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The Synthesis and Preliminary Pharmacological Evaluation of a Series of Substituted 4′-Phenoxypropyl Analogues of the Atypical Antipsychotic Clozapine

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Herein we report the synthesis, characterization, and preliminary pharmacological activity of a new series of substituted 4′-phenoxypropyl tricyclic analogues of clozapine as potential antipsychotic agents for the treatment of schizophrenia. The lead compound (**3**) for this investigation was designed based on a revised model derived from the structural hybridization of the commercial therapeutics clozapine (**1**) and haloperidol (**2**). The compounds described in this paper probe the biochemical effects of introducing a variety of electron-withdrawing and electron-donating substituents with the primary focus on the *para*-position of the introduced distal aromatic ring. The target compounds were readily prepared in three steps using the key intermediate lactam (8-chloro-10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepine-11-one, **9**), piperazine and commercially available substituted phenols. The chemistry and structural characterization of this series of substituted 4′-phenoxypropyl analogues of clozapine are described. Preliminary in vitro results on the pharmacological effects of the ring substituents on affinity for dopamine D_4 and serotonin 5-HT_{2A} receptors are discussed. Psychosis-related in vivo animal behavioural data for compounds identified with potential from the receptor binding screen are also presented.

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Introduction

Schizophrenia is arguably the most debilitating mental illness, affecting ∼1% of the world population. The prominent symptoms of this disease state are divided into positive (hallucinations and delusions) and negative (social and emotional withdrawal) and also encompass cognitive deficits.[1] The cause of schizophrenia remains unknown but many hypotheses postulate neurotransmitter dysfunction involving dopamine and serotonin. Clozapine (**1**) (Fig. 1), an archetypal atypical antipsychotic agent, exhibits strong dopamine D_4 and serotonin 5-HT_{2A} antagonist activity and displays unparalleled efficacy in treatment-resistant patients.[2] Clozapine is also devoid of extrapyramidal side effects (EPS) owing to its low striatal dopamine D_2 affinity. Unfortunately, clozapine's propensity to induce a potentially fatal blood disorder, agranulocytosis,[3,4] in 1–2% of patients excludes its clinical use as a front-line treatment. The immense success of haloperidol (**2**) (Fig. 1) in treating the positive symptoms of schizophrenia[5] is attributable to its strong affinity for mesolimbic dopamine D_2 receptors. Of particular interest to our research group is the synthesis of novel tricyclic chemical entities that exhibit a 'clozapine-like' profile by targeting dopamine D_4 and serotonin 5-HT_{2A} receptors in the central nervous system (CNS). Strong antagonism of the dopamine D_4 and serotonin 5-HT_{2A} receptors relative to the dopamine D_2 receptor is believed to alleviate positive and negative symptoms, respectively, without causing EPS (Parkinsonian-like movement disorders).

The lead compound, 8-chloro-11-[4-(3-phenoxypropyl) piperazino]-5*H*-dibenzo[*b*,*e*][1,4]diazepine (**3**, Y = H) (Fig. 1), published in an earlier study,[6] pharmacologically exhibited a clozapine-like profile. Compound **3** was designed based on a revised model derived from the structural hybridization of the commercial therapeutics clozapine (**1**) and haloperidol (**2**), and this compound forms the basis of the current investigation. The novel compounds described in the present paper investigate the biochemical effects of introducing a variety of electron-withdrawing and electron-donating substituents on the aryl ring of the phenoxypropyl moiety. Substituents on the remote ring were chosen on the basis of favourable biochemical data from previous work.[1] Our primary focus was substituent effects on the *para*-position of the remote aromatic ring; particularly in view of the importance of the fluorine atom in this *para*-position of haloperidol, which is necessary for pronounced antipsychotic activity.[7] The novel compounds were screened for their affinity for the target dopamine D_4 and serotonin 5-HT_{2A} receptors. Promising candidates that displayed a clozapine-like receptor profile were further evaluated for their potential to antagonize apomorphine-induced climbing in mice, a psychosis-related behavioural model predictive of mesolimbic dopaminergic activity and therefore potential antipsychotic activity.

Chemistry

The synthetic approach for the preparation of these novel susbstituted 4′-phenoxypropyl analogues of clozapine was based on initial formation of a series of monosubstituted piperazines (Scheme 1). Commercially available substituted

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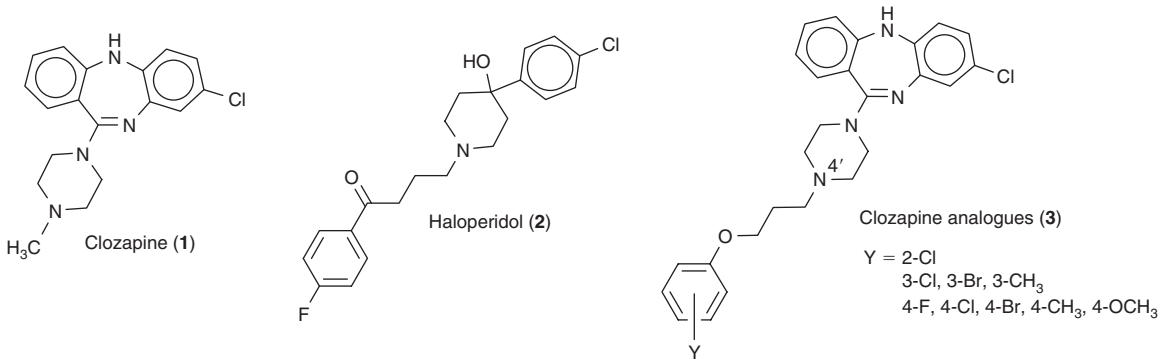


Fig. 1. The chemical structures of the clinically prescribed antipsychotics, clozapine (**1**) and haloperidol (**2**), and the new structural template (**3**) selected for investigation.

phenols (**4a**–**h**), under alkaline conditions in refluxing 1,3-dibromopropane, were converted to their corresponding substituted phenoxypropyl bromides (**6a**–**h**). These compounds were isolated as colourless to yellow liquids in 36–66% yield. Subsequent treatment of the substituted phenoxypropyl bromides (**6a**–**h**) and commercial 3-(4-fluorophenoxy)propyl chloride (**6i**) with piperazine (**7**) in toluene afforded the desired monosubstituted piperazines (**8a**–**i**) as colourless to bright yellow liquids in 33–89% yield. Compound **8d** (1-(3-(3-bromophenoxy)propyl)piperazine) was purified by column chromatography as attempts to distill the product under vacuum resulted in significant decomposition of the crude product and pronounced colouration of the distillate. Interestingly, compounds **8b** (Y = 3-Cl), **8d** (Y = 3-Br), and **8f** (Y = 3-CH_3) are commercially available but not reported in the literature (SciFinder Scholar 2007).

The target amidines (**3a**–**i**) were prepared according to Scheme 2, whereby the synthesized monosubstituted piperazines (as the preformed titanium–amine complex following treatment with the Lewis acid titanium tetrachloride) were coupled to the key tricyclic lactam (**9**),[1] affording yellow crystalline solids in 32–76% yield (except for **3a** and **3d**, which yielded yellow foams). The aforementioned yields are unoptimized and represent the results of a single reaction. The purity and integrity of the compounds were supported by microanalysis whereby the elements C, H, and N were found to be within ±0.4% of their calculated values. Some target compounds, recrystallized from methanol/water, crystallized incorporating methanol in their crystal structure as indicated by their combustion analysis data. In such cases, the methanol of crystallization was also evident in their ^{1}H NMR spectra.

