylamine, methanesulfonyl chloride, dichloromethane, −10°C; (*b*) piperazine, tetrahydrofuran, reflux; (*c*) 5% Pd/$CaSO_4$/Pb (Lindlar catalyst), quinoline, H_2, methanol; (*d*) $TiCl_4$, anisole, 25 to 55°C, reflux.

titanium–amine complex of commercially available (*E*)-1-cinnamylpiperazine (9) was reacted with (7) to generate the (*E*)-arylalkenyl analogue of clozapine (12) as depicted in Scheme 3. The (*Z*)-cinnamyl analogue (18) was furnished in a similar fashion to (12) from the monosubstituted piperazine 1-[(*Z*)-3-phenyl-2-propenyl]piperazine (16) as illustrated in Scheme 4. The *Z* stereochemistry was introduced by hydrogenation using a Lindlar catalyst of the alkyne precursor (15), which was generated from treatment of the mesylate (14) of 3-phenylprop-2-yn-1-ol (13) with piperazine. Reaction of (15) with the lactam (7) in the presence of titanium tetrachloride produced the phenylalkynyl analogue of clozapine (17). The methodology adopted for phenylalkyl analogues of clozapine where $n > 3$ made use of commercially available phenylalkanols (Scheme 5). These alcohols (19a)–(19c) were suitably oxidized to their respective aldehydes (20a)–(20c) (62–79%) using pyridinium chlorochromate (PCC), then reacted under reductive amination conditions with desmethylclozapine (21) in the presence of sodium triacetoxyborohydride to yield the desired phenylalkyl homologues of clozapine (22a)–(22c).

The benzyloxyethyl (25a) and benzyloxypropyl (25b) analogues of clozapine were synthesized to investigate the effect of inserting an oxygen atom in the linker (Scheme 6),

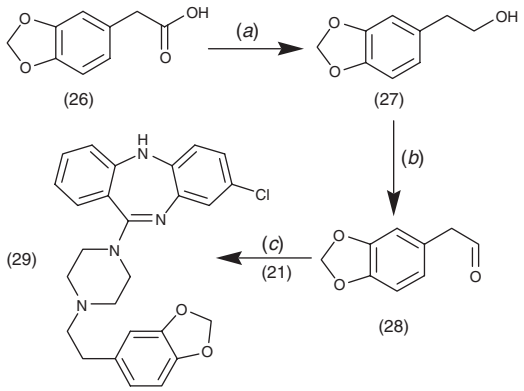


Scheme 5. Reagents and conditions: (*a*) pyridinium chlorochromate (PCC), SiO_2, dichloromethane; (*b*) $NaBH(OAc)_3$, 1,2-dichloroethane.

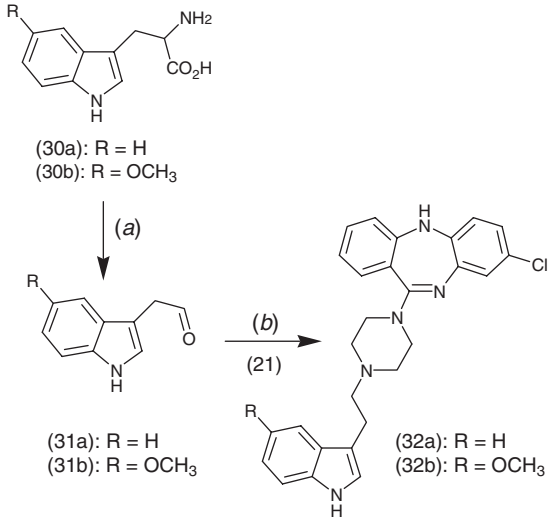


Scheme 6. Reagents and conditions: (*a*) toluene, 85°C; (*b*) tricyclic lactam (7), $TiCl_4$, anisole, 25 to 55°C, reflux; (*c*) tricyclic lactam (7), phosphorus pentachloride, dichloromethane.

particularly in relation to improving aqueous solubility compared with the saturated hydrocarbon linker. We had previously observed that hydrochloride salts of compounds with a hydrocarbon linker were somewhat difficult to dissolve for assay purposes and decided that inclusion of a heteroatom with extensive hydrogen-bond acceptor properties would be one way of inherently improving relative aqueous solubility. The intermediate monosubstituted piperazines (24a) and (24b) were prepared by alkylation of piperazine with the appropriate benzyl bromoalkyl ether (23a) and (23b). Compound (25a) was furnished from reaction of (7) with (24a) in the presence of titanium tetrachloride, whilst (25b) was obtained by treatment of (24b) with the imino chloride intermediate obtained by reaction of (7) with phosphorus pentachloride. Both target compounds (25a) and (25b) were synthesized in reasonable yields (36 and 34%, respectively).



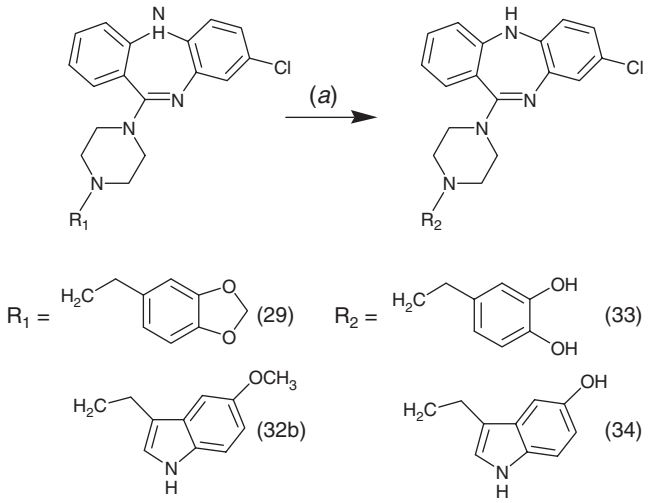
Scheme 7. Reagents and conditions: (*a*) $LiAlH_4$, anhydrous ether; (*b*) PCC, SiO_2, dichloromethane; (*c*) $NaBH(OAc)_3$, 1,2-dichloroethane.



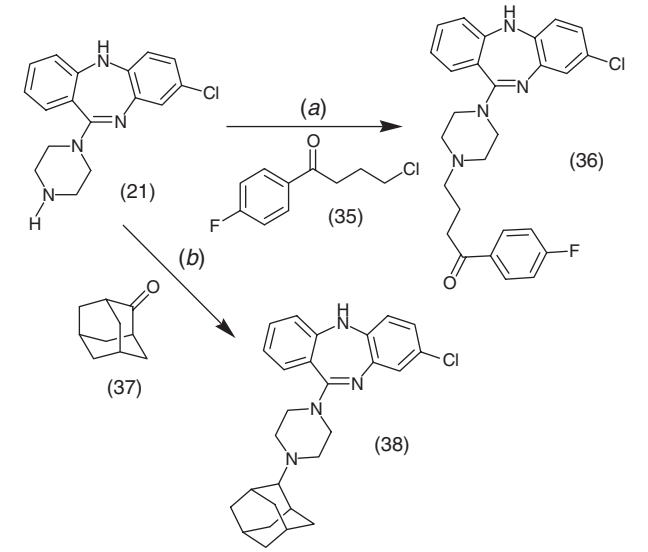
Scheme 8. Reagents and conditions: (*a*) $NaOCl_{(aq.)}$, water/toluene, pH 9; (*b*) $NaBH(OAc)_3$, 1,2-dichloroethane.

The benzodioxole and indole ring systems were investigated as alternatives to the phenyl moiety for inclusion into the structure of clozapine at the N4′ position using a suitable linker. We were particularly interested in the synthesis of the benzo[1,3]dioxol-5-ylethyl ((29), Scheme 7) and 5-methoxyindol-3-ylethyl ((32b), Scheme 8) analogues ($n = 2$) because structurally they incorporate the protected forms of the neurotransmitters dopamine and serotonin, respectively. The benzo[1,3]dioxol-5-ylethyl analogue of clozapine was synthesized according to the method outlined in Scheme 7. The aldehyde (28), obtained from its commercially available corresponding acid (26) by lithium aluminium hydride reduction to the alcohol (27)[6] followed by PCC oxidation,[7] underwent reductive amination with desmethylclozapine (21) in the presence of sodium triacetoxyborohydride affording the target amidine (29) in 41% yield.

The syntheses of indol-3-ylethyl analogues (32a) and (32b) followed a similar pathway to that of (29), involving desmethylclozapine (21) and the corresponding indole-3-acetaldehydes (31a) and (31b), and are outlined in Scheme 8. Synthesis of indole-3-acetaldehyde (31a)[8] from L-tryptophan (30a) was effected in 44% yield. Similar conversion of 5-methoxy-DL-tryptophan (30b) afforded the



Scheme 9. Reagents and conditions: (*a*) boron tribromide, dichloromethane.

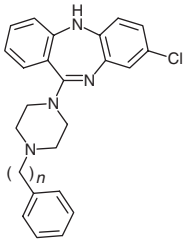


Scheme 10. Reagents and conditions: (*a*) sodium iodide, triethylamine, 1,2-dimethoxyethane; (*b*) $NaBH(OAc)_3$, 1,2-dichloroethane.

desired 5-methoxyindole-3-acetaldehyde (31b). Indole-3-acetaldehydes (31a) and (31b) were systematically treated with desmethylclozapine (21) under reducing conditions giving indol-3-ylethyl analogues of clozapine (32a) and (32b). The benzo[1,3]dioxolylethyl (29) and 5-methoxyindol-3-ylethyl (32b) analogues were further reacted with boron tribromide to afford their catecholethyl (33) and indololethyl (34) analogues (Scheme 9), respectively. These deprotected analogues were of particular interest because they essentially incorporate the structures of the neurotransmitters dopamine and serotonin, respectively.

The effects of incorporating some of the structural features of haloperidol into the molecule of clozapine were investigated. We envisaged the hybrid molecule possessing a 4′-fluorobutyrophenone of haloperidol directly linked to the distal nitrogen atom, N4′, of clozapine. Alkylation of desmethylclozapine (21) with 4-chloro-4′-fluorobutyrophenone (35) in the presence of sodium iodide furnished the hybrid (36) as outlined in Scheme 10.

Table 1. Preliminary binding studies[A]



Compound	*n*	Percentage inhibition (% I) at 10^{-6} M		
		$D_{4.4}$[B] [^{3}H]spiperone	5-HT_{2A}[B] [^{3}H]ketanserin	D_2[C] [^{3}H]spiperone
Clozapine		54	90	76 ± 3
(*N*-benzyl)	1	79	50	81 ± 2
(8)	2	47	93	86 ± 4
(11)	3	40	87	83 ± 5
(22a)	5	47	79	81 ± 6
(22b)	7	48	47	51 ± 14
(22c)	10	20	31	41 ± 20

[A] All compounds were tested as their hydrochloride salts.
[B] Determined in duplicate by PANLABS, Taiwan.
[C] Determined in duplicate at the Victorian College of Pharmacy, Melbourne.

