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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and preliminary in vitro and in vivo pharmacological evaluation of 4-{4-[2-(4-(2-substitutedquinoxalin-3-yl)piperazin-1-yl)ethyl]phenyl}thiazoles as atypical antipsychotic agents

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Abstract A series of 4-{4-[2-(4-(2-substitutedquinoxalin-3-yl)piperazin-1-yl)ethyl] phenyl} thiazoles were synthesized in an effort to prepare novel atypical antipsychotic agents. The compounds were designed, synthesized, and characterized by spectral data (IR, ^{1}H NMR, and MS) and the purity was ascertained by microanalysis. The D_2 and 5-HT_{2A} affinity of the synthesized compounds was screened in vitro by radioligand displacement assays on membrane homogenates isolated from rat striatum and rat cortex, respectively. Furthermore, all the synthesized final compounds (**10a–g**; **11a–g**; **12a–g**) were screened for their in vivo pharmacological activity in *Swiss albino* mice. D_2 antagonism studies were performed using climbing mouse assay model and 5-HT_{2A} antagonism studies were performed using quipazine-induced head twitches in mice. It was observed that none of the new chemical entities exhibited catalepsy and **12d**, **11f**, and **10a** were found to be the most active compounds with 5-HT_{2A}/D_2 ratio of 1.23077, 1.14286, and 1.12857, respectively, while the standard drug risperidone exhibited 5-HT_{2A}/D_2 ratio of 1.0989. Among the twenty one new chemical entities, three compounds (**12d**, **11f**, and **10a**) were found to exhibit better atypical antipsychotic activity as they were found to have higher Meltzer index than the standard drug risperidone.

Keywords Schizophrenia · Atypical antipsychotics · Quinoxalines · Phenyl thiazoles

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Introduction

Schizophrenia is a lifelong, complex psychotic disorder affecting around 1 % of world population (Carpenter and Buchanan, 1994). The characteristic symptoms of the disease have been classified into positive (hallucinations, delusions, and severe thought disorganization), negative (alogia, anhedonia, avolition, and flattened affect), and cognitive (slow thinking, poor concentration, poor memory, and difficulty in understanding) (Mueser and McGurk, 2004). The introduction of antipsychotics in the late 1950 s was a major break through in the management of schizophrenia and all these agents block dopamine D_2 receptors (Lewine *et al.*, 1983). Although blockade of D_2 receptors improves the positive symptoms, it also accounts for severe side effects such as extrapyramidal effects (EPS) (Casey, 1995), tardive dyskinesia (Marder *et al.*, 1991), and hyperprolactinemia (Wieck and Haddad, 2002).

Over the past three decades, much attention regarding the treatment of schizophrenia has focused on a new class of antipsychotics which cause no or minimal EPS at therapeutically relevant doses. These second-generation derivatives, categorized as atypical in contrast to conventional D_2 blockers, exhibit combined D_2 and 5-HT_{2A} antagonism.

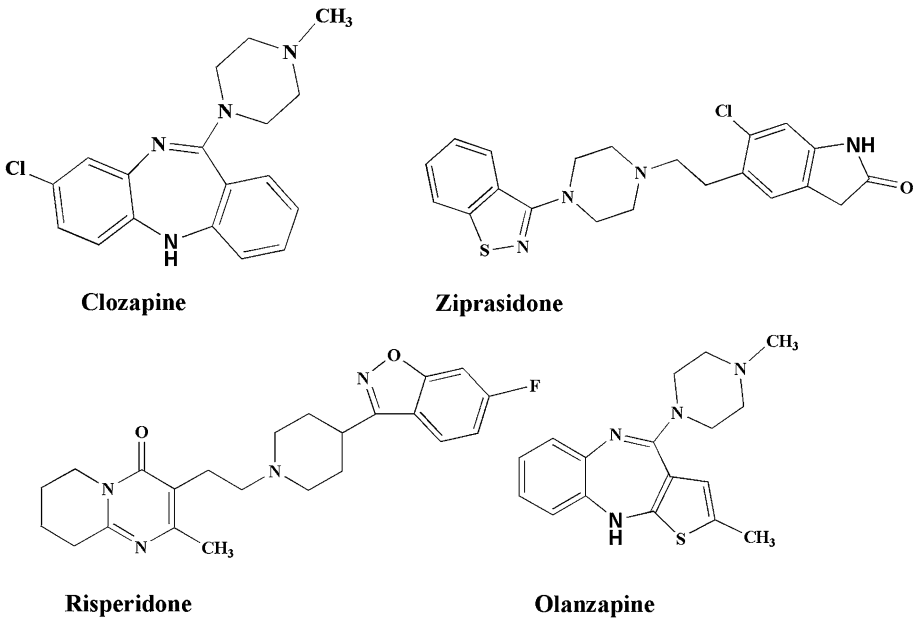


Fig. 1 Structures of some atypical antipsychotics developed based on Meltzer's classification