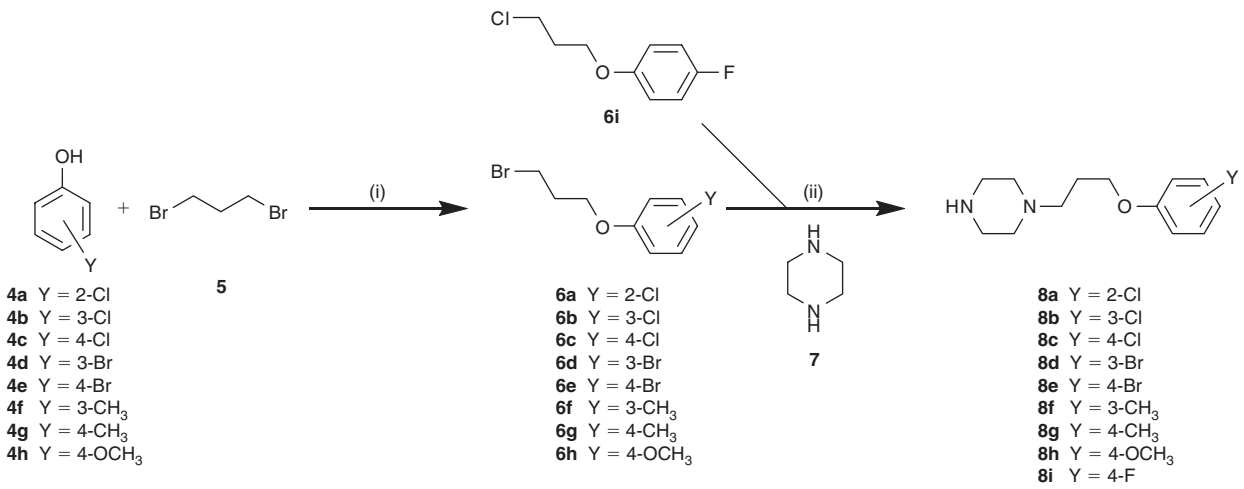
Receptor Binding Studies

Details of the in vitro assays for the synthesized compounds are described in the Experimental section. Table 1 lists percentage inhibition (% I) of radioligand binding at a compound concentration of 10^{-6} M for the central dopamine $D_{4.4}$ (the most common polymorphic variant of the D_4 receptor)[8] and central serotonin 5-HT_{2A} receptors for all test compounds. Data for the compound corresponding to the 4′-phenoxylpropyl analogue of clozapine (**3**, Y = H) are also included for comparative purposes, thereby assisting in the development of structure–activity relationships.

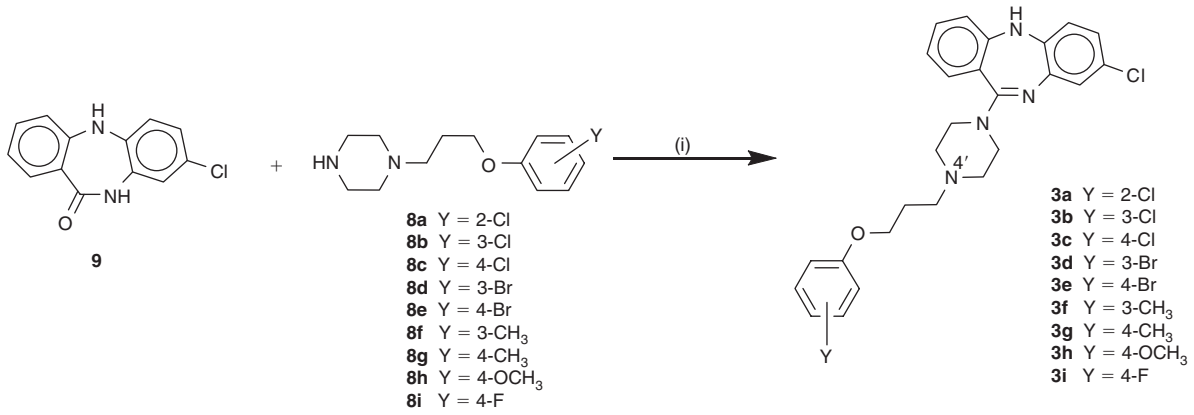
Our preliminary pharmacological results were pleasing, whereby all test compounds showed comparable or better affinities (70–86% I) for the dopamine $D_{4.4}$ receptor relative to clozapine (72% I). In comparison with the 4′-phenoxylpropyl analogue of clozapine (**3**, Y = H, 81% I), compounds **3b**–**e**, which contained the larger halogen atom (Cl and Br) at the *meta*- and *para*-positions, displayed reduced $D_{4.4}$ affinity; however, the difference was only marginal. The affinity of the test compounds for the serotonin 5-HT_{2A} receptor exhibited greater differentiation within the series (60–91% I) when compared with clozapine (85% I) and compound **3** (Y = H, 83% I). The *para*-Cl (**3c**) and *para*-Br (**3e**) analogues demonstrated the least inhibition of radioligand at 67% I and 60% I, respectively. Conversely, the *para*-F analogue (**3i**), which shows a structural similarity to the *para*-F of haloperidol, displayed encouraging clozapine-like affinity (81% I) with an overall trend of F > Cl > Br for 5-HT_{2A} receptor affinity. Interestingly, the inclusion of a CH_3 (**3f**–**g**) or OCH_3 (**3h**) substituent at the *meta*- or *para*-positions was well tolerated at the 5-HT_{2A} receptor. In general, the receptor binding data suggest that substituted 4′-phenoxpropyl analogues have a favourable rather than a detrimental effect on dopamine $D_{4.4}$ and serotonin 5-HT_{2A} affinity relative to clozapine (**1**) and compound **3**. Based on the preliminary affinity data from this receptor binding screen, all compounds were further evaluated in a mouse behavioural assay that is predictive of potential antipsychotic efficacy.

In Vivo Behavioural Studies

The series of substituted 4′-phenoxylpropyl analogues of clozapine (**3a**–**i**) were evaluated in vivo for their ability to antagonize apomorphine-induced climbing in mice, a psychosis-related behavioural model predictive of mesolimbic, dopaminergic activity and, therefore, potential antipsychotic efficacy.[9–12] The mice were pretreated with clozapine (10 mg kg^{-1} intraperitoneal (*ip*)) or the test compounds (10 mg kg^{-1} *ip*) as their hydrochloride salts,[1] 30 min before an injection of apomorphine hydrochloride (3 mg kg^{-1} *ip*), and their climbing behaviour observed. The assessed results of this behavioural assay are displayed in Table 2. Clozapine and compound **3** effectively diminished apomorphine-induced climbing in mice at 10 mg kg^{-1} *ip*, displaying 63 and 71% inhibition of climbing, respectively. The analogues **3h** (Y = 4-OCH_3) and **3i** (Y = 4-F) were the prominent compounds and significantly antagonized the apomorphine-induced climbing behaviour in mice, with the haloperidol-related *p*-fluorophenoxypropyl analogue (**3i**) displaying the best activity with 76% inhibition of climbing. Compounds **3a** (Y = 2-Cl), **3c** (Y = 4-Cl), and **3f** (Y = 3-CH_3), although exhibiting promising receptor binding profiles, showed only marginal anticlimbing activity; however, these values were determined not to be statistically significant. We were pleased



Scheme 1. Reagents and conditions: (i) NaOH(aq), reflux, 2–3 h; (ii) toluene, 85°C.



Scheme 2. Reagents and conditions: (i) $TiCl_4$, anisole, 25 to 55°C, reflux.