The *N*-2-adamantyl analogue (38) was synthesized under reductive amination conditions using desmethylclozapine (21) and 2-adamantanone (37) (Scheme 10). This lipophilic moiety was selected to investigate the effect of a bulky, non-aromatic group directly anchored to the distal nitrogen atom, N4′.

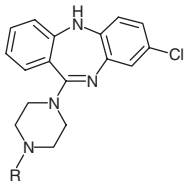
Pharmacological Results and Discussion

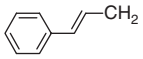
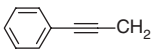
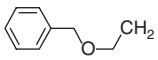
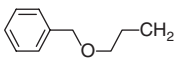
In Vitro Receptor Binding Studies

The synthesized compounds were evaluated in vitro in a series of preliminary receptor binding screens. The compounds were assayed as their hydrochloride salts at a final concentration of 10^{-6} M. Their affinities for cloned human dopamine $D_{4.4}$ receptors,[9] rat cortical serotonin 5-HT_{2A} receptors[10–12] (both of which represent the primary receptors of interest), and rat striatal dopamine D_2 receptors[9] were assessed by measuring the displacement of the designated radioligand (percentage inhibition, % I). The $D_{4.4}$ and 5-HT_{2A} binding data for compounds presented in Tables 1 and 2 were performed by PANLABS, Taiwan Ltd, whilst those presented in Table 3 were performed in-house. There was a discrepancy between the $D_{4.4}$ receptor binding data determined for clozapine by PANLABS (54% I at 10^{-6} M) and data obtained in-house (93% I at 10^{-6} M). This difference was not considered to be a factor as compounds were only compared within their tabulated groups to assess relative affinities in preliminary assays and not across different analyses.

Binding affinities for chain extended phenylalkyl analogues of clozapine are presented in Table 1. Data for the compound corresponding to the *N*-benzyl analogue of clozapine ($n = 1$) were also included for comparison across the series. Its inclusion provided a firmer basis for structure–activity relationships concerning the length of the linker between the distal nitrogen atom N4′, and the introduced

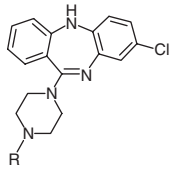
Table 2. Preliminary binding studies[A]

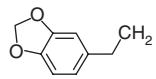
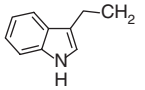
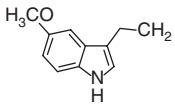
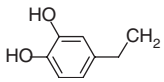
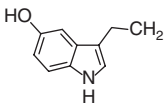
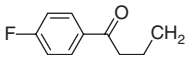


Compound	R	Percentage inhibition (% I) at 10^{-6} M		
		$D_{4.4}$[B] [^{3}H]spiperone	5-HT_{2A}[B] [^{3}H]ketanserin	D_2[C] [^{3}H]spiperone
Clozapine	CH_3	54	90	76 ± 3
(12)		52	80	77 ± 2
(18)		42	70	65 ± 16
(17)		40	36	60 ± 13
(25a)		59	87	n.d.[D]
(25b)		58	82	n.d.

[A] All compounds were tested as their hydrochloride salts.
[B] Determined in duplicate by PANLABS, Taiwan.
[C] Determined in duplicate at the Victorian College of Pharmacy, Melbourne.
[D] Not determined.

Table 3. Preliminary binding studies[A]



Compound	R	Percentage inhibition (% I) at 10^{-6} M		
		$D_{4.4}$[B] [^{3}H]spiperone	5-HT_{2A}[B] [^{3}H]ketanserin	D_2[B] [^{3}H]spiperone
Clozapine	CH_3	93 ± 3	94 ± 1	76 ± 3
(29)		41 ± 1	84 ± 9	57 ± 17
(32a)		33 ± 13	81 ± 6	34 ± 21
(32b)		27 ± 11	83 ± 2	30 ± 2
(33)		42 ± 9	92 ± 5	42 ± 5
(34)		24 ± 15	59 ± 5	34 ± 6
(36)		61 ± 4	90 ± 5	76 ± 12
(38)		13 ± 5	39 ± 6	49 ± 5

[A] All compounds were tested as their hydrochloride salts.
[B] Determined in duplicate at the Victorian College of Pharmacy, Melbourne.

benzene ring. The chain-extended analogues corresponding to $n = 2$ (8), 3 (11), and 5 (22a) showed comparable affinities to clozapine for both $D_{4.4}$ and 5-HT_{2A} receptors. The clozapine analogue (22b) where $n = 7$ displayed $D_{4.4}$ affinity comparable to clozapine but diminished affinity for 5-HT_{2A} receptors. Further chain extension where $n = 10$ (22c) resulted in significantly decreased binding at the $D_{4.4}$ and 5-HT_{2A} receptors.

The (*E*) and (*Z*)-arylalkenyl analogues (12) and (18), respectively, and the arylalkynyl compound (17) were assayed to examine the effect of incorporating unsaturation and also conformational restriction into the linker between the nitrogen atom, N4′, and the introduced aromatic ring. The results are presented in Table 2. Inclusion of the (*E*)-phenylpropenyl moiety (12) produced affinity comparable to that of clozapine for the $D_{4.4}$ and 5-HT_{2A} receptors. The (*Z*)-phenylpropenyl analogue (18) displayed promising 5-HT_{2A} affinity with somewhat diminished activity at the $D_{4.4}$ receptor. Incorporation of a phenylalkynyl group at the N4′ position exhibited reduced affinity at all receptor subtypes examined. The data demonstrate that a degree of unsaturation (alkene) in test compounds can be tolerated by the receptors of interest. The above-mentioned analogues showed favourable D_2 receptor affinity comparable to the parent compound, clozapine. Incorporation of oxygen into the linker (25a) and (25b) afforded compounds with very promising binding profiles that compared favourably to clozapine and represented the best candidates for in vivo evaluation. Preliminary solubility tests showed improved aqueous solubility for the hydrochloride salts of (25a) and (25b) compared with the hydrochloride salt of (22a), which contained the saturated hydrocarbon linker of equal length.

All compounds tabulated in Table 3, except for the indololethyl analogue (34) (59% I) and the adamantyl analogue (38) (58% I), displayed affinity for the 5-HT_{2A} receptor comparable to clozapine (94% I). Of particular note were the catecholethyl (33) and butyrophenone (36) analogues exhibiting 92 and 90% I, respectively. In contrast, all compounds displayed relatively low affinity for the $D_{4.4}$ receptor with compound (36) displaying a maximum value of 61% I (cf. clozapine, 93% I). The catecholethyl analogue (33) showed diminished affinity for the $D_{4.4}$ receptor. Inclusion of the butyrophenone portion of haloperidol into the structure of clozapine (36) produced D_2 affinity comparable with clozapine. The remaining compounds exhibited lower affinity for the D_2 receptor compared with clozapine. Preliminary investigation of steric factors was undertaken by increasing bulk at the N4′ atom with an adamantyl moiety (38). The resultant compound displayed poor activity at both $D_{4.4}$ and 5-HT_{2A} receptors (13

Table 4. Antagonism of apomorphine-induced climbing in mice

Compound	Climbing index[A]	% Inhibition of climbing
Apomorphine	18.2 ± 1.5	–
Vehicle	0.4 ± 0.4	–
Clozapine	12.8 ± 1.3[B]	30
(8)	14.5 ± 2.0	20
(12)	9.1 ± 2.2[B]	50
(25a)	18.8 ± 0.5	0
(25b)	15.6 ± 3.9	14

[A] All compounds were tested as their hydrochloride salts at a dose of $10\,mg\,kg^{-1}$ i.p. Values represent the mean ± SEM climbing index.
[B] Compounds with statistically significant ($P < 0.05$) activity.

and 39% I, respectively) indicating receptor intolerance for bulky substituents at the distal N4′ position. Compounds were selected for further investigation in a preliminary in vivo assay predictive of antipsychotic efficacy using the criterion that the % I (compound) > [% I (clozapine) − 10%] for both $D_{4.4}$ and 5-HT_{2A} receptors. Compounds selected on this basis include the phenylalkyl (8) ($n = 2$) (*E*)-phenylpropenyl (12) and benzyloxyalkyl analogues (25a,b).

In Vivo Behavioural Studies

Promising compounds from the in vitro assays were investigated in vivo for their ability to antagonize apomorphine-induced climbing in mice; a behavioural model predictive of mesolimbic, dopaminergic activity and potential antipsychotic efficacy.[13–16] The mice were pretreated with clozapine ($10\,mg\,kg^{-1}$ i.p.) and test compounds ($10\,mg\,kg^{-1}$ i.p.), as their hydrochloride salts, 30 min prior to an injection of apomorphine hydrochloride ($3.0\,mg\,kg^{-1}$ i.p.) and their climbing behaviour assessed. The results are displayed in Table 4. Clozapine effectively diminished apomorphine-induced climbing in mice at $10\,mg\,kg^{-1}$ i.p., displaying 30% inhibition of climbing. Disappointingly, the phenylethyl (8), benzyloxyethyl (25a), and benzyloxypropyl (25b) analogues of clozapine, although exhibiting some anti-climbing activity at higher doses, failed to significantly antagonize apomorphine-induced climbing at the administered dose of $10\,mg\,kg^{-1}$ i.p. The (*E*)-phenylpropenyl analogue of clozapine (12) significantly antagonized the apomorphine-induced climbing (50% inhibition) and proved to be the first compound of the series assayed to display any significant anti-climbing activity, exhibiting an appreciably greater potency compared with clozapine.