Compounds such as clozapine, risperidone, olanzapine, and ziprasidone (Fig. 1) developed based on this approach (Horacek *et al.*, 2006). Meltzer et al. (Meltzer *et al.*, 1989; Roth *et al.*, 1998) related the special clinical profile of clozapine and other atypical antipsychotics to an empirical ratio, the so-called Meltzer Index, between 5-HT_{2A} and D_2 receptors (Lowe, 1994). They proposed that this ratio may be used to discriminate atypical antipsychotics (ratio >1.12) from classical antipsychotics (<1.09). Antagonism at 5-HT_{2A} and D_2 receptors by these molecules is responsible for subsiding the negative and positive symptoms of the disorder, respectively (Meltzer *et al.*, 2003; Meltzer, 2004). Experimental and clinical studies seem to confirm the major role of the 5-HT_{2A} receptor for the atypical profile of the antipsychotics (Oekelen *et al.*, 2003; Okuyama *et al.*, 1997). However, these compounds are also not completely devoid of side effects. Side effects caused by "atypical antipsychotics" are a result of their significant binding to numerous receptors other than required for atypical antipsychotic activity. Side effects associated with these drugs include, weight gain (serotonergic 5-HT_{2C} and histaminic H_1 receptors blockade) (Wirshing *et al.*, 1999); postural or orthostatic hypotension; sedation; dizziness (α_1-adrenergic blockade); somnolence (histaminic H_1 receptor blockade); seizures (muscarinic receptor blockade) (Owens, 1996); newonset type2 diabetes mellitus (Cohen, 2004); hyperlipidemia; atropine-like side effects such as dry mouth, constipation, and urinary retention (muscarinic M_1 receptor blockade); cardiac ventricular arrhythmias (prolongation of QT interval due to the blockade of Ikr channels); myocarditis; insomnia; headache; and other possible secondary cardiovascular complications (Tamminga, 1997). Hence the search for more effective and less toxic therapies for schizophrenia continues.

The rationale for the development of the antipsychotic drugs recently introduced, and currently under investigation is predominantly based on the dopamine and serotonin hypotheses of schizophrenia (Graham *et al.*, 2008; Garzya *et al.*, 2007). In continuation of our quest for novel atypical antipsychotics (Chandra Sekhar *et al.*, 2008, 2009, 2011), we synthesized 4-{4-[2-(4-(2-substitutedquinoxalin-3-yl)piperazin-1-yl)ethyl]phenyl}thiazole derivatives and evaluated them for their in vitro and in vivo pharmacological activity.

The strategy of Ariens has been employed for the design of the compounds (Ariens *et al.*, 1979). Ariens strategy in brief, involves modification of the structure of a receptor agonist; in this case, dopamine, with a large lipophilic group on the amino position, binds to the accessory binding site adjacent to the agonist binding site and transforms the agonist into an antagonist (Figs. 2, 3). Using this strategy, the currently marketed drug ziprasidone was developed

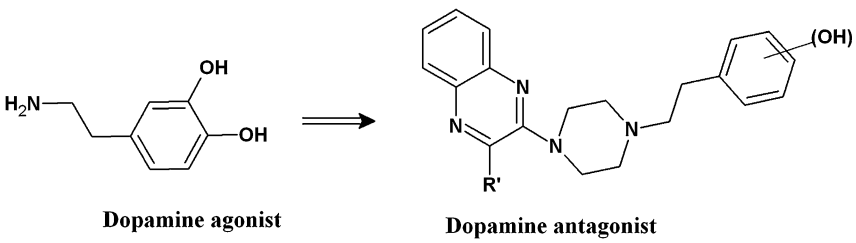
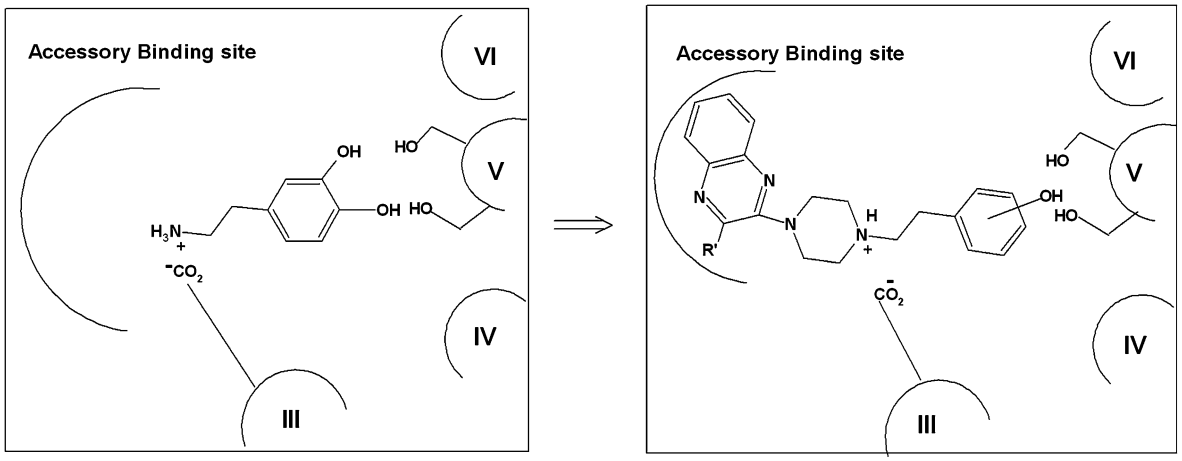