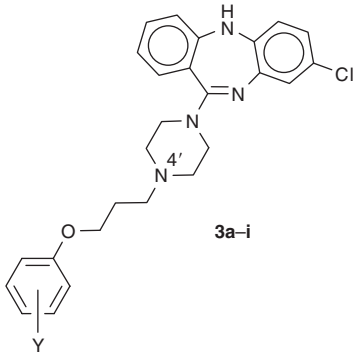
to observe that compound **3e** (Y = 4-Br), which exhibited the least favourable receptor binding profile, was equivalent in potency to the vehicle and displayed no anticlimbing activity whatsoever. On the whole, the in vivo data suggest that ring substitution of the introduced aryl ring of **3** with the designated electron-withdrawing and electron-donating groups has quite a variable effect on behavioural activity with no definitive structure–activity correlation. This may be attributed to insufficient receptor binding data at target and other receptor systems implicated in this complex behavioural model, thereby making it difficult to infer a correlation between in vitro binding data and in vivo behavioural findings. Pharmacokinetic factors may also influence the variability of the intercompound relationship from a pharmacological point of view.

Conclusions

A series of substituted 4′-phenoxypropyl analogues of clozapine were synthesized and characterized to investigate the biochemical effects of introducing various electron-withdrawing and electron-donating substituents on the aryl ring of the phenoxypropyl moiety. The in vitro receptor binding data revealed that all target analogues displayed favourable affinity for the dopamine $D_{4.4}$ and serotonin 5-HT_{2A} receptors compared with clozapine and compound **3**, with compounds **3b** (Y = 3-Cl), **3c** (Y = 4-Cl), and **3e** (Y = 4-Br) demonstrating reduced inhibition of radioligand at the 5-HT_{2A} receptor. From the binding data, it was proposed that both receptor systems are certainly tolerant to ring substitution of the aryl system, with reduced activity associated with the larger halogens in the *para*-position.

An in vivo behavioural investigation of this series identified two noteworthy target compounds **3h** (Y = 4-OCH_3) and **3i** (Y = 4-F) that significantly diminished apomorphine-induced climbing in mice with the haloperidol-derived *p*-fluorophenoxypropyl analogue (**3i**) as the standout. These results compared favourably with the anticlimbing properties of clozapine and compound **3**. An interesting structural feature associated with **3h** and **3i** is that both substituents are located at the *para*-position and contain the hydrogen-bonding acceptor atoms oxygen and fluorine, respectively. These atoms may be involved in a key hydrogen-bond interaction with a significant amino acid residue(s) of the target receptors, thereby highlighting and discriminating their anticlimbing activity from the remaining members of the series. The propensity for fluorine to exhibit hydrogen-bond acceptor properties is well documented in the literature, wherein the $C(sp^2)$–F···H–O bond is approximately one-quarter the strength of a C–O···H–O bond.[13] A further series of substituents containing a range of hydrogen-bonding groups would need to be explored in order to support and strengthen this hypothesis; for example, a prospective variant

Table 1. Preliminary binding studies



3a–i

Compound	Y	Binding affinity Percentage inhibition (% I) at 10^{-6} M	
		Dopamine $D_{4.4}$ [^{3}H]spiperone	Serotonin 5-HT_{2A} [^{3}H]ketanserin
Clozapine	–	72 ± 1	85 ± 1
3	H	81 ± 3	83 ± 1
3a	2-Cl	80 ± 1	91 ± 3
3b	3-Cl	74 ± 3	70 ± 1
3c	4-Cl	71 ± 1	67 ± 2
3d	3-Br	74 ± 2	83 ± 4
3e	4-Br	70 ± 1	60 ± 5
3f	3-CH_3	85 ± 1	85 ± 1
3g	4-CH_3	84 ± 3	80 ± 5
3h	4-OCH_3	86 ± 1	82 ± 2
3i	4-F	84 ± 3	81 ± 2

Determined in duplicate by MDS Pharma Services (Taiwan).

Table 2. Antagonism of apomorphine-induced climbing in mice
Compounds were tested as their hydrochloride salts at a dose of 10 mg kg^{-1} *ip* (intraperitoneal). *Compounds with statistically significant ($P < 0.05$) activity

Compound	Climbing index[A]	% Inhibition of climbing
Apomorphine	18.2 ± 1.5	–
Vehicle	0.4 ± 0.4	–
Clozapine	6.8 ± 2.6*	63
3	5.2 ± 3.2*	71
3a	14.2 ± 3.1	22
3b	15.8 ± 3.2	13
3c	13.8 ± 3.4	24
3d	17.8 ± 1.0	2
3e	18.4 ± 0.8	0
3f	12.2 ± 3.0	33
3g	15.0 ± 2.6	18
3h	8.4 ± 3.7*	54
3i	4.3 ± 3.6*	76

[A]Values represent the mean ± s.e.m. climbing index.

could be the phenolic analogue (Y = 4-OH), which is simply derived from treatment of the *p*-methoxy analogue **3h** with boron tribromide. This novel phenolic analogue, in addition to possessing a hydrogen-bond acceptor atom, also contains a hydrogen-bond donor atom, which may exhibit greater in vivo efficacy through reinforced hydrogen-bonding interactions with the receptors of interest.

The behavioural results herein have identified two additional unique analogues that may afford potential antipsychotic activity. These compounds, and others recognized previously, require further in vivo pharmacological evaluations to elucidate their propensity to induce significant side-effects such as EPS and drug-induced agranulocytosis. This information is absolutely necessary in order to confirm an atypical profile and identify a potential successor to clozapine that exhibits a clinical advantage in the treatment of schizophrenia.

Experimental

General

Melting points were determined on a Reichert Micromelting point apparatus and are uncorrected. Elemental analyses of samples dried under vacuum were carried out by Microanalytical Service, Chemistry Department, University of Queensland, Brisbane or Chemical and Micro Analytical Services Pty Ltd, Belmont, Victoria, Australia. IR spectra were recorded on Bio-Rad FTS 3500GX utilizing *Merlin* software for solids with KBr powder as background and on a Hitachi 270-30 infrared spectrophotometer with NaCl discs for oils, or as a neat compound on a Scimitar Series Varian 800 Fourier-transform (FT)-IR spectrophotometer with a PIKE Technologies MIRacle attenuated total reflectance (ATR) accessory. UV-Vis spectra were recorded as ethanolic solutions on a Pharmacia Biotech Ultraspec 2000 UV-VIS spectrometer utilizing Swift II software. Wavelengths of maximum absorbance (λ_{max}) are quoted with respective absorptivities (ε). ^{1}H and ^{13}C NMR spectra were recorded at 300.13 and 75.47 MHz respectively in $CDCl_3$ using a Brüker Avance DPX 300 spectrometer equipped with a Silicon Graphics work station. Chemical shifts (δ) for all ^{1}H and ^{13}C spectra are reported in parts per million (ppm) using tetramethylsilane (TMS, 0 ppm) and deuterated chloroform ($CDCl_3$, 77.16 ppm[14]) as the reference, respectively, unless otherwise stated. In reporting spectral data, the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; p, quintet; m, multiplet; br, broad; app, apparent; *J*, coupling constant in Hz; C, quaternary carbon; CH, methine carbon; CO, carbonyl carbon; CH_2, methylene carbon; CH_3, methyl carbon. Electrospray ionization (ESI) mass spectra (MS) were determined in positive ion mode using a Micromass Platform II mass spectrometer. High-resolution MS were determined using a Brüker BioApex II FTICR mass spectrometer. TLC was carried out routinely on silica gel $60F_{254}$ precoated plates (0.25 mm, Merck). Flash column chromatography was carried out using Merck silica gel 60, 230–400 mesh ASTM. All solvents were distilled before use. All chemicals used were purchased from Sigma–Aldrich Pty Ltd.

General Procedure for the Preparation of Substituted Phenoxypropyl Bromides[15]

A substituted phenol (10 g) was dissolved with stirring in a solution of sodium hydroxide (1.1 equiv.) in water (10 mL). The resulting solution was added dropwise to excess refluxing 1,3-dibromopropane (2 equiv.). The reaction mixture was heated at reflux for 2–3 h, cooled to room temperature, then extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with aqueous 0.5 M NaOH (2 × 30 mL), water (3 × 30 mL), dried over anhydrous sodium sulfate, filtered and then concentrated under vacuum to yield a liquid. Vacuum distillation or column chromatography afforded the title compound as a colourless liquid, unless otherwise indicated.