Conclusions

A series of 4′-arylalkyl analogues of clozapine were synthesized based upon the structural hybridization of clozapine and haloperidol. Preliminary in vitro binding data revealed a collection of analogues that exhibited desirable affinity for $D_{4.4}$ and 5-HT_{2A} receptors comparable to clozapine. Compounds exploring the effect of chain length corresponding to 2 methylene units (8), linking the ionizable nitrogen atom N4′ and the introduced benzene ring, showed promising data. Similarly, incorporation of the (*E*)-phenylpropenyl moiety (12), possessing a constrained three-carbon spacer between N4′ and the aryl system, produced an excellent profile. The incorporation of an oxygen atom into the linker, as demonstrated by (25a) and (25b), also produced favourable binding profiles compared with clozapine. The introduction of other aryl moieties (benzodioxoles, indoles, and catechols) produced compounds with significantly reduced receptor affinity compared with clozapine. Steric bulk directly attached to the distal nitrogen atom N4′ associated with analogue (38) (*N*-adamantyl) was not well tolerated by the $D_{4.4}$ receptor compared with clozapine. In vivo analysis of promising candidates showed compound (12) effectively inhibiting apomorphine-induced climbing in mice comparable to clozapine. Compounds (8), (25a), and (25b), although displaying very favourable binding profiles, failed to significantly antagonize apomorphine-induced climbing in mice. It should be noted that an absence of effect in the apomorphine model does not necessarily preclude antipsychotic activity given the multifactorial nature of the neurotransmitters implicated in the etiology of schizophrenia. This may be related to pharmacokinetic and pharmacodynamic factors and requires further behavioural investigation. With respect to chain length, it appears from the preliminary results of binding at $D_{4.4}$ and 5-HT_{2A} that the optimal length is 3–5 atoms, which gives valuable insights into the spatial requirements in the region of clozapine's distal nitrogen atom. Thus compound (12), for example, could be used as the basis for further structural modification and pharmacological evaluation with the aim of more precisely defining the structural requirements for antipsychotic activity devoid of clinically limiting side-effects.

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 IR spectrophotometer as KBr discs unless indicated otherwise. UV-vis spectra were recorded as ethanolic solutions on a Pharmacia Biotech Ultraspec 2000 UV-vis spectrophotometer utilising 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 and 75.4 MHz, respectively, using a Bruker Avance DPX 300 spectrometer equipped with a Silicon Graphics work station. Chemical shifts for all ^1H spectra are reported in parts per million (ppm), using tetramethylsilane as the internal reference. Proton assignments were based upon coupling constants and 2D-homonuclear ($^1H/^1H$) correlation spectroscopy. Chemical shifts for all ^{13}C spectra are reported in ppm, using the solvent chemical shift as the reference.[17] *J*-Modulated Spin-Echo experiments (JMOD) were routinely performed. Fast atom bombardment (FAB) mass spectra were determined using a JEOL JMS-DX300 Mass Spectrometer. The thioglycerol/glycerol matrix was used for samples analyzed 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 high-performance liquid chromatography (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% trifluoroacetate (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^{-1}) and gradient (100% A to 100% B over 30 min, flow rate 1.5 mL min^{-1}) 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 chromatography[18] was carried out routinely using Merck Silica gel 60, 230–400 mesh ASTM. Elemental analyses were carried out on target compounds 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. The results are within 0.4% of the theoretical values for the indicated formula. All solvents used were redistilled prior to use. Tetrahydrofuran was distilled over sodium metal/benzophenone ketyl under nitrogen immediately prior to use. Dry dichloromethane and 1,2-dichloroethane were obtained by distillation over phosphorus pentoxide followed by storage over 3A molecular sieves. Dry ethanol and methanol were distilled from their respective magnesium alkanolates and stored over type 4A and 3A molecular sieves, respectively.

1-(2-Phenylethyl)piperazine (6)

To a solution of (2-bromoethyl)benzene (15.0 g, 81.1 mmol) in toluene (300 mL) was added piperazine (27.9 g, 324 mmol). 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 was 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 a pale yellow oil. Vacuum distillation afforded the product (10.7 g, 69%) as a colourless liquid, bp 110–111°C (0.5 mmHg) [lit.[19] bp 92–96°C (0.15 mmHg)]. δ_H (300 MHz; $CDCl_3$) 7.31–7.23 (2 H, m, H3″, H5″), 7.22–7.14 (3 H, m, H2″, H4″, H6″), 2.91 (4 H, m, H3, H5), 2.80 (2 H, m, H2′), 2.58 (2 H, m, H1′), 2.48 (4 H, m, H2, H6), 1.38 (1 H, s, H4). δ_C (75 MHz; $CDCl_3$) 140.4, 128.6, 128.3, 125.9, 61.1, 54.6, 46.1, 33.4. ESI mass spectrum m/z 191.2.

1-(3-Phenylpropyl)piperazine (10)

A mixture of (*E*)-1-cinnamylpiperazine (5.00 g, 24.7 mmol), palladium-on-carbon (10%, 300 mg), and absolute ethanol (30 mL) was hydrogenated at 60 psi for 30 min at ambient temperature. The catalyst was removed by filtration through a celite pad and the filtrate was concentrated under vacuum. Vacuum distillation afforded the title compound (10) (3.50 g, 69%) as a colourless liquid, bp 108–110°C (0.1 mmHg) [lit.[20] bp 122–128°C (0.5 mmHg)]. δ_H (300 MHz; $CDCl_3$) 7.27–7.19 (2 H, m, H3″, H5″), 7.17–7.09 (3 H, m, H2″, H4″, H6″), 2.87 (4 H, m, H3, H5), 2.62 (2 H, t, *J* 7.5, H3′), 2.38 (4 H, m, H2, H6), 2.33 (2 H, t, *J* 7.5, H1′), 1.80 (2 H, app p, *J* 7.5, H2′), 1.78 (1 H, s, H4). δ_C (75 MHz; $CDCl_3$) 142.2, 128.4, 128.3, 125.8, 58.7, 54.6, 46.2, 33.7, 28.4. ESI mass spectrum m/z 205.2.

*8-Chloro-11-[4-(2-phenylethyl)piperazino]-5*H*-dibenzo[*b*,e][1,4]diazepine (8)*

To a solution of 1-(2-phenylethyl)piperazine (0.583 g, 3.07 mmol) in anhydrous anisole (5 mL) under nitrogen was added a solution of titanium tetrachloride in toluene (1.0 M, 0.67 mL, 0.67 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 (7) (150 mg, 0.613 mmol) in dry 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 over anhydrous sodium sulfate, and then evaporated to dryness. The resulting oily residue was purified using flash chromatography (ethyl acetate/hexane; 2 : 1) and the major product was evaporated to dryness to afford (8) as a yellow solid, which recrystallized from methanol as bright yellow prisms (225 mg, 88%), mp 95°C (softens), 152–154°C (melts) (Found: C 69.6, H 6.4, N 12.3%. $C_{25}H_{25}ClN_4 \cdot CH_3OH$ requires C 69.6, H 6.5, N 12.5%) (Found: C 71.6, H 5.8, N 13.1%. $C_{25}H_{25}ClN_4$ (dichloromethane/hexane) requires C 72.0, H 6.0, N 13.4%). ν_{max} (KBr)/cm^{-1} 3300, 1604, 1562. λ_{max} ($\log_{10}\varepsilon$)/nm 227 (4.40), 260 (4.21), 297 (4.07). δ_H (300 MHz; CD_2Cl_2) 7.35−7.14 (7 H, m, H1, H3, H2‴, H3‴, H4‴, H5‴, H6‴), 7.04 (1 H, dd, *J* 7.5, 1, H2), 7.00 (1 H, d, *J* 2.5, H9), 6.85 (1 H, dd, *J* 8, 1, H4), 6.81 (1 H, dd, *J* 8.5, 2.5, H7), 6.64 (1 H, d, *J* 8.5, H6), 4.98 (1 H, s, H5), 3.44 (4 H, m, H2′, H6′), 2.81 (2 H, m, H2″), 2.64 (2 H, m, H1″), 2.59 (4 H, m, H3′, H5′). δ_C (75 MHz; [D_6]acetone) 164.1, 155.1, 143.5, 143.0, 141.7, 132.8, 131.0, 129.7, 129.2, 128.6, 127.0, 126.8, 124.7, 123.5, 123.4, 121.4, 121.2, 61.1, 53.8, 48.3, 34.3. FAB mass spectrum m/z 417.2.

*8-Chloro-11-[4-(3-phenylpropyl)piperazino]-5*H*-dibenzo[*b*,e][1,4]diazepine (11)*

1-(3-Phenylpropyl)piperazine (626 mg, 3.07 mmol) in anhydrous anisole (5 mL) was treated with a solution of titanium tetrachloride in toluene (1.0 M, 0.67 mL, 0.67 mmol), followed by a solution of 8-chloro-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (7) (0.150 mg, 0.613 mmol) in dry anisole (10 mL) and worked up as described in the preparation of (8). The resulting residue was purified using flash chromatography (ethyl acetate:hexane; 1 : 1) and product (11) recrystallized from methanol/water as bright yellow prisms (229 mg, 87%), mp 65°C (softens), 103°C (melts) (Found: C 70.3, H 6.7, N 12.1%. $C_{26}H_{27}ClN_4 \cdot CH_3OH$ requires C 70.0, H 6.7, N 12.1%). ν_{max} (KBr)/cm^{-1} 3288, 1602, 1562. λ_{max} ($\log_{10}\varepsilon$)/nm 229 (4.38), 261 (4.20), 296 (4.00). δ_H (300 MHz; [D_3]acetonitrile) 7.33 (1 H, app td, *J* 7.5, 1.5, H3), 7.29–7.13 (6 H, m, H1, H2‴, H3‴, H4‴, H5‴, H6‴), 7.02 (1 H, app t, *J* 7.5, 1, H2), 6.98 (1 H, dd *J* 7.5, 1, H4), 6.94 (1 H, d, *J* 2.5, H9), 6.82 (1 H, dd, *J* 8.5, 2.5, H7), 6.77 (1 H, d, *J* 8.5, H6), 5.83 (1 H, s, H5), 3.36 (4 H, m, H2′, H6′), 2.63 (1 H, t, *J* 7.5, H3″), 2.44 (4 H, m, H3′, H5′), 2.34 (1 H, t, *J* 7, H1″), 1.76 (1 H, app p, *J* 7.5, H2″). δ_C (75 MHz; [D_3]acetonitrile) 164.2, 154.7, 143.7, 143.4, 142.7, 133.1, 131.2, 129.5, 129.3, 129.0, 126.9, 126.7, 124.5, 123.9, 123.7, 121.5, 121.2, 58.5, 53.9, 48.3, 34.2, 29.6. FAB mass spectrum m/z 431.3.