Fig. 2 Conversion of dopamine agonist into an antagonist



D_2 Receptor - Agonist Binding **D_2 Receptor - Antagonist Binding**

Fig. 3 Model of D_2 receptor, based on studies of the β-adrenergic receptor, showing proposed agonist and antagonist binding used in receptor antagonist design (Lowe et al. 1991)

(Howard *et al.*, 1996). We adapted this strategy and employed piperazinyl quinoxalines, which have affinity toward serotonin receptors (Monge *et al.*, 1993; Lumma Jr. *et al.*, 1981) as one portion of the molecule and chloroethylphenylthiazoles was selected as the other portion as Pfizer group has come up with potent atypical antipsychotics using the heterocycle 1-Naphthyl piperazine. (Lowe *et al.*, 1991).

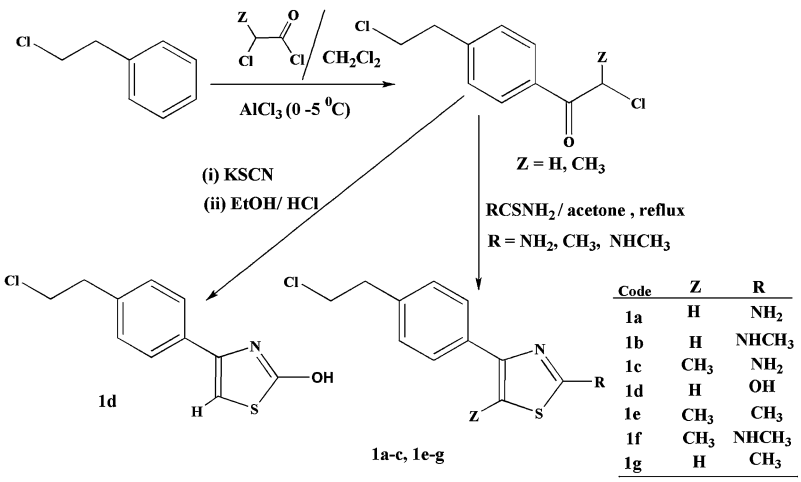
Results and discussion

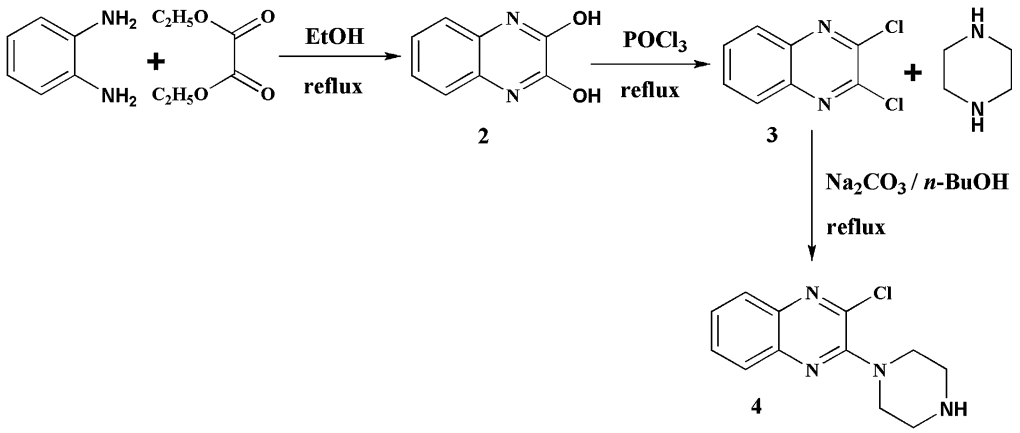
The synthetic steps of the new compounds are summarized in Schemes 1, 2, 3, 4, and 5. 2- and 5-substituted chloroethylphenylthiazoles (**1a**–**g**) were prepared according to the literature protocol with modifications in some steps (Scheme 1) (Lowe *et al.*, 1991). Equimolar amounts of *o*-phenylenediamine and diethyloxalate on refluxing for 6 h in ethanol afforded 2,3-dihydroxyquinoxaline (**2**) (Hinsberg and Pollak, 1896). Chlorination of dihydroxy compound with phosphorous oxychloride yielded 2,3-dichloroquinoxaline (**3**) (Reddy Sastry *et al.*, 1991). The chloro compound in the presence of anhydrous sodium carbonate on reaction with anhydrous piperazine gave 2-chloro-3-piperazinyl quinoxaline (**4**) (Scheme 2).

Synthesis of compound **6** is depicted in Scheme 3. Compound **3** on stirring with methanol in the presence of phase transfer catalyst—benzyltriethylammonium chloride at room temperature yielded compound **5** (Krishnan and Srinivasulu, 2000). 2-chloro-3-methoxyquinoxaline (**5**) on stirring at room temperature with anhydrous piperazine in the presence of acetonitrile gave 2-methoxy-3-piperazinylquinoxaline (**6**).