The following substituted phenoxypropyl bromides (**6a**–**h**) were prepared in this manner.

3-(2-Chlorophenoxy)propyl Bromide ***6a***

Pale yellow liquid (11.3 g, 58%), bp 120–125°C/3.5 mmHg (lit.[16] 118–120°C/5 mmHg). δ_H 7.43 (1H, dd, *J* 8, 2, H3′), 7.31 (1H, app td, *J* 7.5, 2, H5′), 7.03–6.95 (2H, m, H4′, H6′), 4.23 (2H, t, *J* 6, H3), 3.73 (2H, t, *J* 6.5, H1), 2.43 (2H, app p, *J* 6, H2). δ_C 154.3 (C), 130.2 (CH), 127.7 (CH), 123.2 (C), 121.7 (CH), 113.7 (CH), 66.5 (CH_2), 32.4 (CH_2), 30.0 (CH_2).

3-(3-Chlorophenoxy)propyl Bromide[17] ***6b***

Pale yellow liquid (11.1 g, 57%), bp 115–118°C/3 mmHg. δ_H 7.21 (1H, app t, *J* 8, H5′), 6.92–6.98 (2H, m, H2′, H4′), 6.81 (1H, m, H6′), 4.10 (2H, t, *J* 6, H3), 3.60 (2H, t, *J* 6.5, H1), 2.33 (2H, app p, *J* 6, H2). δ_C 159.6 (C), 135.1 (C), 130.4 (CH), 121.3 (CH), 115.2 (CH), 113.2 (CH), 65.8 (CH_2), 32.4 (CH_2), 29.9 (CH_2).

3-(4-Chlorophenoxy)propyl Bromide ***6c***

Pale yellow liquid (11.0 g, 57%), bp 135–138°C/0.4 mmHg (lit.[18] 108–110°C/0.2 mmHg; lit.[15] 128–134°C/0.2 mmHg). δ_H 7.22 (2H, d, *J* 7.5, H3′, H5′), 6.82 (1H, d, *J* 7.5, H2′, H6′), 4.08 (2H, t, *J* 6, H1), 3.58 (2H, t, *J* 6.5, H3), 2.30 (2H, p, *J* 6, H2). δ_C 157.5 (C), 129.5 (CH), 126.0 (C), 116.0 (CH), 65.9 (CH_2), 32.5 (CH_2), 30.0 (CH_2).

3-(3-Bromophenoxy)propyl Bromide[19] ***6d***

Yellow liquid (11.0 g, 62%), bp 124–126°C/0.9 mmHg. δ_H 7.16–7.05 (3H, m, H2′, H4′, H5′), 6.83 (1H, d app t, *J* 6, 2, H6′), 4.08 (2H, t, *J* 5.5, H3), 3.58 (2H, t, *J* 6.5, H1), 2.30 (2H, app p, *J* 6, H2). δ_C 159.5 (C), 130.6 (CH), 124.0 (CH), 122.9 (C), 118.1 (CH), 113.8 (CH), 65.8 (CH_2), 32.3 (CH_2), 29.8 (CH_2).

3-(4-Bromophenoxy)propyl Bromide ***6e***

Pale yellow liquid (11.2 g, 66%), bp 118–124°C/0.7 mmHg (lit.[20] 169°C/12 mmHg). δ_H 7.37 (2H, d, *J* 9, H3′, H5′), 6.78 (2H, d, *J* 9, H2′, H6′), 4.06 (2H, t, *J* 5.5, H3), 3.58 (2H, t, *J* 6.5, H1), 2.30 (2H, app p, *J* 6, H2). δ_C 158.0 (C), 132.5 (CH), 118.0 (C), 116.5 (CH), 65.2 (CH_2), 32.4 (CH_2), 30.0 (CH_2).

3-(3-Methylphenoxy)propyl Bromide ***6f***

Colourless liquid (11.0 g, 52%), bp 100–102°C/1.5 mmHg (lit.[21] 144–148°C/10 mmHg). δ_H 7.22 (1H, app t, *J* 7.5, H5′), 6.84–6.75 (3H, m, H2′, H4′, H6′), 4.13 (2H, t, *J* 6, H3), 3.64 (2H, t, *J* 6.5, H1), 2.38 (3H, s, CH_3), 2.33 (2H, app p, *J* 6.5, H2). δ_C 158.9 (C), 139.7 (C), 129.4 (CH), 115.6 (CH), 65.4 (CH_2), 32.7 (CH_2), 30.2 (CH_2), 21.7 (CH_3).

3-(4-Methylphenoxy)propyl Bromide ***6g***

Colourless liquid (8.45 g, 40%), bp 112–114°C/0.2 mmHg (lit.[22] 155–160°C/21 mmHg). δ_H 7.07 (2H, d, *J* 8.5, H3′, H5′), 6.79 (2H, d, *J* 8.5, H2′, H6′), 4.05 (2H, t, *J* 6, H3), 3.58 (2H, t, *J* 6.5, H1), 2.29 (2H, app p, *J* 6, H2), 2.28 (1H, s, CH_3). δ_C 156.7 (C), 130.3 (C), 130.1 (CH), 114.6 (CH), 65.6 (CH_2), 32.6 (CH_2), 30.2 (CH_2), 20.6 (CH_3).

3-(4-Methoxyphenoxy)propyl Bromide ***6h***

Colourless liquid (7.30 g, 36%), bp 128–130°C/0.5 mmHg (lit.[23] 126–127°C/1 mmHg). δ_H 6.84 (4H, app s, H2′, H3′, H5′, H6′), 4.05 (2H, t, *J* 6, H3), 3.76 (3H, s, OCH_3), 3.59 (2H, t, *J* 6.5, H1), 2.29 (2H, app p, *J* 6.5, H2). δ_C 154.2 (C), 153.0 (CH), 115.7 (CH), 114.8 (C), 66.2 (CH_2), 55.9 (CH_3), 32.6 (CH_2), 30.2 (CH_2).

General Procedure for the Preparation of Monosubstituted Piperazines[1]

To a solution of a substituted phenoxypropyl bromide (**6a**–**h**), or commercially available 3-(4-fluorophenoxy)propyl chloride (**6i**) (1 equiv.), in toluene was added anhydrous piperazine (4 equiv.). The solution was heated at 85°C for 2 h, unless otherwise stated, 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, then extracted with dichloromethane (3 × 100 mL). The 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 or flash column chromatography afforded the title compound as a liquid, unless otherwise indicated.

The following monosubstituted piperazines (**8a**–**i**) were prepared in this manner.

1-(3-(2-Chlorophenoxy)propyl)piperazine ***8a***

A solution of 3-(2-chlorophenoxy)propyl bromide (**6a**, 7.55 g, 30.2 mmol) in toluene (150 mL) reacted with piperazine (10.8 g, 125 mmol), and after workup afforded a yellow liquid (2.83 g, 37%). Bp 170–178°C/1.4 mmHg (lit.[24] 174–175°C/2 mmHg). δ_H 7.34 (1H, dd, *J* 8, 1.5, H3″), 7.18 (1H, app td, *J* 7.5, 1.5, H5″), 6.94–6.83 (2H, m, H4″, H6″), 4.08 (2H, t, *J* 6.5, H3′), 2.89 (4H, m, H3, H5), 2.54 (2H, t, *J* 7.5, H1′), 2.48 (4H, m, H2, H6), 2.00 (2H, app p, *J* 6.5, H2′), 1.72 (1H, s, H4). δ_C 154.6 (C), 129.9 (CH), 127.6 (CH), 123 (C), 121.3 (CH), 113.6 (CH), 67.4 (CH_2), 55.2 (CH_2), 54.6 (CH_2), 46.1 (CH_2), 26.4 (CH_2).