*8-Chloro-11-{4-[(*E*)-3-phenyl-2-propenyl]piperazino}-5*H*-dibenzo[*b*,e][1,4]diazepine (12)*

(*E*)-1-Cinnamylpiperazine (1.24 g, 6.13 mmol) in anhydrous anisole (10 mL) was treated with a solution of titanium tetrachloride in toluene (1.0 M, 1.35 mL, 1.35 mmol), followed by a solution of 8-chloro-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (7) (300 mg, 1.23 mmol) in dry anisole (20 mL) and worked up as described in the preparation of (8). The resulting residue was purified using flash chromatography (ethyl acetate/hexane; 7 : 3) and the product (12) recrystallized from dichloromethane/methanol as yellow prisms (462 mg, 88%), mp 92°C (softens), 147–149°C (melts) (Found: C 70.2, H 6.2, N 12.1%. $C_{26}H_{25}ClN_4 \cdot CH_3OH$ requires C 70.3, H 6.3, N, 12.2%). ν_{max} (KBr)/cm^{-1} 3372, 1602, 1560. λ_{max} ($\log_{10}\varepsilon$)/nm 236 (4.37), 250 (4.53), 294 (4.08). δ_H (300 MHz; [D_6]acetone) 7.44 (2 H, m, H2‴, H6‴), 7.36–7.26 (4 H, m, H1, H3, H3‴, H5‴), 7.22 (1 H, m, H4‴), 7.06 (1 H, dd, *J* 8, 1, H4), 7.02 (1 H, app td, *J* 8, 1, H2), 6.95 (1 H, d, *J* 2.5, H9), 6.88 (1 H, d, *J* 8.5, H6), 6.81 (1 H, dd, *J* 8.5, 2.5, H7), 6.59 (br d, *J* 16, 1H, H3″), 6.52 (1 H, s, H5), 6.31 (1 H, dt, *J* 16, 6.5, H2″), 3.43 (4 H, m, H2′, H6′), 3.18 (2 H, dd, *J* 6.5, 1 Hz, H1″), 2.56 (4 H, m, H3′, H5′). δ_C (75 MHz; [D_6]acetone) 164.1, 155.1, 143.5, 143.0, 138.2, 133.5, 132.9, 131.1, 129.5, 128.6, 128.3, 128.0, 127.3, 127.1, 124.7, 123.54, 123.45, 121.4, 121.2, 61.6, 53.8, 48.4. FAB mass spectrum m/z 429.2.

1-(3-Phenylprop-2-yn-1-yl)piperazine (15)

Methanesulfonyl chloride (4.42 g, 38.6 mmol) was added dropwise using a syringe to a stirred solution of 3-phenylprop-2-yn-1-ol

(3.00 g, 22.7 mmol) and triethylamine (4.59 g, 45.4 mmol) in dry dichloromethane (25 mL) at −50°C. The reaction was warmed to 0°C and stirred at this temperature for 1 h. The reaction mixture was transferred to a separatory funnel and washed with water (2 × 30 mL), dried over dried magnesium sulfate, and then evaporated to dryness affording a yellow liquid. The crude mesylate was dissolved in anhydrous tetrahydrofuran (25 mL) and piperazine was added (7.82 g, 90.8 mmol). The mixture was stirred and heated at reflux for 24 h then cooled. The solvent was removed under vacuum and the residue partitioned between aqueous hydrochloric acid (2 M, 50 mL) and dichloromethane (50 mL) and the organic layer separated. The aqueous layer was washed with dichloromethane (50 mL), adjusted to pH 14 by the addition of solid potassium hydroxide, and then extracted with dichloromethane (3 × 50 mL). The organic fractions were combined, washed with water (2 × 30 mL), dried over dried magnesium sulfate, and then concentrated under vacuum. The resulting oil was distilled affording the product (15)[21] (2.49 g, 55%) as a colourless liquid, bp 125–130°C (0.05 mmHg) that crystallized on standing. δ_H (300 MHz; $CDCl_3$) 7.46–7.38 (2 H, m, H2″, H6″), 7.30–7.22 (3 H, m, H3″, H4″, H5″), 3.47 (2 H, s, H1′), 2.91 (4 H, m, H3, H5), 2.58 (4 H, m, H2, H6), 1.78 (1 H, s, H4). δ_C (75 MHz; $CDCl_3$) 131.6, 128.1, 127.9, 123.1, 85.2, 84.5, 53.2, 48.2, 45.9. ESI mass spectrum m/z 201.1.

1-[(Z)-3-Phenyl-2-propenyl]piperazine (16)

A mixture of 1-(3-phenylprop-2-yn-1-yl)piperazine (1.00 g, 4.99 mmol), quinoline (250 μL) and Lindlar catalyst (5% $Pd/CaCO_3/Pb(OAc)_2$, 500 mg) in methanol (25 mL) was hydrogenated until one equivalent of hydrogen gas was consumed. The catalyst was removed by filtration (celite) and the filtrate concentrated under vacuum. The residue was purified by flash chromatography initially using ethyl acetate and methanol (1 : 1) as eluent to remove quinoline, followed by a mixture of dichloromethane, methanol, and ammonia (25 : 4.5 : 0.5) to elute the product (16)[22] that distilled as a colourless liquid (0.810 g, 80%), bp 150–155°C (0.5 mmHg). δ_H (300 MHz; $CDCl_3$) 7.37−7.28 (2 H, m, H2″, H6″), 7.28−7.18 (3 H, m, H3″, H4″, H5″), 6.57 (1 H, br d, *J* 12, H3′), 5.79 (1 H, dt, *J* 12, 6.5, H2′), 3.26 (2 H, dd, *J* 6.5, 2, H1′), 2.90 (4 H, m, H3, H5), 2.43 (4 H, m, H2, H6), 1.72 (1 H, s, H4). δ_C (75 MHz; $CDCl_3$) 137.1, 131.2, 129.5, 128.8, 128.1, 126.8, 56.8, 54.6, 46.1. ESI mass spectrum m/z 203.1.

*8-Chloro-11-{4-[(Z)-3-phenyl-2- propenyl]piperazino}-5*H*-dibenzo[*b,e*][1,4]diazepine (18)*

(*Z*)-1-Cinnamylpiperazine (0.620 g, 3.07 mmol) in anhydrous anisole (5 mL) was treated with a solution of titanium tetrachloride in toluene (1.0 M, 0.67 mL, 0.67 mmol), followed by a solution of 8-chloro-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (7) (150 mg, 0.613 mmol) in dry anisole (10 mL) and worked up as described in the preparation of (8). The resulting residue was purified using flash chromatography (ethyl acetate/hexane; 2 : 1) and the product (18) recrystallized from dichloromethane/methanol as yellow prisms (215 mg, 82%), mp 75°C (softens), 99°C (melts) (Found: C 72.7, H 5.9, N 13.1%. $C_{26}H_{25}ClN_4$ requires C 72.8, H 5.9, N 13.1%). ν_{max} (KBr)/cm^{-1} 3288, 1604, 1562. λ_{max} ($\log_{10}$ ε)/nm 233 (4.52), 250 (4.42), 295 (4.02). δ_H (300 MHz; [D_6]acetone) 7.39−7.22 (7 H, m, H1, H3, H2‴, H3‴, H4‴, H5‴, H6‴), 7.07 (1 H, dd, *J* 8, 1, H4), 7.02 (1 H, app td, *J* 7.5, 1, H2), 6.95 (1 H, d, *J* 2.5, H9), 6.88 (1 H, d, *J* 8.5, H6), 6.81 (1 H, dd, *J* 8.5, 2.5, H7), 6.61 (1 H, dt, *J* 12, 2 Hz, H3″), 6.55 (1 H, s, H5), 5.83 (1 H, dt, *J* 12, 6.5, H2″), 3.43 (4 H, m, H2′, H6′), 3.31 (2 H, dd, *J* 6.5, 2, H1″), 2.54 (4 H, m, H3′, H5′). δ_C (75 MHz; [D_6]acetone) 164.0, 155.0, 143.4, 143.0, 138.1, 132.8, 132.0, 131.0, 130.8, 129.9, 129.1, 128.5, 127.8, 127.0, 124.6, 123.5, 123.4, 121.4, 121.2, 59.9, 53.8, 48.3. ESI mass spectrum m/z 429.4.

*8-Chloro-11-[4-(3-phenyl-2-propynyl)piperazino]-5*H*-dibenzo[*b,e*][1,4]diazepine (17)*

1-(3-Phenylprop-2-yn-1-yl)piperazine (0.615 g, 3.07 mmol) in anhydrous anisole (5 mL) was treated with a solution of titanium tetrachloride in toluene (1.0 M, 0.67 mL, 0.67 mmol), followed by a solution of 8-chloro-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (7) (150 mg, 0.613 mmol) in dry anisole (10 mL) and worked up as described in the preparation of (8). The residue was purified using flash chromatography (ethyl acetate/hexane; 1 : 1) and the product (17) was recrystallized from dichloromethane/hexane as pale yellow microneedles (115 mg, 44%), mp 139.5–141°C (Found: C 73.2, H 5.5, N 13.1%. $C_{26}H_{23}ClN_4$ requires C 73.1, H 5.4, N 13.1%). ν_{max} (KBr)/cm^{-1} 3364, 1600, 1560. λ_{max} ($\log_{10}$ ε)/nm 234 (4.59), 239 (4.60), 251 (4.51), 297 (4.04). δ_H (300 MHz; [D_6]acetone) 7.49–7.42 (2 H, m, H2‴, H6‴), 7.37–7.28 (5 H, m, H1, H3, H3‴, H4‴, H5‴), 7.08 (1 H, br d, *J* 8, H4), 7.03 (1 H, m, H2), 6.96 (1 H, d, *J* 2.5 Hz, H9), 6.89 (1 H, d, *J* 8.5, H6), 6.82 (1 H, dd, *J* 8.5, 2.5 Hz, H7), 6.56 (1 H, s, H5), 3.58 (2 H, s, H1″), 3.46 (4 H, m, H2′, H6′), 2.71 (4 H, m, H3′, H5′). δ_C (75 MHz; [D_6]acetone) 164.0, 155.0, 143.4, 142.9, 132.9, 132.5, 131.0, 129.4, 129.1, 128.6, 127.0, 124.6, 124.2, 123.54, 123.48, 121.4, 121.2, 85.9, 85.8, 52.4, 48.2, 48.0. ESI mass spectrum m/z 427.4.

General Procedure for the Preparation of Aldehydes

Pyridinium chlorochromate (1 mole equivalent) was ground with silica gel (1 weight equivalent) using a mortar and pestle, and the resulting free-running light orange solid was suspended in dichloromethane (200 mL) at room temperature. To the stirred suspension was added a solution of the phenylalkanol (10.0 g) in dichloromethane (10 mL) and stirring maintained for 3 h. The mixture was filtered (celite) and the brown granular residue washed with dichloromethane (2 × 500 mL). The resulting filtrate was concentrated under vacuum, the residue taken up in dichloromethane (10 mL), filtered through a silica gel plug, and the residue washed with dichloromethane. The combined filtrate was concentrated under vacuum to yield an oil. Vacuum distillation afforded the title compound as a colourless liquid, unless otherwise indicated. Aldehydes (20a)–(20c) were prepared in this manner.