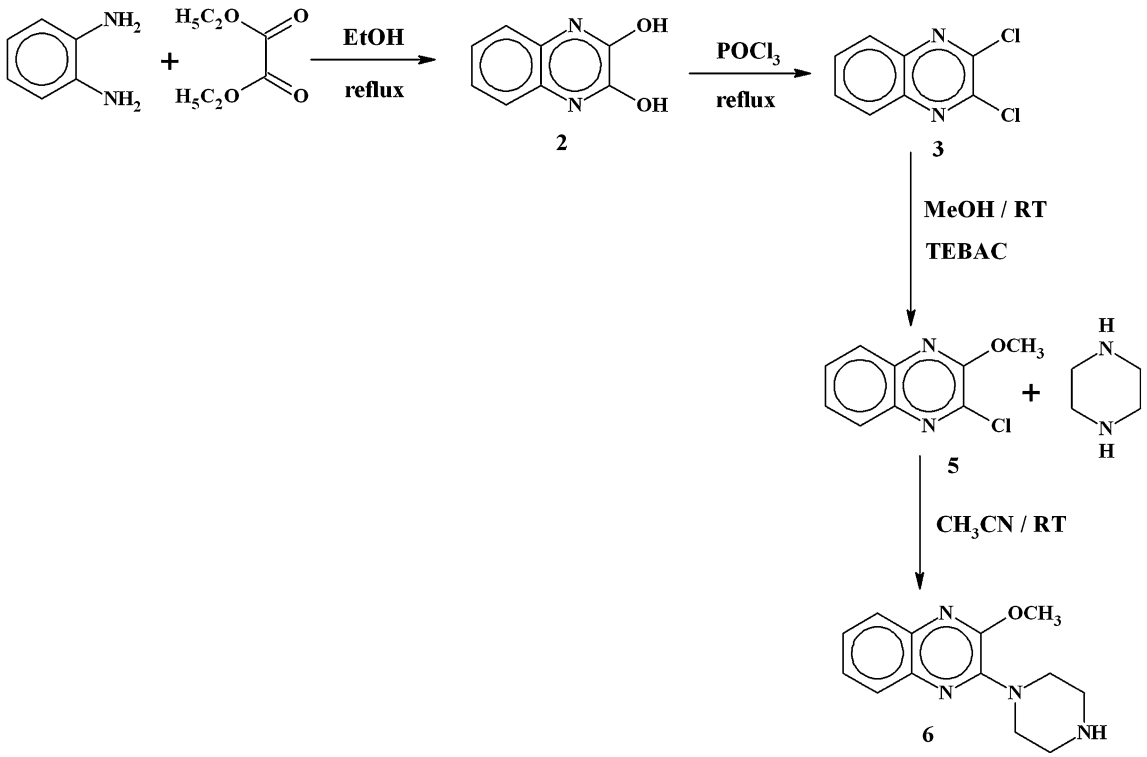
Scheme 4 illustrates the preparation of compound **9**, which was according to the literature (Lumma Jr. *et al.*, 1981). Refluxing equimolar amounts of *n*-butyl glyoxalate and

Scheme 1 Synthesis of chloroethylphenylthiazoles (**1a–g**)





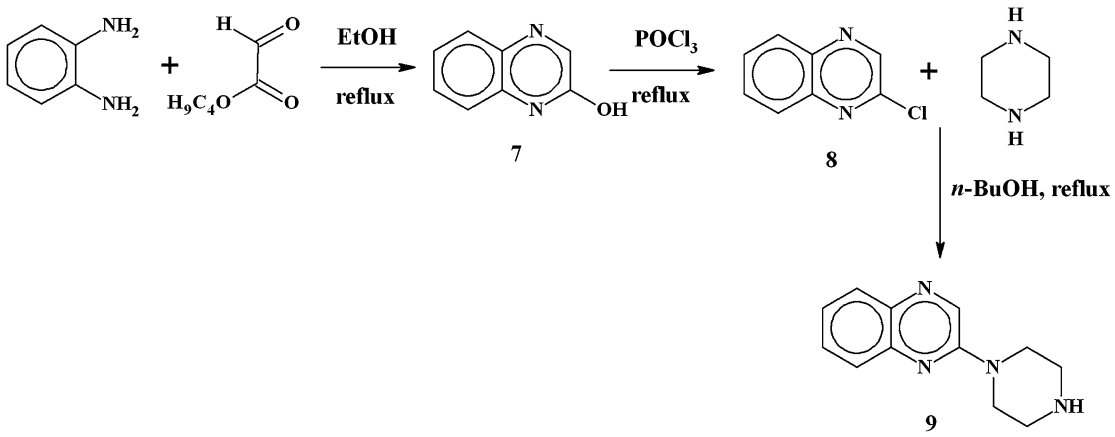
Scheme 2 Synthesis of 2-chloro-3-piperazinyl quinoxaline (**4**)