1-(3-(3-Chlorophenoxy)propyl)piperazine ***8b***

A solution of 3-(3-chlorophenoxy)propyl bromide (**6b**, 8.00 g, 32.6 mmol) in toluene (200 mL) reacted with piperazine (11.2 g, 130 mmol) and after workup afforded a bright yellow liquid (4.37 g, 53%). Bp 181–184°C/40 mmHg. δ_H 7.11–7.16 (1H, m, H5″), 6.86–6.89 (2H, m, H2″, H4″), 6.73–6.76 (1H, m, H6″), 3.96 (2H, t, *J* 6.5, H3′), 2.86 (4H, m, H3, H5), 2.45 (2H, t, *J* 7, H1′), 2.39 (4H, m, H2, H6), 1.92 (2H, app p, H2′), 1.69 (1H, s, H4). δ_C 159.9 (C), 130.2 (CH), 120.2 (CH), 115.0 (CH), 113.2 (CH), 66.6 (CH_2), 55.7 (CH_2), 54.7 (CH_2), 46.2 (CH_2), 26.6 (CH_2).

1-(3-(4-Chlorophenoxy)propyl)piperazine ***8c***

A solution of 3-(4-chlorophenoxy)propyl bromide (**6c**, 5.04 g, 20.2 mmol) in toluene (100 mL) reacted with piperazine (7.02 g, 81.5 mmol) and after workup afforded a pale yellow liquid (3.45 g, 67%). Bp 170–174°C/0.4 mmHg (lit.[25] 158°C/0.2 mmHg). δ_H 7.17 (2H, d, *J* 9, H3″, H5″), 6.78 (2H, d, *J* 9, H2″, H6″), 3.94 (2H, t, *J* 6.5, H3′), 2.85 (4H, m, H3, H5), 2.45 (2H, t, *J* 7.5, H1′), 2.40 (4H, m, H2, H6), 1.91 (2H, app p, *J* 7, H2′), 1.57 (1H, s, H4). δ_C 157.6 (C), 129.1 (CH_2), 124 (C),

115.7 (CH_2), 66.5 (CH_2), 55.5 (CH_2), 54.6 (CH_2), 46.0 (CH_2), 26.4 (CH_2).

1-(3-(3-Bromophenoxy)propyl)piperazine ***8d***

A solution of 3-(3-bromophenoxy)propyl bromide (**6d**, 7.56 g, 25.7 mmol) in toluene (150 mL) reacted with piperazine (9.22 g, 107 mmol) and after workup and flash column chromatography (90:9:1, dichloromethane/methanol/25% w/v aqueous ammonia) afforded a pale yellow liquid (6.86 g, 89%). δ_H 7.12 (1H, app t, *J* 8.5, H5″), 7.08–7.03 (2H, m, H2″, H4″), 6.82 (1H, ddd, *J* 8, 2.5, 1, H6″), 3.99 (2H, t, *J* 6.5, H3′), 2.90 (4H, m, H3, H5), 2.49 (2H, t, *J* 7.5, H1′), 2.44 (4H, m, H2, H6), 1.96 (1H, s, H4), 1.94 (2H, app p, *J* 7, H2′). δ_C 159.5 (C), 130.2 (CH), 123.3 (CH), 122.4 (C), 117.4 (CH), 113.2 (CH), 66.1 (CH_2), 55.4 (CH_2), 54.3 (CH_2), 45.8 (CH_2), 26.1 (CH_2).

1-(3-(4-Bromophenoxy)propyl)piperazine[26] ***8e***

A solution of 3-(4-bromophenoxy)propyl bromide (**6e**, 5.0 g, 17.0 mmol) in toluene (100 mL) reacted with piperazine (5.86 g, 68.0 mmol) and after workup and flash column chromatography (90:9:1, dichloromethane/methanol/25% w/v aqueous ammonia) afforded a colourless liquid (4.03 g, 52%). δ_H 7.33 (2H, d, *J* 7, H3″, H5″), 6.78 (2H, d, *J* 9, H2″, H6″), 3.96 (2H, t, *J* 6.5, H3′), 2.88 (4H, m, H3, H5), 2.47 (2H, t, *J* 7.5, H1′), 2.42 (4H, m, H2, H6), 1.93 (3H, app p, *J* 7, H2′), 1.72 (1H, s, H4). δ_C 158.3 (C), 132.3 (CH), 116.5 (CH), 112.8 (C), 66.7 (CH_2), 55.8 (CH_2), 54.7 (CH_2), 46.2 (CH_2), 26.6 (CH_2).

1-(3-(3-Methylphenoxy)propyl)piperazine ***8f***

A solution of 3-(3-methylphenoxy)propyl bromide (**6f**, 8.00 g, 34.9 mmol) in toluene (200 mL) reacted with piperazine (12.0 g, 140 mmol) and after workup afforded a pale yellow liquid (2.73 g, 33%). Bp 180–184°C/0.5 mmHg. δ_H 7.12 (1H, app t, *J* 7.5, H5″), 6.74–6.67 (3H, m, H2″, H4″, H6″), 3.97 (2H, t, *J* 6.5, H3′), 2.87 (4H, m, H3, H5), 2.47 (2H, t, *J* 7.5, H1′), 2.40 (4H, m, H2, H6), 2.30 (3H, s, CH_3), 1.93 (2H, app p, *J* 6.5, H2′), 1.64 (1H, s, H4). δ_C 159.1 (C), 139.4 (CH), 129.2 (C), 121.4 (CH), 115.4 (CH), 111.5 (CH), 66.2 (CH_2), 55.9 (CH_2), 54.7 (CH_2), 46.2 (CH_2), 26.7 (CH_2), 21.6 (CH_3).

1-(3-(4-Methylphenoxy)propyl)piperazine[27] ***8g***

A solution of 3-(4-methylphenoxy)propyl bromide (**6g**, 8.02 g, 35.0 mmol) in toluene (100 mL) reacted with piperazine (12.0 g, 140 mmol) and after workup afforded a pale yellow liquid (5.35 g, 66%). Bp 177–180°C/0.5 mmHg. δ_H 7.05 (2H, d, *J* 8.5, H3″, H5″), 6.78 (2H, d, *J* 8.5, H2″, H6″), 3.96 (2H, t, *J* 6.5, H3′), 2.87 (4H, m, H3, H5), 2.41–2.50 (6H, m, H1′, H2, H6), 2.26 (3H, s, CH_3), 1.94 (2H, app p, *J* 6.5, H2′), 1.75 (1H, s, H4). δ_C 156.9 (C), 129.8 (CH), 129.7 (C), 114.4 (CH), 66.4 (CH_2), 55.8 (CH_2), 54.7 (CH_2), 46.2 (CH_2), 26.7 (CH_2), 20.4 (CH_3).

1-(3-(4-Methoxyphenoxy)propyl)piperazine[25] ***8h***

A solution of 3-(4-methoxyphenoxy)propyl bromide (**6h**, 5.11 g, 0.02 mol) in toluene (100 mL) reacted with piperazine (7.17 g, 0.08 mol) and after flash column chromatography (90:9:1, dichloromethane/methanol/25% w/v aqueous ammonia) afforded a pale yellow liquid (2.68 g, 52%). δ_H 6.81 (4H, br s, H2″, H3″, H5″, H6″), 3.94 (2H, t, *J* 6.5, H3′), 3.74 (3H, s, H2‴), 2.87 (4H, m, H3, H5), 2.46 (6H, m, H1′, H2, H6), 1.95 (3H, m, H2′, H4). δ_C 153.9 (C), 153.4 (C), 115.7 (CH), 114.8 (CH), 67.1 (CH_2), 56.0 (CH_2), 55.9 (CH_3), 54.7 (CH_2), 46.2 (CH_2), 26.8 (CH_2).