5-Phenylpentanal (20a).[23,24] (7.84 g, 79%), bp 84–86°C (0.4 mmHg) [lit.[25] bp 129–131°C (10 mmHg)]. δ_H (300 MHz; [D_6]acetone) 9.69 (1 H, t, *J* 2, H1), 7.29−7.21 (2 H, m, H3′, H5′), 7.11–7.20 (3 H, m, H2′, H4′, H6′), 2.60 (t, *J* 7.5 Hz, 2H, H5), 2.38 (2 H, dt, *J* 7.5, 1.5, H2), 1.69–1.58 (m, 4H, H3, H4). δ_C (75 MHz; [D_6]acetone) 202.5, 141.9, 128.4, 128.3, 125.8, 43.7, 35.6, 30.8, 21.7. ESI mass spectrum m/z 509.5 ($3M + Na^+$).

7-Phenylheptanal (20b).[26] (7.61 g, 77%), bp 125–130°C (0.25 mmHg). δ_H (300 MHz; [D_6]acetone) 9.73 (1 H, t, *J* 2, H1), 7.30−7.21 (2 H, m, H3′, H5′), 7.19−7.11 (3 H, m, H2′, H4′, H6′), 2.59 (2 H, t, *J* 7.5, H7), 2.39 (2 H, dt, *J* 7.5, 2, H2), 1.70−1.55 (4 H, m, H3, H6), 1.40−1.30 (4 H, m, H4, H5). δ_C (75 MHz; [D_6]acetone) 203.0, 142.8, 128.6, 128.4, 125.8, 44.0, 36.0, 31.4, 29.2, 29.1, 22.2. EI mass spectrum m/z 190.2.

10-Phenyldecanal (20c).[27] (6.13 g, 62%), bp 130–134°C (0.4 mmHg) that solidified on standing. δ_H (300 MHz; [D_6]acetone) 9.71 (1 H, t, *J* 2, H1), 7.28−7.20 (2 H, m, H3′, H5′), 7.17−7.10 (3 H, m, H2′, H4′, H6′), 2.58 (2 H, t, *J* 7.5, H10), 2.36 (2 H, dt, *J* 7.5, 2, H2), 1.67–1.53 (4 H, m, H3, H9), 1.37−1.23 (10 H, m, H4, H5, H6, H7, H8). δ_C (75 MHz; [D_6]acetone) 202.6, 143.0, 128.5, 128.4, 125.7, 44.0, 36.1, 31.6, 29.54, 29.46 (2 × CH_2), 29.4, 29.3, 22.2. EI mass spectrum m/z 232.2.

General Procedure for the Preparation of (22a)–(22c)

To a stirred solution of 8-chloro-11-piperazino-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (21) (250 mg, 0.799 mmol) in dry 1,2-dichloroethane (20 mL) under nitrogen was added the phenylalkanal (20a–c) (1.05 equivalents) in 1,2-dichloroethane (5 mL) followed by sodium triacetoxyborohydride (1.4 equivalents). Stirring was maintained for 2 h after which aqueous hydrochloric acid (2 M, 30 mL) was added to produce a bright yellow/orange precipitate (gum-like, sparingly soluble in water). The organic layer was separated and discarded and the aqueous layer washed with dichloromethane (2 × 25 mL). The aqueous layer and precipitate were combined, adjusted to pH 14 by the addition of solid potassium hydroxide then extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with water (30 mL), dried over dried magnesium sulfate, and then concentrated under vacuum. The resulting oil was purified using flash chromatography and the major product

evaporated to dryness. Where appropriate, the residual solid was recrystallized from a suitable solvent system. Amidines (22a)–(22c) were prepared in this manner.

*8-Chloro-11-[4-(5-phenylpentyl)piperazino]-5*H*-dibenzo[*b,e*][1,4]-diazepine (22a).* Column chromatography (ethyl acetate/hexane; 2 : 3) gave the title compound, which recrystallized from dichloromethane/hexane as yellow microprisms (201 mg, 55%), mp 60°C (softens), 110°C (melts) (Found: C 72.9, H 7.2, N 11.8%. $C_{28}H_{31}ClN_4$ requires C 73.3, H 6.8, N 12.2%). ν_{max} (KBr)/cm^{-1} 3316, 2944, 1616, 1566. λ_{max} ($\log_{10}\varepsilon$)/nm 229 (4.39), 261 (4.20), 297 (4.00). δ_H (300 MHz; [D$_6$]acetone) 7.37−7.11 (7 H, m, H1, H3, H2‴, H3‴, H4‴, H5‴, H6‴), 7.07 (1 H, dd, *J* 8, 1, H4), 7.02 (1 H, app td, *J* 7.5, 1, H2), 6.93 (1 H, d, *J* 2.5, H9), 6.87 (1 H, d, *J* 8.5, H6), 6.80 (1 H, dd, *J* 8.5, 2.5, H7), 6.51 (1 H, s, H5), 3.39 (4 H, m, H2′, H6′), 2.62 (2 H, t, *J* 7.5, H5″), 2.49 (4 H, m, H3′, H5′), 2.36 (t, *J* 7, 2H, H1″), 1.66 (2 H, app p, *J* 7.5, H4″), 1.54 (2 H, app p, *J* 7, H2″), 1.39 (m, 2H, H3″). δ_C (75 MHz; [D$_6$]acetone) 164.1, 155.1, 143.7, 143.6, 143.0, 132.8, 131.1, 129.3, 129.2, 128.7, 127.1, 126.5, 124.8, 123.50, 123.45, 121.4, 121.2, 59.2, 54.0, 48.4, 36.6, 32.2, 27.9, 27.6. ESI mass spectrum *m*/*z* 459.4.

*8-Chloro-11-[4-(7-phenylheptyl)piperazino]-5*H*-dibenzo[*b,e*][1,4]-diazepine (22b).* Column chromatography (ethyl acetate/hexane; 2 : 1) gave the title compound, which recrystallized from methanol/water as bright yellow microcrystals (225 mg, 58%), mp 62°C (softens), 90°C (melts) (Found: C 74.1, H 7.4, N 11.4%. $C_{30}H_{35}ClN_4$ requires C 74.0, H 7.2, N 11.5%). ν_{max} (KBr)/cm^{-1} 3320, 2936, 1614, 1566. λ_{max} ($\log_{10}\varepsilon$)/nm 229 (4.41), 261 (4.23), 297 (4.03). δ_H (300 MHz; [D$_6$]acetone) 7.36–7.10 (7 H, m, H1, H3, H2‴, H3‴, H4‴, H5‴, H6‴), 7.06 (1 H, br d, *J* 8, H4), 7.01 (1 H, app t, *J* 7.5, H2), 6.94 (1 H, d, *J* 2.5, H9), 6.87 (1 H, d, *J* 8.5, H6), 6.80 (1 H, dd, *J* 8.5, 2.5, H7), 6.47 (1 H, s, H5), 3.39 (4 H, m, H2′, H6′), 2.61 (2 H, t, *J* 7.5, H7″), 2.48 (4 H, m, H3′, H5′), 2.35 (2 H, t, *J* 7, H1″), 1.62 (2 H, app p, *J* 7, H6″), 1.49 (2 H, app p, *J* 7, H2″), 1.42–1.28 (6 H, m, H3″, H4″, H5″). δ_C (75 MHz; [D$_6$]acetone) 164.1, 155.1, 143.8, 143.6, 143.0, 132.8, 131.1, 129.3, 129.2, 128.7, 127.1, 126.5, 124.8, 123.50, 123.45, 121.4, 121.3, 59.3, 54.0, 48.4, 36.6, 32.4, 30.2, 30.0, 28.2, 27.7. ESI mass spectrum *m*/*z* 487.4.

*8-Chloro-11-[4-(10-phenyldecyl)piperazino]-5H-dibenzo[*b,e*][1,4]-diazepine (22c).* Column chromatography (ethyl acetate/hexane; 2 : 1) gave the title compound as a bright yellow oil that solidified on standing (289 mg, 68%), mp 80.5–82°C (Found: C 75.0, H 8.0, N 10.5%. $C_{33}H_{41}ClN_4$ requires C 74.9, H 7.8, N 10.6%). ν_{max} (KBr)/cm^{-1} 3364, 2932, 1608, 1566. λ_{max} ($\log_{10}\varepsilon$)/nm 228 (4.42), 261 (4.24), 296 (4.03). δ_H (300 MHz; [D$_6$]acetone) 7.36−7.11 (7 H, m, H1, H3, H2‴, H3‴, H4‴, H5‴, H6‴), 7.06 (1 H, br d, *J* 8, H4), 7.01 (1 H, app td, *J* 8, 1, H2), 6.94 (1 H, d, *J* 2, H9), 6.87 (1 H, d, *J* 8, H6), 6.80 (1 H, dd, *J* 8, 2, H7), 6.51 (1 H, s, H5), 3.39 (4 H, m, H2′, H6′), 2.61 (2 H, t, *J* 7.5, H10″), 2.48 (4 H, m, H3′, H5′), 2.35 (2 H, t, *J* 7, H1″), 1.62 (2 H, app p, *J* 7, H9″), 1.49 (2 H, app p, *J* 7, H2″), 1.41–1.26 (12 H, m, H3″, H4″, H5″, H6″, H7″, H8″). δ_C (75 MHz; [D$_6$]acetone) 164.0, 155.0, 143.6, 143.5, 142.8, 132.7, 131.0, 129.2, 129.1, 128.6, 127.1, 126.4, 124.7, 123.4, 123.3, 121.3, 121.2, 59.3, 53.9, 48.3, 36.6, 32.4, 30.4, 30.34 (2 × CH$_2$), 30.25, 30.1, 28.2, 27.7. ESI mass spectrum *m*/*z* 529.5.

1-[2-(Benzyloxy)ethyl]piperazine (24a)

Benzyl 2-bromoethyl ether (23a) (0.85 g, 3.95 mmol) in toluene (20 mL) was treated with piperazine (1.60 g, 18.6 mmol) and worked up as described in the preparation of (6). The crude product was purified using flash chromatography (chloroform/methanol/25% aqueous ammonia solution; 19 : 1 : 0.1) affording a pale yellow oil that solidified upon standing forming waxy needles (0.67 g, 77%), mp 30–34°C. δ_H (300 MHz; $CDCl_3$) 7.34–7.26 (5 H, m, H2″, H3″, H4″, H5″, H6″), 4.54 (2 H, s, H4′), 3.59 (2 H, t, *J* 6, H2′), 2.90 (4 H, m, H3, H5), 2.60 (2 H, t, *J* 6, H1′), 2.46 (4 H, m, H2, H6), 1.56 (1 H, br s, H4). δ_C (75 MHz; $CDCl_3$) 138.5, 128.5, 127.8, 127.7, 73.2, 67.7, 58.7, 55.1, 46.2. ESI mass spectrum *m*/*z* 221.2.