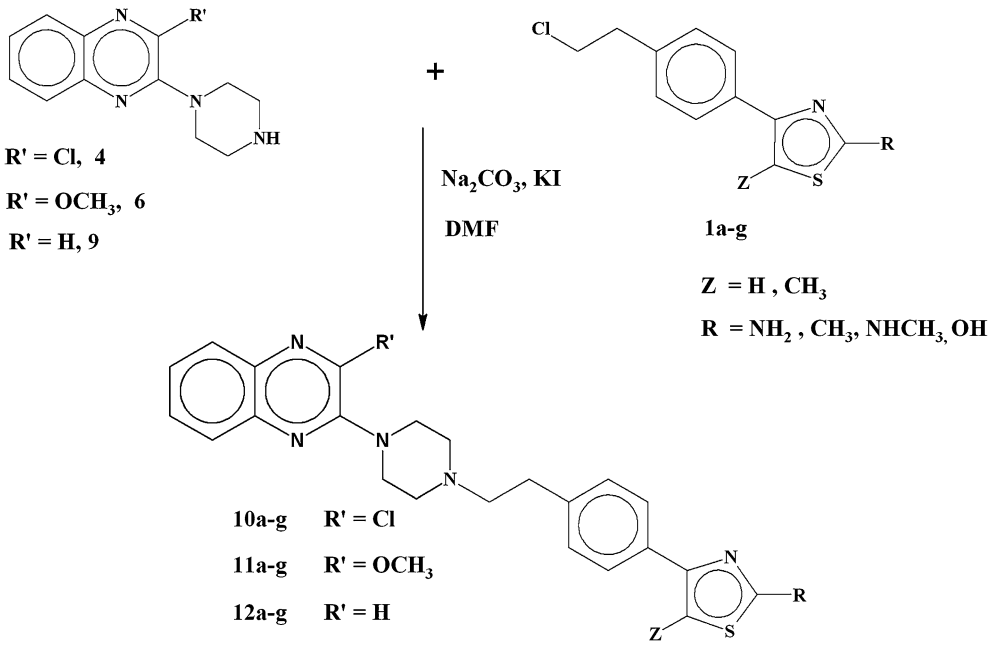
Scheme 3 Synthesis of 2-methoxy-3-piperazinylquinoxaline (**6**)

o-phenylenediamine in ethanol yielded 2-hydroxyquinoxaline (**7**), which on further chlorination with phosphorous oxychloride gave the chloro derivative (**8**). 2-chloroquinoxaline (**8**) was further converted to 2-piperazinylquinoxaline (**9**).

Preparation of the final compounds is outlined in Scheme 5. Equimolar amounts of **4**, **6**, or **9** and any one of the compounds **1a**–**g** along with 2.125 equivalents of anhydrous Na_2CO_3 and catalytic amount of KI (2 mg) in DMF as solvent when refluxed for 48 h afforded the title compounds (**10 a**–**g**; **11a**–**g**; **12a**–**g**). All the synthesized compounds were characterized by spectral (IR, ^{1}H NMR, and HRMS) and elemental analysis data. Infrared analysis of the final compounds showed strong peaks at ~3440 cm^{-1} (NH stretch); ~3065 cm^{-1} (aromatic C–H stretch); ~2825 cm^{-1} (aliphatic C–H stretch); ~710 cm^{-1} (C–S–C stretch); ~1610 cm^{-1} (aromatic C=C stretch); ~1640 cm^{-1} (C=N ring stretch); ~1100 cm^{-1} (aliphatic C–O stretch for **11a**–**g**); ~1260 cm^{-1} (aliphatic C–N stretch); ~810 cm^{-1} (para disubstituted benzene); ~770 cm^{-1} (C–Cl stretch for **10a**–**g**). In ^{1}H-NMR spectra, methylene protons (cyclic) adjacent to N^1 nitrogen of piperazine showed triplet in the range of δ 3.06–3.21,



Scheme 4 Synthesis of 2-piperazinylquinoxaline (**9**)



Scheme 5 Synthesis of 4-{4-[2-(4-(2-substitutedquinoxalin-3-yl)piperazin-1-yl)ethyl] phenyl} thiazoles (**10a–g**; **11a–g**; **12a–g**)

whereas methylene protons (cyclic) adjacent to N^4 nitrogen of piperazine showed triplet in the range of δ 2.59–2.68. The final compounds showed the ^{1}H-NMR signals at δ 7.18–8.19 (for the aromatic protons as a multiplet) and δ 2.61–2.69 (for four protons of the ethyl linker as multiplet). Elemental (CHNS) analysis indicated that the calculated and observed values were within the acceptable limits (±0.4 %).