1-(3-(4-Fluorophenoxy)propyl)piperazine[28] ***8i***

A solution of 1-(3-chloropropoxy)-4-fluorobenzene (**6i**, 10.0 g, 53.0 mmol) in toluene (250 mL) reacted with piperazine (18.3 g, 212 mmol) and after workup afforded a pale yellow liquid, (8.01 g, 63%). Bp 175–176°C/0.9 mmHg. δ_H 6.95 (2H, app t, *J* 8.5, H3″, H5″), 6.82 (2H, dd, *J* 8.5, 4.5, H2″, H6″), 3.94 (2H, t, *J* 6.5, H3′), 2.87 (4H, m, H3, H5), 2.47 (2H, t, *J* 7.5, H1′), 2.41 (4H, m, H2, H6), 1.93 (2H, app p, *J* 6.5, H2′), 1.63 (1H, s, H4). δ_C 156.4 (d, *J* 261, CF), 154.9 (C), 115.1 (d, *J* 23, C), 114.9 (d, *J* 8, C), 66.3 (CH_2), 55.2 (CH_2), 54.1 (CH_2), 45.6 (CH_2), 26.0 (CH_2).

*General Procedure for the Preparation of the Tricyclic Amidines (**3a–i**)*

To a solution of the monosubstituted piperazine (**8a–i**)[1,29] (5.10 mmol, 5 equiv.) in anhydrous anisole (5 mL) under nitrogen was added a solution of titanium tetrachloride in toluene (1.0 M, 1.12 mL, 1.12 mmol, 1.1 equiv.). The mixture was warmed to 50°C and a hot solution of 8-chloro-10,11-dihydro-5*H*-dibenzo[*b,e*][1,4]diazepine-11-one (**9**) (250 mg, 1.02 mmol) in anhydrous anisole (15 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 filtered under vacuum and the residue washed with ethyl acetate (20 mL). The organic layer was separated and the aqueous phase extracted with ethyl acetate (2 × 50 mL). The organic fractions were combined, washed with water (2 × 30 mL), dried (anhydrous sodium sulfate), evaporated to dryness and the resulting oily residue purified using flash column chromatography. The major product fractions were evaporated to dryness, and where appropriate, the residual solid recrystallized from a suitable solvent system.

The following compounds were prepared in this manner.

*8-Chloro-11-(4-(3-(2-chlorophenoxy)propyl)piperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepine* ***3a***

Purified by flash chromatography (4:1 ethyl acetate/hexane), yellow foam, yield 66% (Found: C 64.5, H 5.6, N 11.9. $C_{26}H_{26}Cl_2N_4O$ requires C 64.8, H 5.4, N 11.7%.) ν_{max}(FTIR)/cm^{-1} 3298, 1598, 1555. λ_{max}/nm (ε/M^{-1} cm^{-1}) 229 (41500), 262 (18400), 291 (12300). δ_H 7.35–7.06 (4H, m, H1, H3, H3‴, H5‴), 7.01–6.78 (6H, m, H2, H4, H6, H9, H4‴, H6‴), 6.59 (1H, d, *J* 8, H7), 5.00 (1H, s, H5), 4.10 (2H, t, *J* 6.5, H3″), 3.46 (4H, m, H2′, H6′), 2.61 (2H, t, *J* 7, H1″), 2.55 (4H, m, H3′, H5″), 2.02 (2H, app p, *J* 6.5, H2″). δ_C 162.8 (C), 154.6 (C), 152.9 (C), 141.9 (C), 140.6 (C), 131.9 (CH), 130.3 (CH), 129.0 (C), 127.8 (CH), 126.8 (CH), 123.5 (C), 123.1 (CH), 121.4 (CH), 120.0 (CH), 113.6 (CH), 67.3 (CH_2), 55.0 (CH_2), 53.2 (CH_2), 47.3 (CH_2), 26.6 (CH_2). *m/z* (ESI 20 V) 485.2 (M[$^{37}Cl_2$]H^+, 12%), 483.3 (M[^{37}Cl,^{35}Cl]H^+, 66%), 481.2 (M[$^{35}Cl_2$]H^+, 100).

*8-Chloro-11-(4-(3-(3-chlorophenoxy)propyl)piperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepine* ***3b***

Purified by flash chromatography (1:1 ethyl acetate/hexane), yellow microprisms (acetone/hexane), yield 63%. Mp 106.5–107°C (Found: C 64.8, H 5.4, N 11.8. $C_{26}H_{26}Cl_2N_4O$ requires C 64.8, H 5.4, N 11.7%.) ν_{max}(FTIR)/cm^{-1} 3296, 1596, 1557. λ_{max}/nm

(ε/M^{-1} cm^{-1}) 262 (19100), 297 (11700). δ_H (acetone[D_6]) 7.36–7.25 (3H, m, H1, H3, H5‴), 7.08–6.98 (2H, m, H4, H2), 6.98–6.79 (6H, m, H6, H7, H9, H2‴, H4‴, H6‴), 6.52 (1H, s, H5), 4.11 (2H, t, *J* 6.5, H3″), 3.42 (4H, m, H2′, H6′), 2.55 (2H, t, *J* 7, H1″), 2.52 (4H, m, H3′, H5′), 1.97 (2H, app p, *J* 6.5, H2″). δ_C 164.0 (C), 161.2 (C), 155.0 (C), 143.5 (C), 142.9 (C), 135.3 (C), 132.8 (CH), 131.5 (CH), 131.0 (CH), 128.6 (C), 127.0 (CH), 124.7 (C), 123.5 (CH), 123.4 (CH), 121.4 (CH), 121.3 (CH), 121.2 (CH), 115.6 (CH), 114.3 (CH), 67.3 (CH_2), 55.5 (CH_2), 53.9 (CH_2), 48.3 (CH_2), 27.5 (CH_2). *m/z* (ESI 20 V) 485.2 (M[$^{37}Cl_2$]H^+, 11%), 483.3 (M[^{37}Cl,^{35}Cl]H^+, 65%), 481.2 (M[$^{35}Cl_2$]H^+, 100).

*8-Chloro-11-(4-(3-(4-chlorophenoxy)propyl)piperazin-1-yl)-5*H*-dibenzo[b,e][1,4]diazepine* ***3c***

Purified by flash chromatography (4:1 ethyl acetate/hexane), yellow prisms (methanol/water), yield 47%. Mp 172–173°C (Found: C 64.9, H 5.5, N 11.6. $C_{26}H_{26}Cl_2N_4O$ requires: C 64.9, H 5.4, N 11.6%.) ν_{max} (FTIR)/cm^{-1} 3362, 1594, 1558. λ_{max}/nm (ε/M^{-1} cm^{-1}) 229 (40700), 261 (18200), 290 (12600). δ_H (acetone[D_6]) 7.38–7.24 (4H, m, H1, H3, H3‴, H5‴), 7.10–6.78 (7H, m, H2, H4, H6, H7, H9, H2‴, H6‴), 6.52 (1H, s, H5), 4.08 (2H, t, *J* 6.5, H3″), 3.42 (4H, m, H2′, H6′), 2.49–2.59 (6H, m, H3′, H5′, H1″), 1.96 (2H, app p, *J* 6.5, H2″). δ_C (acetone[D_6]) 163.1 (C), 158.1 (C), 154.1 (C), 142.5 (C), 142.0 (C), 131.9 (CH), 130.1 (CH), 129.2 (CH), 127.6 (C), 126.0 (CH), 124.7 (C), 123.7 (C), 122.5 (CH), 122.4 (CH), 120.4 (CH), 120.3 (CH), 120.2 (CH), 120.1 (CH), 116.1 (CH), 66.3 (CH_2), 54.6 (CH_2), 52.9 (CH_2), 47.4 (CH_2), 26.5 (CH_2). *m/z* (ESI 20 V) 483.2 (M[$^{37}Cl_2$]H^+, 62%), 481.2 (M[^{37}Cl,^{35}Cl]H^+, 100), 479.2 (M[$^{35}Cl_2$]H^+, 19).