1-[3-(Benzyloxy)propyl]piperazine (24b)

Benzyl 3-bromopropyl ether (23b) (1.17 g, 5.09 mmol) in toluene (30 mL) was treated with piperazine (1.76 g, 20.4 mmol) and worked up as described in the preparation of (6). The crude product was purified using flash chromatography (chloroform/methanol/25% aqueous ammonia solution; 19 : 1 : 0.1) affording a pale yellow oil that solidified upon standing, forming waxy needles (0.99 g, 82%), mp 54–56°C. δ_H (300 MHz; $CDCl_3$ and D_2O) 7.34–7.25 (5 H, m, H2″, H3″, H4″, H5″, H6″), 4.66 (2 H, s, H5′), 3.51 (2 H, t, *J* 6.5, H3′), 2.86 (4 H, t, *J* 5, H3, H5), 2.41 (6 H, m, H2, H6, H1′), 1.81 (2 H, app p, *J* 7, H2′). δ_C (75 MHz; $CDCl_3$) 138.5, 128.2, 127.5, 127.4, 72.8, 68.6, 56.0, 54.5, 46.0, 26.9. ESI mass spectrum *m*/*z* 235.2.

*11-{4-[2-(Benzyloxy)ethyl]piperazino}-8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepine (25a)*

1-[2-(Benzyloxy)ethyl]piperazine (24a) (0.650 g, 2.95 mmol) in anhydrous anisole (5 mL) was treated with a solution of titanium tetrachloride in toluene (1.0 M, 0.75 mL, 0.75 mmol), followed by a solution of lactam (7) (180 mg, 0.738 mmol) in dry anisole (10 mL) and worked up as described in the preparation of (8). The product was purified using flash chromatography (ethyl acetate) and recrystallized from methanol/water as yellow platelets (119 mg, 36%), mp 154–155°C (Found: C 69.7, H 6.0, N 12.1%. $C_{26}H_{27}ClN_4O$ requires C 69.9, H 6.1, N 12.5%). ν_{max} (KBr)/cm^{-1} 3326, 1610, 1563. λ_{max} (log ε)/nm 229 (4.34), 260 (4.17), 297 (3.97). δ_H (300 MHz; $CDCl_3$) 7.34–7.23 (7 H, m, H1, H3, H2‴, H3‴, H4‴, H5‴, H6‴), 7.05 (1 H, d, *J* 2.5, H9), 6.99 (1 H, m, H2), 6.79 (2 H, dd, *J* 8, 2.5, H4, H7), 6.58 (1 H, d, *J* 8.5, H6), 4.87 (1 H, s, H5), 4.54 (2 H, s, H4″), 3.61 (2 H, t, *J* 5.5, H2″), 3.47 (4 H, m, H2′, H6′), 2.67 (2 H, t, *J* 5.5, H1″), 2.59 (4 H, m, H3′, H5′). δ_C (75 MHz; $CDCl_3$) 162.9, 152.9, 142.0, 140.5, 138.5, 132.0, 130.4, 129.2, 128.5, 127.9, 127.8, 126.9, 123.6, 123.1 (2 × CH), 120.2, 120.1, 73.3, 67.7, 58.1, 53.6, 47.4. ESI mass spectrum *m*/*z* 447.2.

*11-{4-[3-(Benzyloxy)propyl]piperazino}-8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepine (25b)*

A mixture of phosphorus pentachloride (199 mg, 0.957 mmol) and lactam (7) (213 mg, 0.870 mmol) in dry dichloromethane (20 mL) was heated at reflux for 1 h. The solvent was removed under vacuum and the residue was azeotroped twice with benzene and evaporated to dryness. The crude iminochloride (20) was dissolved in anhydrous 1,4-dioxan (15 mL) and treated with 1-[3-(benzyloxy)propyl]piperazine (24b) (398 mg, 1.70 mmol) in anhydrous 1,4-dioxan (5 mL). The reaction mixture was heated at reflux for 16 h, then cooled and evaporated to dryness. The dark red-brown residue was partitioned between ethyl acetate and aqueous hydrochloric acid solution (2 M, 20 mL) and the organic layer extracted with aqueous hydrochloric acid solution (2 M, 3 × 20 mL). The aqueous fraction was made alkaline with ammonia solution (25%, 20 mL) and the product was extracted with ethyl acetate (3 × 20 mL), washed with water, dried over dried magnesium sulfate, and evaporated to dryness. The product was purified using flash chromatography (ethyl acetate) affording (25b) as a yellow oil (136 mg, 34%). ν_{max} (KBr)/cm^{-1} 3304, 1605, 1564. λ_{max} (log ε)/nm 227 (4.36), 259 (4.20), 290 (3.92). δ_H (300 MHz; $CDCl_3$) 7.35–7.20 (7 H, m, H1, H3, H2‴, H3‴, H4‴, H5‴, H6‴), 7.06 (1 H, d, *J* 2.5, H9), 6.99 (1 H, m H2), 6.80 (2 H, m, H4, H7), 6.60 (1 H, d, *J* 8.5, H6), 4.87 (1 H, s, H5), 4.51 (2 H, s, H5″), 3.53 (4 H, m, H2′, H6′), 3.46 (2 H, br s, H3″), 2.50 (6 H, m, H1″, H3′, H5′), 1.84 (2 H, app p, *J* 7.5, H2″). δ_C (75 MHz; $CDCl_3$) 162.9, 152.9, 142.0, 140.5, 138.7, 132.0, 130.4, 129.2, 128.5, 127.7, 127.6, 126.9, 123.6, 123.1 (2 × CH), 120.2, 120.1, 73.0, 68.7, 55.6, 53.3, 47.4, 27.6. ESI high-resolution mass spectrum (Found: *m*/*z* 461.210. Calc. for $C_{27}H_{30}ClN_4O$: *m*/*z* 461.211). The title compound was converted into the hydrochloride salt by treatment with 3 M hydrogen chloride in ethyl acetate, evaporated to dryness, and then analyzed chromatographically. HPLC (λ 254 nm) t_R 10.18 min (isocratic), t_R 25.30 min (gradient).

2-(Benzo[1,3]dioxol-5-yl)ethanol (27)

The title compound was prepared according to the procedure of Semmelhack et al.[6] from 3,4-methylenedioxyphenylacetic acid (26). Following workup, the resulting pale yellow oil was purified using flash chromatography (ether/hexane; 1 : 1) to afford the alcohol as a colourless oil (1.25 g, 90%) which was used in the following reaction without

further purification. δ_H (300 MHz; $CDCl_3$) 6.74 (1 H, d, *J* 8, H7′), 6.71 (1 H, d, *J* 1.5, H4′), 6.66 (1 H, dd, *J* 8, 1.5, H6′), 5.91 (2 H, s, H2′), 3.79 (2 H, t, *J* 6.5, H1), 2.77 (2 H, t, *J* 6.5, H2), 1.68 (1 H, br s, OH). δ_C (75 MHz; $CDCl_3$) 148.0, 146.3, 132.4, 122.1, 109.5, 108.5, 101.0, 63.9, 39.0. ESI mass spectrum *m*/*z* 166.9.

2-(Benzo[1,3]dioxol-5-yl)ethanal (28)

2-(1,3-Benzodioxol-5-yl)ethanol (27) (0.500 g, 3.01 mmol) in dichloromethane (25 mL) was treated with a finely ground mixture of pyridinium chlorochromate (0.973 g, 4.51 mmol) and silica gel (0.973 g) and worked up as for the preparation of (20a)–(20c) to give the title compound (28) (0.404 g, 82%) as a pale yellow liquid[7] which was used in the following reaction without further purification. δ_H (300 MHz; CD_2Cl_2) 9.66 (1 H, t, *J* 2, H1), 6.78 (1 H, d, *J* 8, H7′), 6.67 (1 H, d, *J* 1.5, H4′), 6.64 (1 H, dd, *J* 8, 1.5, H6′), 5.92 (2 H, s, H2′), 3.56 (2 H, d, *J* 2 Hz, H2). δ_C (75 MHz; CD_2Cl_2) 199.7, 148.7, 147.5, 126.3, 123.3, 110.4, 109.0, 101.8, 50.5. EI mass spectrum *m*/*z* 164.0.

*11-{4-[2-(Benzo[1,3]dioxol-5-yl)ethyl]piperazino}-8- chloro-5*H*-dibenzo[*b*,e][1,4]diazepine (29)*

8-Chloro-11-piperazino-5*H*-dibenzo[*b*,*e*][1,4]diazepine (21) (250 mg, 0.799 mmol) in dry 1,2-dichloroethane (20 mL) under nitrogen was treated with 2-(1,3-benzodioxol-5-yl)ethanal (28) (138 mg, 0.839 mmol) in 1,2-dichloroethane (5 mL) followed by sodium triacetoxyborohydride (237 mg, 1.12 mmol) and worked up as for the preparation of (22a)–(22c). The residue was purified using flash chromatography (ethyl acetate/hexane; 2 : 1) and the product (29) recrystallized from dichloromethane/hexane as bright yellow prisms (151 mg, 41%), mp 156–157.5°C (Found: C 67.4, H 5.5, N 11.9%. $C_{26}H_{25}ClN_4O_2$ requires C 67.7, H 5.5, N 12.2%). ν_{max} (KBr)/cm^{-1} 3292, 1600, 1562. λ_{max} ($\log_{10}$ ε)/nm 231 (4.49), 262 (4.26), 290 (4.18). δ_H (300 MHz; [D_6]acetone) 7.33 (1 H, ddd, *J* 8, 7.5, 1.5, H3), 7.29 (1 H, dd, *J* 7.5, 1.5, H1), 7.07 (1 H, dd, *J* 8, 1, H4), 7.02 (1 H, app td, *J* 7.5, 1, H2), 6.95 (1 H, d, *J* 2.5, H9), 6.88 (1 H, d, *J* 8.5, H6), 6.83–6.78 (2 H, m, H7, H4‴), 6.74 (1 H, dd, *J* 8, 0.5, H7‴), 6.70 (1 H, dd, *J* 8, 1.5, H6‴), 6.52 (1 H, s, H5), 5.93 (2 H, s, H2‴), 3.41 (4 H, m, H2′, H6′), 2.73 (2 H, m, H2″), 2.52–2.62 (6 H, m, H3′, H5′, H1″). δ_C (75 MHz; [D_6]acetone) 164.0, 155.0, 148.6, 146.8, 143.5, 142.9, 135.5, 132.8, 131.0, 128.6, 127.0, 124.7, 123.5, 123.4, 122.4, 121.4, 121.2, 110.0, 108.4, 101.7, 61.3, 53.8, 48.3, 33.9. ESI mass spectrum *m*/*z* 461.3.