Receptor binding studies

In vitro pharmacological studies

The D_2 and 5-HT_{2A} affinity of the new chemical entities (NCEs) was screened in vitro by radioligand displacement assays on membrane homogenates isolated from rat striatum and rat cortex, respectively. For D_2 affinity test, striatal membranes were incubated with 0.5 nM [^{3}H]spiperone (101 Ci/mmol; Amersham) and 10 or 100 μM of the NCEs in 50 mM TRIS–HCl, pH 7.4, at 21 °C for 60 min. Non-specific binding of [^{3}H]spiperone was determined with 10 μM haloperidol and accounted for 30 % of the total binding. For 5-HT_{2A} affinity test, cortical membranes were incubated with 0.6 nM [^{3}H]ketanserin (67 Ci/mmol; Perkin Elmer) and 10 μM of the NCEs in 50 mM TRIS–HCl, pH 7.4, at 21 °C for 90 min. Nonspecific binding of [^{3}H]ketanserin was determined with 10 μM mianserin and accounted for 20 % of the total binding. The incubation was terminated by rapid filtration on a Brandel cell harvester, and filter-bound radioactivity was measured by

Table 1 Results of radioligand displacement on D_2 ([^{3}H]spiperone-labeled rat striatum) and 5-HT_{2A} ([^{3}H]ketanserin-labeled rat cortex) of the final compounds (**10a–g**; **11a–g**; **12a–g**)

S. no.	Code	R	Z	R′	D_2% displacement at 100 μM (mean; $n = 2$)	5-HT_{2A} % displacement at 10 μM (mean; $n = 2$)
1	**10a**	NH_2	H	Cl	0	4
2	**10b**	$NHCH_3$	H	Cl	0	14
3	**10c**	NH_2	CH_3	Cl	0	0
4	**10d**	OH	H	Cl	0	0
5	**10e**	CH_3	CH_3	Cl	0	31
6	**10f**	$NHCH_3$	CH_3	Cl	0	31
7	**10g**	CH_3	H	Cl	0	30
8	**11a**	NH_2	H	OMe	24	49
9	**11b**	$NHCH_3$	H	OMe	40	58
10	**11c**	NH_2	CH_3	OMe	nd	nd
11	**11d**	OH	H	OMe	0	28
12	**11e**	CH_3	CH_3	OMe	nd	nd
13	**11f**	$NHCH_3$	CH_3	OMe	nd	nd
14	**11g**	CH_3	H	OMe	82	68
15	**12a**	NH_2	H	H	26	51
16	**12b**	$NHCH_3$	H	H	0	57
17	**12c**	NH_2	CH_3	H	0	58
18	**12d**	OH	H	H	0	22
19	**12e**	CH_3	CH_3	H	nd	nd
20	**12f**	$NHCH_3$	CH_3	H	nd	nd
21	**12g**	CH_3	H	H	30	63

nd Not determined

liquid scintillation counting. All assays were performed in triplicate and repeated twice. The aim of this study is to synthesize new second-generation antipsychotics, which exhibit combined D_2 and 5-HT_{2A} antagonism. At 100 μM, 5 out of 16 NCEs displaced 80–24 % of the D_2-specific radiotracer, while at 10 μM no inhibition was found. Regarding the 5-HT_{2A} affinity in the **11** and **12** series all NCEs investigated and in the **10** series 3 out of the 7 NCEs investigated displaced 68–22 % of the 5-HT_{2A}-specific radiotracer at 10 μM. The results with respect to the 5-HT_{2A} receptor indicate a clear interaction of nearly all NCEs with the orthosteric binding site of this target at pharmacologically relevant concentrations. In vitro findings are tabulated in Table 1. The observed stronger 5-HT_{2A} receptor affinity of most derivatives is in accordance with the expected atypical profile of the new antipsychotics.

The Institutional Animal Ethics Committee of the Birla Institute of Technology and Science, Pilani, India, approved experimentation on animals (Protocol No. IAEC/RES/11/2). *Swiss albino* mice (25–30 g) of either sex obtained from Hissar Agricultural University, Haryana, India were used for the pharmacological studies. Inhibition or reversal of Apomorphine induced cage-climbing behavior in mice by a test compound is an indication of mesolimbic dopaminergic D_2 receptor antagonism (Costall *et al.*, 1978).

Pharmacokinetic studies carried out showed that the exposure at 10 mg/kg dose was similar to the exposure of several atypical antipsychotics at therapeutically relevant doses, and hence this dose was chosen to carry out the in vivo pharmacological tests. The effect of pretreatment with 10 mg/kg dose of the test compounds on apomorphine (0.5 mg/kg s.c.) induced cage-climbing behavior was studied by the literature method (Costall *et al.*, 1978). Haloperidol (1.0 mg/kg i.p.) was used as control as it completely inhibited the climbing induced by apomorphine. Inhibition or reversal of quipazine-induced head twitches in mice by the test molecule (10 mg/kg dose) is an indication of central serotonergic 5-HT_{2A} receptor antagonism and this behavior was studied by the literature method (Malick *et al.*, 1977). Risperidone (0.6 mg/kg i.p) was used as control as it completely inhibits quipazine-induced head twitches in mice. Cataleptic effect of NCEs was evaluated and scoring was done according to the literature method (Joshi *et al.*, 1979).