*8-Chloro-11-(4-(3-(3-bromophenoxy)propyl)piperazin-1-yl)-5*H*-dibenzo[b,e][1,4]diazepine* ***3d***

Purified by flash chromatography (4:1 ethyl acetate/hexane), yellow foam, yield 36% (Found: C 59.5, H 5.1, N 10.4. $C_{26}H_{26}BrClN_4O$ requires: C 59.4, H 5.0, N 10.7%.) ν_{max}(FTIR)/cm^{-1} 3355, 1598, 1556. λ_{max}/nm ($\log_{10}\varepsilon$) 229 (41800), 263 (18900), 292 (12600). δ_H (acetone[D_6]) 7.35–7.28 (2H, m, H1, H3), 7.21 (1H, app td, *J* 8, 2, H5‴), 7.08–6.92 (6H, m, H2, H4, H9, H2‴, H4‴, H6‴), 6.88 (1H, d, *J* 8, H6), 6.80 (1H, dd, *J* 8.5, 2.5, H7), 6.51 (1H, s, H5), 4.09 (2H, t, *J* 6, H3″), 3.42 (4H, m, H2′, H6′), 2.62–2.46 (6H, m, H3′, H5′, H1″), 1.95 (2H, app p, *J* 6.5, H2″). δ_C (acetone[D_6]) 163.1 (C), 160.3 (C), 154.1 (C), 142.5 (C), 142.0 (C), 131.9 (CH), 130.9 (CH), 130.1 (CH), 127.6 (C), 126.1 (CH), 123.7 (C), 123.4 (CH), 122.5 (CH), 122.4 (C), 120.4 (CH), 117.6 (CH), 113.8 (CH), 66.3 (CH_2), 54.5 (CH_2), 52.9 (CH_2), 47.4 (CH_2), 26.5 (CH_2). *m/z* (ESI 20 V) 529.5 (M[^{81}Br,^{37}Cl]H^+, 26%), 527.3 (M[^{79}Br,^{37}Cl or ^{81}Br,^{35}Cl]H^+, 100), 525.3 (M[^{79}Br,^{35}Cl]H^+, 83).

*8-Chloro-11-(4-(3-(4-bromophenoxy)propyl)piperazin-1-yl)-5*H*-dibenzo[b,e][1,4]diazepine* ***3e***

Purified by flash chromatography (4:1 ethyl acetate/hexane), yellow microprisms (methanol/water), yield 70%. Mp 160–161°C (Found: C 57.7, H 5.8, N 9.8. $C_{26}H_{26}BrClN_4O{\cdot}CH_3OH$ requires: C 58.1, H 5.4, N 10.0%.) ν_{max}(FTIR)/cm^{-1} 3364, 1595, 1557. λ_{max}/nm (ε/M^{-1} cm^{-1}) 229 (42700), 261 (19100), 291 (12900). δ_H (acetone[D_6]) 7.45–7.38 (2H, m, H1, H3), 7.26–7.37 (2H, m, H3‴, H5‴), 7.11–6.98 (2H, m, H2‴, H6‴), 6.97–6.78 (5H, m, H2, H4, H6, H7, H9), 6.52 (1H, s, H5), 4.09 (2H, t, *J* 6.5, H3″), 3.42 (4H, m, H2′, H6′), 2.61–2.49 (6H, m, H3′, H5′, H1″), 1.97 (2H, app p, *J* 6.5, H2″). δ_C (acetone[D_6]) 163.6 (C), 159.2 (C), 155.2 (C), 143.1 (C), 142.5 (C), 133.0 (CH), 132.8 (CH), 131.0 (CH), 128.3 (C), 126.9 (CH), 124.4 (C), 123.42 (CH), 123.36 (CH), 121.3 (CH), 121.1 (CH), 117.5 (CH), 112.5 (C), 67.2 (CH_2), 55.5 (CH_2), 53.8 (CH_2), 48.3 (CH_2), 27.4 (CH_2). *m/z* (ESI 20 V) 529.5 (M[^{81}Br,^{37}Cl]H^+, 26%) 527.3 (M[^{79}Br,^{37}Cl or ^{81}Br,^{35}Cl]H^+, 100), 525.3 (M[^{79}Br,^{35}Cl]H^+, 86). ESI high-resolution MS: found *m/z* 525.1063 (MH^+). Calculated for $C_{26}H_{27}{}^{79}Br^{35}ClN_4O$: *m/z* 525.1057.

*8-Chloro-11-(4-(3-(3-methylphenoxy)propyl)piperazin-1-yl)-5*H*-dibenzo[b,e][1,4]diazepine* ***3f***

Purified by flash chromatography (4:3 ethyl acetate/hexane), yellow microneedles (dichloromethane/hexane), yield 76%. Mp 112.5–113°C (Found: C 70.0, H 6.7, N 11.8. $C_{27}H_{29}ClN_4O$ requires: C 70.3, H 6.3, N 12.2%.) ν_{max}(FTIR)/cm^{-1} 3294, 1597, 1556. λ_{max}/nm (ε/M^{-1} cm^{-1}) 262 (18600), 297 (11500). δ_H (acetone[D_6]) 7.36–7.29 (2H, m, H1, H3), 7.13 (1H, app t, *J* 7.5, H5‴), 7.08–6.70 (2H, m, H2, H4), 6.95 (1H, d, *J* 2.5, H9), 6.88 (1H, d, *J* 8.5, H6), 6.81 (1H, dd, *J* 8.5, 2.5, H7), 6.75–6.71 (3H, m, H2‴, H4‴, H6‴), 6.52 (1H, s, H5), 4.05 (2H, t, *J* 6.5, H3″), 3.42 (4H, m, H2′, H6′), 2.57–2.52 (6H, m, H3′, H5′, H1″), 2.28 (3H, s, CH_3), 1.95 (2H, app p, *J* 6.5, H2″). δ_C (acetone[D_6]) 164.1 (C), 160.3 (C), 155.0 (C), 143.5 (C), 142.9 (C), 140.1 (C), 132.8 (CH), 131.0 (CH), 130.1 (CH), 128.6 (C), 127.0 (CH), 124.7 (C), 123.5 (CH), 123.4 (CH), 122.1 (CH), 121.4 (CH), 121.2 (CH), 116.2 (CH), 112.4 (CH), 66.7 (CH_2), 55.7 (CH_2), 54.0 (CH_2), 48.4 (CH_2), 27.7 (CH_2), 21.6 (CH_3). *m/z* (ESI 20 V) 463.3 (M[^{37}Cl]H^+, 35%), 461.3 (M[^{35}Cl]H^+, 100), 459.3 (20). ESI high-resolution MS: found *m/z* 461.2118 (MH^+). Calculated for $C_{27}H_{30}{}^{35}ClN_4O$: *m/z* 461.2108.