*2-(1*H*-Indol-3-yl)ethanal (31a)*

The title compound was prepared according to the procedure of Schlecht et al.[8] from L-tryptophan. The product was purified by flash chromatography (ethyl acetate/hexane; 2 : 5) affording the aldehyde as a yellow oil (491 mg, 42%) which was used in a subsequent reaction without further purification. ν_{max} (KBr)/cm^{-1} 3430, 1722. δ_H (300 MHz; [D_6]acetone) 10.18 (1 H, br s, H1′), 9.70 (1 H, t, *J* 2.5, H1), 7.52 (1 H, m, H4′), 7.42 (1 H, app dt, *J* 8, 1, H7′), 7.32 (1 H, br d, *J* 2.5, H2′), 7.13 (1 H, m, H6′), 7.04 (1 H, ddd, *J* 8, 7, 1, H5′), 3.79 (2 H, br d, *J* 2.5, H2). δ_C (75 MHz; [D_6]acetone) 200.1, 136.9, 128.0, 124.2, 122.9, 120.3, 119.0, 111.9, 106.7, 40.9. EI mass spectrum *m*/*z* 159.1.

*2-(5-Methoxy-1*H*-indol-3-yl)ethanal (31b)*

The title aldehyde was prepared from 5-methoxy-DL-tryptophan according to the procedure previously described.[8] The product was purified by flash chromatography (ethyl acetate/hexane; 1 : 3) to afford the aldehyde (31b) as a yellow oil (139 mg, 34%) which was used in a subsequent reaction without further purification. ν_{max} (NaCl)/cm^{-1} 3428, 1718. δ_H (300 MHz; CD_2Cl_2) 9.71 (1 H, t, *J* 2.5, H1), 8.31 (1 H, br s, H1′), 7.23 (1 H, d, *J* 9, H7′), 7.07 (1 H, br d, *J* 2.5, H2′), 6.93 (1 H, d, *J* 2.5, H4′), 6.83 (1 H, dd, *J* 9, 2.5, H6′), 3.80 (3 H, s, OCH_3), 3.73 (2 H, br d, *J* 2.5, H2). δ_C (75 MHz; CD_2Cl_2) 200.2, 154.9, 132.0, 128.5, 125.0, 113.1, 112.7, 106.3, 100.7, 56.3, 40.9. EI mass spectrum *m*/*z* 189.1.

*8-Chloro-11-{4-[(1*H*-indol-3- yl)ethyl]piperazino)-5*H*-dibenzo[*b*,e][1,4]diazepine (32a)*

8-Chloro-11-piperazino-5*H*-dibenzo[*b*,*e*][1,4]diazepine (21) (180 mg, 0.575 mmol) in dry 1,2-dichloroethane (20 mL) under nitrogen was treated with 2-(1*H*-indol-3-yl)ethanal (31a) (101 mg, 0.633 mmol) in 1,2-dichloroethane (5 mL) followed by sodium triacetoxyborohydride (183 mg, 0.863 mmol) and worked up as for the preparation of (22a)–(22c). The residue was purified using flash chromatography (ethyl acetate) and the product recrystallized from dichloromethane/hexane as yellow prisms (184 mg, 70%), mp 130–132°C (Found: C 71.2, H 5.7, N 15.3%. $C_{27}H_{26}ClN_5$ requires C 71.1, H 5.7, N 15.4%). ν_{max} (KBr)/cm^{-1} 3448, 1600, 1556. λ_{max} ($\log_{10}$ ε)/nm 223 (4.63), 264 (4.27), 292 (4.17). δ_H (300 MHz; [D_6]acetone) 9.93 (1 H, br s, H1‴), 7.58 (1 H, m, H4‴), 7.27–7.39 (3 H, m, H3, H1, H7‴), 7.19 (1 H, m, H2‴), 6.97–7.11 (4 H, m, H2, H4, H5‴, H6‴), 6.96 (1 H, d, *J* 2.5, H9), 6.88 (1 H, d, *J* 8.5, H6), 6.80 (1 H, dd, *J* 8.5, 2.5, H7), 6.52 (1 H, s, H5), 3.45 (4 H, m, H2′, H6′), 2.96 (2 H, m, H2″), 2.71 (2 H, m, H1″), 2.63 (4 H, m, H3′, H5′). δ_C (75 MHz; [D_6]acetone) 164.1, 155.0, 143.5, 142.9, 137.8, 132.8, 131.1, 128.8, 128.6, 127.0, 124.7, 123.48, 123.45, 123.2, 122.1, 121.4, 121.2, 119.40, 119.39, 114.5, 112.1, 60.2, 53.9, 48.4, 23.8. ESI mass spectrum *m*/*z* 456.3.

*8-Chloro-11-{4-[2-(5-methoxy-1*H*-indol-3- yl)ethyl]piperazino)-5*H*-dibenzo[*b*,e][1,4]diazepine (32b)*

8-Chloro-11-piperazino-5*H*-dibenzo[*b*,*e*][1,4]diazepine (21) (203 mg, 0.649 mmol) in dry 1,2-dichloroethane (20 mL) under nitrogen was treated with 2-(5-methoxy-1*H*-indol-3-yl)ethanal (31b) (135 mg, 0.713 mmol) in 1,2-dichloroethane (5 mL) followed by sodium triacetoxyborohydride (206 mg, 0.973 mmol) and worked up as for the preparation of (22a)–(22c). The residue was purified using flash chromatography (ethyl acetate) using the technique of solid addition and the product recrystallized from methanol/water as yellow microprisms (191 mg, 61%), mp 255–257°C (Found: C 67.2, H 5.9, N 13.2%. $C_{28}H_{28}ClN_5O \cdot CH_3OH$ requires C 67.2, H 6.2, N 13.5%). ν_{max} (KBr)/cm^{-1} 3432, 3300, 1598, 1554. λ_{max} ($\log_{10}$ ε)/nm 226 (4.73), 263 (4.38), 297 (4.23). δ_H (300 MHz; [D_6]acetone) 9.78 (1 H, br s, H1‴), 7.37–7.29 (2 H, m, H1, H3), 7.25 (1 H, d, *J* 9, H7‴), 7.16 (1 H, br s, H2‴), 7.09 (1 H, m, H4‴), 7.07 (1 H, m H4), 7.03 (1 H, m, H2), 6.95 (1 H, d, *J* 2.5, H9), 6.88 (1 H, d, *J* 8.5, H6), 6.81 (1 H, dd, *J* 8.5, 2.5, H7), 6.75 (1 H, dd, *J* 9, 2.5, H6‴), 6.53 (1 H, s, H5), 3.81 (3 H, s, OCH_3), 3.42 (4 H, m, H2′, H6′), 2.93 (2 H, m, H2″), 2.71 (2 H, m, H1″), 2.64 (4 H, m, H3′, H5′). δ_C (75 MHz; [D_6]DMSO) 162.7, 154.0, 152.9, 142.1, 141.9, 131.9, 131.3, 129.8, 127.5, 126.6, 125.5, 123.1, 123.0, 122.4, 122.2, 120.5, 120.3, 112.2, 111.9, 110.9, 100.2, 58.7, 55.4, 52.5, 46.9, 23.3. ESI mass spectrum *m*/*z* 486.3.

*4-{2-[4-(8-Chloro-5*H*-dibenzo[*b*,e][1,4]diazepin-11-yl)piperazino]ethyl}benzene-1,2-diol (33)*

To a solution of 11-[4-(1,3-benzodioxol-5-ylethyl)piperazino]-8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepine (29) (50 mg, 0.108 mmol) in anhydrous dichloromethane (10 mL) at room temperature was added a solution of boron tribromide in dichloromethane (1.0 M, 1.08 mL, 1.08 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 (25 mL) and ethyl acetate (25 mL) and the aqueous layer extracted with ethyl acetate (2 × 25 mL). The organic fractions were pooled, washed with water (50 mL), brine (50 mL), dried over dried magnesium sulfate, and then evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate/methanol; 40 : 1). The column fractions were combined, then evaporated to dryness affording the title compound (33) as a pale yellow foam (33 mg, 68%) (Found: C 52.9, H 5.3, N 9.5%. $C_{25}H_{25}ClN_4O_2 \cdot 2HCl \cdot 2½H_2O$ requires C 53.0, H 5.7, N 9.9%). ν_{max} (KBr)/cm^{-1} 3600–3000, 3368, 1600, 1560. λ_{max} ($\log_{10}$ ε)/nm 228 (4.47), 262 (4.22), 291 (4.08). δ_H (300 MHz; [D_4]methanol) 7.32 (1 H, app td, *J* 7.5, 1.5, H3‴), 7.26 (1 H, dd, *J* 7.5, 1.5, H1‴), 6.98–7.02 (2 H, m, H2‴, H4‴), 6.96 (1 H, d, *J* 2.5, H9‴), 6.83 (1 H, dd, *J* 8.5,

2.5, H7‴), 6.78 (1 H, d, *J* 8.5, H6‴), 6.69 (1 H, d, *J* 8, H6), 6.66 (1 H, d, *J* 2, H3), 6.53 (1 H, dd, *J* 8, 2, H5), 3.43 (4 H, m, H2″, H6″), 2.52–2.73 (8H, m, H1′, H2′, H3″, H5″). δ_C (75 MHz; [D_4]methanol) 165.4, 155.6, 146.4, 144.8, 143.7, 143.2, 133.5, 132.8, 131.5, 129.6, 127.3, 124.6, 124.5, 124.0, 121.6, 121.4, 121.0, 117.0, 116.6, 61.9, 54.1, 48.3, 33.5. ESI high-resolution mass spectrum (Found: *m*/*z* 449.1730. Calc. for $C_{25}H_{26}ClN_4O_2$: *m*/*z* 449.1744).