In vivo Pharmacological Studies

Percentage inhibition (expressed as mean (μ) ± standard error mean (S.E.M.)), in antagonizing dopamine D_2 receptors, is calculated at 10, 20, and 30 min after injecting apomorphine hydrochloride and the results obtained are detailed in Table 2. The results clearly indicate that all the NCEs have the capability of antagonizing mesolimbic dopaminergic D_2 receptors with % inhibition varying between 25 and 95 % at the studied dose level. A maximum of 95 % inhibition was observed for **10f** and **12c**, while a minimum of 25 % inhibition was observed for **12b** and **12e**. Percentage inhibition (expressed as mean (μ) ± standard error mean (SEM) in antagonizing central serotonergic 5-HT_{2A} receptors is calculated and the results obtained are detailed in Table 2 as per the literature protocol (Lee *et al.*, 2003). The results clearly indicate that all the NCEs have the capability of antagonizing central serotonergic 5-HT_{2A} receptors with % inhibition varying between 12 % and 86 % at the studied dose level. A maximum of 86 % inhibition was observed for **10c**, while a minimum of 12 % inhibition was observed for **11a**.

Average cataleptic time calculated after injecting NCEs at *t*th hour for all the final compounds is outlined in Table 2. The table also describes the maximum average cataleptic time and the maximum average score for each compound. The results tabulated in Table 3 clearly indicate that the maximum average cataleptic score observed is either 0 or 1 for the NCEs at studied dose level indicating that most of the compounds are noncataleptic. Among the final compounds, **10c** and **10d** exhibited maximum score of 1 each indicating

Table 2 Results of D_2 and 5-HT_{2A} antagonism and catalepsy test of the final compounds (**10a–g**; **11a–g**; **12a–g**)

S. no.	Code	% D_2 inhibition (mean ± SEM)			% 5-HT_{2A} inhibition (mean ± SEM)	Max. average cataleptic time (s)	Max. average cataleptic score
		10th Min	20th Min	30th Min			
1	**10a**	65 ± 10	60 ± 10	70 ± 9.35	79 ± 6.90	18.24	0
2	**10b**	60 ± 10	80 ± 12.25	80 ± 12.25	41 ± 2.78	3.96	0
3	**10c**	80 ± 6.12	80 ± 6.12	65 ± 10	86 ± 2.78	23.5	1
4	**10d**	60 ± 10	60 ± 10	50 ± 5.81	58 ± 3.65	28.25	1
5	**10e**	60 ± 10	60 ± 10	80 ± 12.25	51 ± 5.55	9.25	0
6	**10f**	95 ± 5	95 ± 5	70 ± 12.25	81 ± 2.78	8.12	0
7	**10g**	80 ± 12.25	65 ± 6.12	75 ± 11.18	62 ± 1.67	3.25	0
8	**11a**	60 ± 10	60 ± 6.96	65 ± 10	12 ± 2.78	14.12	0
9	**11b**	60 ± 10	85 ± 6.12	65 ± 8.71	51 ± 3.74	10.67	0
10	**11c**	65 ± 10	80 ± 12.25	65 ± 8.71	60 ± 2.37	10.78	0
11	**11d**	65 ± 6.12	60 ± 10	60 ± 10	67 ± 2.78	7.90	0
12	**11e**	85 ± 6.12	70 ± 9.35	65 ± 6.12	65 ± 8.53	11.25	0
13	**11f**	60 ± 10	50 ± 5.81	70 ± 12.25	80 ± 5.02	3.12	0
14	**11g**	85 ± 10	70 ± 12.25	65 ± 6.12	62 ± 11.23	6.25	0
15	**12a**	60 ± 10	75 ± 11.18	65 ± 6.96	15 ± 2.78	9.21	0
16	**12b**	25 ± 5.81	50 ± 5	60 ± 10	36 ± 6.26	9.32	0
17	**12c**	95 ± 5	80 ± 12.25	60 ± 10	31 ± 2.37	2.64	0
18	**12d**	60 ± 8.71	65 ± 10	65 ± 10	80 ± 3.74	3.19	0
19	**12e**	25 ± 5.81	50 ± 5.81	70 ± 12.25	32 ± 4.95	9.32	0
20	**12f**	60 ± 10	75 ± 7.91	65 ± 10	55 ± 5.98	3.88	0
21	**12g**	75 ± 11.18	55 ± 6.58	85 ± 10	77 ± 4.10	5.17	0
Risperidone		91 ± 5	91 ± 5	90 ± 5	100 ± 0	2.54	0

that these compounds exhibit slight catalepsy. Hence, it can be concluded that all NCEs except **10c** and **10d** do not antagonize nigrostriatal dopaminergic D_2 receptors.

Although none of the NCEs tested inhibited either the specific binding of the 5-HT_{2A} ligand [^{3}H]ketanserine or the D_2 ligand [^{3}H]spiperone up to 1 μM in vitro (Table 1), in vivo pharmacological data clearly indicate an atypical antipsychotic efficacy of the NCEs. This inconsistency might be attributed to the difference in the extent of uptake or distribution of NCEs into the target cells. The difference in the uptake or distribution into the cells could be because of the mechanism involved in the transportation of the NCEs such as carrier-mediated transport in the in vivo studies, while such mechanism might be absent in case of in vitro studies (Goodman and Gilman's, 2006; Chandra Sekhar *et al.*, 2011). Further studies are in progress in our laboratory to determine the exact mechanism of action of the NCEs.