*8-Chloro-11-(4-(3-(4-methylphenoxy)propyl)piperazin-1-yl)-5*H*-dibenzo[b,e][1,4]diazepine* ***3g***

Purified by flash chromatography (4:1 ethyl acetate/hexane), yellow prisms (methanol/water), yield 53%. Mp 154.5–156.5°C (Found: C 70.4, H 6.4, N 12.2. $C_{27}H_{29}ClN_4O$ requires: C 70.3, H 6.3, N 12.2%.) ν_{max}(KBr)/cm^{-1} 3292, 2920, 2852, 1598, 1558. λ_{max}/nm (ε/M^{-1} cm^{-1}) 225 (35500), 261 (18200), 297 (12000). δ_H (acetone[D_6]) 7.36–7.26 (m, 2H, H1, H3), 7.08–6.99 (m, 4H, H2, H4, H3‴, H5‴), 6.96 (m, 1H, H9), 6.88–6.75 (m, 4H, H6, H7, H2‴, H6‴), 6.52 (s, 1 H, H5), 4.02 (t, *J* 6.5, 2H, H3″), 3.41 (m, 4H, H2′, H6′), 2.60–2.50 (m, 6H, H1″, H3′, H5′), 2.23 (s, 3H, C*H*$_3$), 1.93 (2H, app p, *J* 6.5, H2″). δ_C (acetone[D_6]) 164.0 (C), 158.1 (C), 154.9 (C), 143.4 (C), 142.9 (C), 132.7 (CH), 130.9 (CH), 130.6 (CH), 130.1 (C), 128.5 (C), 126.9 (CH), 124.6 (C), 123.40 (CH), 123.35 (CH), 121.3 (CH), 121.1 (CH), 115.2 (CH), 66.8 (CH_2), 55.7 (CH_2), 53.8 (CH_2), 48.2 (CH_2), 27.6 (CH_2), 20.5 (CH_3). *m/z* (ESI 20 V) 463.3 (M[^{37}Cl]H^+, 36%), 461.3 (M[^{35}Cl]H^+, 100).

*8-Chloro-11-(4-(3-(4-methoxyphenoxy)propyl)piperazin-1-yl)-5*H*-dibenzo[b,e][1,4]diazepine* ***3h***

Purified by flash chromatography (4:1 ethyl acetate/hexane), yellow prisms (methanol/water), yield 40%. Mp 157.5–158°C (Found: C 68.4, H 6.5, N 11.6. $C_{27}H_{29}ClN_4O_2$ requires: C 68.0, H 6.1, N 11.8%.) ν_{max}(FTIR)/cm^{-1} 3358, 1595, 1552. λ_{max}/nm (ε/M^{-1} cm^{-1}) 227 (38000), 261 (18600), 294 (14100). δ_H (acetone[D_6]) 7.37–7.27 (2H, m, H1, H3), 7.10–6.98 (2H, m, H2, H4), 6.94 (1H, d, *J* 2.5, H9), 6.77–6.90 (6H, m, H6, H7, H3‴,

H4‴, H5‴, H6‴), 6.52 (1H, s, H5), 4.01 (2H, t, *J* 6.5, H3″), 3.73 (3H, s, OCH_3), 3.42 (4H, m, H2′, H6′), 2.54 (6H, m, H3′, H5′, H1″), 1.93 (2H, app p, *J* 6.5, H2″). δ_C (acetone[D_6]) 163.1 (C), 154.1 (C), 153.9 (C), 153.3 (C), 142.5 (C), 142.0 (C), 131.9 (CH), 130.0 (CH), 127.6 (C), 126.0 (CH), 123.7 (C), 122.5 (CH), 122.5 (CH), 120.4 (CH), 120.2 (CH), 120.1 (CH), 115.4 (CH), 114.5 (CH), 66.4 (CH_2), 55.0 (CH_3), 54.8 (CH_2), 53.0 (CH_2), 47.4 (CH_2), 26.8 (CH_2). *m/z* (ESI 20 V) 479.2 (M[^{37}Cl]H^+, 33%), 477.3 (MH^+, 100). ESI high-resolution MS: found *m/z* 477.209 (M[^{35}Cl]H^+). Calculated for $C_{27}H_{30}{}^{35}ClN_4O_2$: *m/z* 477.206.

*8-Chloro-11-(4-(3-(4-fluorophenoxy)propyl)piperazin-1-yl)-5*H*-dibenzo[b,e][1,4]diazepine **3i***

Purified by flash chromatography (4:1 ethyl acetate/hexane), yellow microprisms (methanol/water), yield 32%. Mp 172–174°C (Found: C 65.0, H 6.1, N 11.2. $C_{26}H_{26}ClFN_4O{\cdot}CH_3OH$ requires: C 65.3, H 6.1, N 11.3%.) ν_{max}(FTIR)/cm^{-1} 3359, 1595, 1558. λ_{max}/nm (ε/M^{-1} cm^{-1}) 269 (17800), 298 (12500). δ_H (acetone[D_6]) 7.38–7.27 (2H, m, H1, H3), 7.11–6.77 (9H, m, H2, H4, H6, H7, H9, H2‴, H3‴, H5‴, H6‴), 6.52 (1H, s, H5), 4.06 (2H, t, *J* 6.5, H3″), 3.42 (4H, m, H2′, H6′), 2.55 (6H, m, H3′, H5′, H1″), 1.96 (2H, app p, *J* 6.5, H2″). δ_C (acetone[D_6]) and δ_C (acetone[D_6]) 162.9 (C), 157.3 (d, *J* 238, CF), 155.2 (C), 152.8 (C), 141.9 (C), 140.5 (C), 132.0 (CH), 130.4 (CH), 129.1 (C), 126.8 (CH), 123.5 (C), 123.19 (CH), 123.16 (CH), 120.2 (CH), 120.1 (CH), 115.9 (d, *J* 23, C), 115.5 (d, *J* 8, C), 66.8 (CH_2), 55.2 (CH_2), 53.2 (CH_2), 47.3 (CH_2), 26.7 (CH_2). *m/z* (ESI 20 V) 467.3 (M[^{37}Cl]H^+, 33%), 465.3 (M[^{35}Cl]H^+, 100), 463.3 (20).

Pharmacology Procedures

Receptor Binding Assays

Receptor affinities were determined by MDS Pharma Services (Taiwan), by the ability of the tested compounds to displace selective radioligands. All assayed compounds were dissolved in dimethylsulfoxide (DMSO) to a stock concentration of 10^{-2} M, then diluted with assay buffer to a final concentration of 10^{-6} M. The assays were carried out using the following: (i) for dopamine $D_{4.4}$ receptors: human recombinant (expressed in mammalian CHO-K_1 cells), [^{3}H]spiperone (0.3 nM) as radioligand, and haloperidol (10 μM) as reference compound for non-specific binding; (ii) for serotonin 5-HT_{2A} receptors: rat cortex, [^{3}H]ketanserin (0.5 nM) as radioligand, and ketanserin (1 μM) as reference compound for non-specific binding. The binding results are expressed as the percentage inhibition (% I) of specific binding at a concentration of 10^{-6} M for the tested compound and represent the mean of duplicate tubes ± the maximum standard error in the mean.

Antagonism of Apomorphine-Induced Climbing in Mice

Adult female mice (20 to 30 g) were used for all the experiments and housed five per cage under controlled conditions of temperature (20 ± 1°C) and 12-h light–dark cycle (lights on 0600–1800 hours), with free access to food and tap water. The animals were brought into the laboratory and weighed 1 h before the commencement of the experiments to allow for acclimatization. All compounds assayed were prepared as their hydrochloride salts and dissolved in water for injections BP (British Pharmacopoeia) before *ip* injection. Mice (five per dose) were pretreated with test compound (10 mg kg^{-1} *ip*; 0.1 mL per 10 g bodyweight) 30 min before an injection of apomorphine hydrochloride (3 mg kg^{-1} *ip*). Climbing behaviour was assessed[30] 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 number of paws on the cage at a particular time point, at the moment the animal 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 results of the experiment were expressed as a mean value per mouse ± s.e.m (standard error of mean calculated by $^s/_{\sqrt{n}}$, where *s* is the sample standard deviation and *n* is the sample size). The value of percentage inhibition of climbing was calculated using the following formula.

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

Statistical Analysis

The statistical analysis was carried out by one-way analysis of variance (ANOVA) followed by Dunnett's test for pair-wise comparison of drug-treated groups and apomorphine-treated control, using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA, USA), with $P < 0.05$ being considered as statistically significant.

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