*8-Chloro-11-{4-[(5-hydroxy-1*H*-3-indolyl)ethyl]piperazino)-5*H*-dibenzo[*b,e*][1,4]diazepine (34)*

8-Chloro-11-{4- [2- (5-methoxy-1*H*-indol-3-yl)ethyl] piperazino)-5*H*-dibenzo[*b*,*e*]-[1,4]diazepine (32b) (60 mg, 0.123 mmol) in anhydrous dichloromethane (10 mL) was treated with a solution of boron tribromide in dichloromethane (1.0 M, 1.23 mL, 1.23 mmol) and worked up as for the preparation of (33). The resulting residue was purified using flash chromatography (ethyl acetate/methanol; 20 : 1) to afford the product as a tan foam (42 mg, 72%). ν_{max} (KBr)/cm^{-1} 3442, 3368, 1601, 1561. λ_{max} ($\log_{10}$ ε)/nm 227 (4.53), 260 (4.21), 300 (4.13). δ_H (300 MHz; [D_4]methanol) 7.34 (1 H, app td, *J* 8, 1.5, H3), 7.28 (1 H, dd, *J* 7.5, 1.5, H1), 7.16 (1 H, d, *J* 8.5, H7‴), 7.07–6.98 (3 H, m, H2, H4, H2‴), 6.97 (1 H, d, *J* 2.5, H9), 6.94 (1 H, d, *J* 2.5, H4‴), 6.85 (1 H, dd, *J* 8.5, 2.5, H7), 6.80 (1 H, d, *J* 8.5, H6), 6.68 (1 H, dd, *J* 8.5, 2.5, H6‴), 3.51 (4 H, m, H2′, H6′), 2.96 (2 H, m, H2″), 2.87 (2 H, m, H1″), 2.82 (4 H, m, H3′, H5′). δ_C (75 MHz; [D_4]methanol) 165.2, 155.6, 151.4, 143.7, 143.1, 133.7, 133.3, 131.5, 129.6, 129.4, 127.4, 124.8, 124.4, 124.3, 124.1, 121.7, 121.5, 112.9, 112.6, 112.3, 103.6, 60.2, 53.9, 47.9, 23.3. ESI high-resolution mass spectrum (Found: *m*/*z* 472.1883. Calc. for $C_{27}H_{27}ClN_5O$: *m*/*z* 472.1904). The title compound was converted into the hydrochloride salt by treatment with 3 M hydrogen chloride in ethyl acetate, evaporated to dryness, and then analyzed chromatographically. HPLC (λ 260 nm) t_R 2.80 min (isocratic), t_R 19.07 min (gradient).

*4-[-4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)piperazino]-1-(4-fluorophenyl)-1-butanone (36)*

To a stirred solution of 8-chloro-11-piperazino-5*H*-dibenzo[*b*,*e*][1,4]-diazepine (21) (150 mg, 0.480 mmol), triethylamine (97.2 mg, 130 μL 0.960 mmol) and sodium iodide (72 mg, 0.480 mmol) in dry 1,2-dimethoxyethane (20 mL) was added to commercial 4-chloro-4′-fluorobutyrophenone (160 μL, 0.960 mmol). The mixture was heated at reflux for 24 h, concentrated under reduced pressure, and the resulting oily residue acidified with aqueous hydrochloric acid (2 M, 25 mL) to produce a pale yellow precipitate. The aqueous mixture was warmed and stirred until dissolution was complete, and then washed with dichloromethane (3 × 25 mL). The aqueous layer was adjusted to pH 10 by the addition of solid potassium bicarbonate, and then extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with water (25 mL), dried over dried magnesium sulfate, and then concentrated under vacuum. The resulting residue was purified using flash chromatography (ethyl acetate) to afford the product as a pale yellow foam (62 mg, 27%) (Found: C 68.0, H 5.6, N 11.4%. $C_{27}H_{26}ClFN_4O$ requires C 68.0, H 5.5, N 11.7%). ν_{max} (KBr)/cm^{-1} 3352, 1677, 1599, 1563. λ_{max} ($\log_{10}$ ε)/nm 235 (4.48), 258 (4.32), 295 (4.02). δ_H (300 MHz; [D_6]acetone) 8.10 (2 H, m, H2‴, H6‴), 7.33 (1 H, app td, *J* 7.5, 1.5, H3″), 7.29–7.21 (3 H, m, H1″, H3‴, H5‴), 7.06 (1 H, br d, *J* 8, H4″), 7.01 (1 H, app td, *J* 7.5, 1, H2″), 6.93 (1 H, d, *J* 2.5, H9″), 6.87 (1 H, d, *J* 8.5, H6″), 6.80 (1 H, dd, *J* 8.5, 2.5, H7″), 6.51 (1 H, s, H5″), 3.34 (4 H, m, H3′, H5′), 3.07 (2 H, t, *J* 7, H2), 2.50 (4 H, m, H2′, H6′), 2.45 (1 H, t, *J* 7, H4), 1.93 (2 H, app p, *J* 7, H3). δ_C (75 MHz; [D_6]acetone) 198.8 (C═O), 166.4 (d, *J* 252, CF), 164.0, 154.0, 143.5, 142.9, 135.3, 132.8, 131.8 (d, *J* 9, CH), 131.0, 128.6, 127.0, 124.7, 123.5, 123.4, 121.4, 121.2, 116.3 (d, *J* 22, CH), 58.3, 53.8, 48.2, 36.6, 22.5. ESI mass spectrum *m*/*z* 477.2.

*11-[4-(2-Adamantyl)piperazino]-8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepine (38)*

8-Chloro-11-piperazino-5*H*-dibenzo[*b*,*e*][1,4]diazepine (21) (200 mg, 0.639 mmol) in dry 1,2-dichloroethane (20 mL) was treated with 2-adamantanone (101 mg, 0.671 mmol) followed by sodium triacetoxyborohydride (190 mg, 0.895 mmol) and worked up as described in the preparation of (22a)–(22c). The residue was purified using flash chromatography (ethyl acetate/hexane; 1 : 3) and the product (38) recrystallized from methanol/water as yellow microprisms (125 mg, 44%), mp 119°C (softens), 127°C (melts) (Found: C 70.3, H 7.1, N 11.7%. $C_{27}H_{31}ClN_4 \cdot CH_3OH$ requires C 70.2, H 7.4, N 11.7%). ν_{max} (KBr)/cm^{-1} 3320, 2916, 1604, 1562. λ_{max} ($\log_{10}$ ε)/nm 228 (4.39), 261 (4.19), 298 (4.02). δ_H (300 MHz; [D_6]acetone) 7.35–7.25 (2 H, m, H1, H3), 7.05 (1 H, dd, *J* 8, 1, H4), 7.00 (1 H, app td, *J* 7.5, 1, H2), 6.95 (1 H, d, *J* 2.5, H9), 6.86 (1 H, d, *J* 8.5, H6), 6.79 (1 H, dd, *J* 8.5, 2.5, H7), 6.45 (1 H, s, H5), 3.42 (4 H, m, H2′, H6′), 2.51 (4 H, m, H3′, H5′), 2.17–2.03 (5 H, m), 1.63–1.91 (8H, m), 1.42 (1 H, br s), 1.38 (1 H, br s). δ_C (75 MHz; [D_6]acetone) 164.0, 155.1, 143.6, 142.9, 132.8, 131.1, 128.7, 127.1, 124.7, 123.41, 123.36, 121.4, 121.2, 68.7, 50.4, 48.7, 38.6, 38.1, 32.2, 30.5, 28.6, 28.4. ESI mass spectrum *m*/*z* 447.4.

Pharmacology Procedures

Test Compounds. The synthetic targets were tested in preliminary in vitro and in vivo 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 to precipitate the compounds as their 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, then 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 a 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 40 000 × *g* at 0°C. The resulting supernatant was then discarded, and the remaining pellet resuspended in buffer and re-centrifuged for 15 min at 40 000 × *g* at 0°C. The supernatant was discarded and the remaining pellet resuspended in assay buffer to a final concentration of 2.0 mg mL^{-1} (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: (a) 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 (b) 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, and 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). 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 (% I) and represent the mean of duplicate tubes at the tested concentration of 1 μM in a single experiment.

PANLABS Assay. Receptor binding affinities for dopamine $D_{4.4}$ and serotonin 5-HT_{2A} were determined by PANLABS (Taiwan) for selected compounds. The assays were carried out using the following: (a) for $D_{4.4}$; human recombinant (mammalian CHO-K_1 cells), [^{3}H]spiperone (0.3 nM) as radioligand, and haloperidol (10 μM) as reference compound for non-specific binding; (b) for 5-HT_{2A}; rat brain, [^{3}H]ketanserin (0.5 nM) as radioligand, and ketanserin (1 μM) as reference compound for non-specific binding. Test compounds were evaluated as hydrochloride salts at a final concentration of 1 μM for their ability to displace the radioligand. Biochemical assay results are presented as percent inhibition (% I) of specific binding.

In Vivo Studies: Antagonism of Apomorphine-Induced Climbing in Mice

Animals. Adult female mice (25 to 30 g) were used for all the experiments. The mice were housed 6 per cage under controlled conditions of temperature (20 ± 1°C) and 12 h light/dark cycle (lights on 6:00 a.m. to 6:00 p.m.), with free access to food and tap water. The animals were brought into the laboratory and weighed one hour before the commencement of the experiments to allow for acclimatization.

Materials and Method. All compounds assayed were prepared as their hydrochloride salts and dissolved in B.P. water for injection. Mice (5 per dose) were pretreated with clozapine (10 mg kg^{-1} i.p.) and test compounds (10 mg kg^{-1} i.p.) 30 min prior to an injection of apomorphine hydrochloride (3.0 mg kg^{-1} i.p.). Climbing behaviour was assessed[28] at 5 min intervals over a period of 25 min commencing 5 min after apomorphine administration, using the following scoring system: 0, no paws on the cage; 1, one paw on the cage; 2, two paws on the cage; 3, three paws on the cage; 4, four paws on the cage. The score recorded for each animal was based on the position of the animal at the moment it was first observed. The mean climbing score (m.c.s.) was calculated by summation of the total score per mouse for all mice per dose over the course of the experiment, and dividing that figure by the number of mice per dose. The % inhibition climbing value was calculated using Equation (*1*).

$$\%\ \text{Inhibition Climbing} = \frac{[\text{m.c.s. (apomorphine)} - \text{m.c.s. (drug)}]}{\text{m.c.s. (apomorphine)}} \times 100 \quad (1)$$

Statistical Analysis. The statistical analysis was carried out by one-way analysis of variance (ANOVA) followed by Dunnett's test for pairwise comparison of drug treated groups and apomorphine-treated control, using SigmaStat for Windows software (Version 2, 1992–1995), with $P < 0.05$ being considered as statistically significant.

Accessory Material

Accessory material is available from the *Australian Journal of Chemistry*, until September 2008, or from the author.

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