Experimental

Chemistry

Melting points were determined in open capillaries using Büchi 530 melting point apparatus without correction. The reactions were monitored and the purity of the compounds was checked by ascending thin layer chromatography (TLC) on silica gel-coated aluminum plates (Merck 60 F254, 0.25 mm) using mixture of chloroform and methanol and the spots were visualized under ultra violet light at 254 and 366 nm. Infra red (IR) spectra were recorded in KBr pellets on Schimadzu IR Prestige-21 FT-IR spectrophotometer (cm^{-1}). ^{1}H-NMR spectra were obtained from Bruker DRX300 spectrometer using tetramethylsilane as internal standard [chemical shifts in δ, parts per million (ppm)], mass spectra on a VG-70-S mass spectrometer and elemental analysis on a Perkin Elmer 2400 CHNS elemental analyzer. All compounds showed >95 % purity.

2-chloro-3-piperazinylquinoxaline (**4**): A mixture of 2,3–dichloroquinoxaline (4.97 g, 25 mmol), anhydrous piperazine (10 g, 116 mmol), and anhydrous sodium carbonate (5 g, 47 mmol) in 75 ml of *n*-butanol was initially stirred for 2 h at room temperature and then refluxed for 20 h in oil bath. The reaction mixture was cooled and concentrated in vacuo to yield light yellow solid which is recrystallised with ethanol to yield 84 % (5.22 g) of 2-chloro-3-piperazinyl quinoxaline (**4**) melting at 130–132 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.52–2.63 (t, 4H, J = 4.8 Hz, $N^4(CH_2)_2$); 3.10–3.16 (t, 4H, J = 4.8 Hz, $N^1(CH_2)_2$); 5.26 (s, 1H, NH); 7.63–8.07 (m, 4H, Ar–H). IR

Table 3 Summary of results of in vivo pharmacological studies of the final compounds (**10a–g**; **11a–g**; **12a–g**)

S. no.	Code	% 5-HT_{2A} inhibition	% Max. D_2 inhibition	5-HT_{2A}/D_2 ratio	Max. avg. cataleptic score
1	**10a**	79 ± 6.90	70 ± 9.35	1.12857	0
2	**10b**	41 ± 2.78	80 ± 12.25	0.51250	0
3	**10c**	86 ± 2.78	80 ± 6.12	1.07500	1
4	**10d**	58 ± 3.65	60 ± 10	0.96667	1
5	**10e**	51 ± 5.55	80 ± 12.25	0.63750	0
6	**10f**	81 ± 2.78	95 ± 5	0.85260	0
7	**10g**	62 ± 1.67	80 ± 12.25	0.77500	0
8	**11a**	12 ± 2.78	65 ± 10	0.18462	0
9	**11b**	51 ± 3.74	85 ± 6.12	0.60000	0
10	**11c**	60 ± 2.37	80 ± 12.25	0.75000	0
11	**11d**	67 ± 2.78	65 ± 6.12	1.03077	0
12	**11e**	65 ± 8.53	85 ± 6.12	0.76470	0
13	**11f**	80 ± 5.02	70 ± 12.25	1.14286	0
14	**11g**	62 ± 11.23	85 ± 10	0.72941	0
15	**12a**	15 ± 2.78	75 ± 11.18	0.20000	0
16	**12b**	36 ± 6.26	60 ± 10	0.60000	0
17	**12c**	31 ± 2.37	95 ± 5	0.32632	0
18	**12d**	80 ± 3.74	65 ± 10	1.23077	0
19	**12e**	32 ± 4.95	70 ± 12.25	0.45714	0
20	**12f**	55 ± 5.98	75 ± 7.91	0.73333	0
21	**12g**	77 ± 4.10	85 ± 10	0.90589	0
Risperidone		100 ± 0	91 ± 5	1.09890	0

(KBr, *v*) cm^{-1}: 3340 (NH stretch); 3065, 3015 (aromatic C–H stretch); 2825, 2758 (aliphatic C–H stretch); 1644, 1608 (aromatic C=C stretch); 1596 (C=N ring stretch); 760 (C–Cl stretch); 735 (ortho substituted). HRMS (ESI) calcd for $C_{12}H_{13}ClN_4$ $[M + H]^+$: 248.0432; found: 248.0419. Anal. calculated for $C_{12}H_{13}ClN_4$: C 57.95, H 5.27, N 22.53; found: C 57.76, H 5.19, N 22.47.

2-methoxy-3-piperazinylquinoxaline (**6**): A mixture of 2-chloro-3-methoxyquinoxaline (3.9 g, 20 mmol) and anhydrous piperazine (5.184 g, 60 mmol) in 30 mL of acetonitrile was stirred at room temperature for 5 h. Once the reaction showed completion on TLC (9:1 $CHCl_3$, MeOH as mobile phase), the reaction mixture was poured into ice-water mixture and extracted with 3 × 50 mL portions of ethyl actetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to yield 2-methoxy-3-piperazinylquinoxaline (**6**), which is recrystallised from ethanol to afford 84 % (4.1 g) of 2-methoxy-3-piperazinylquinoxaline (**6**) melting at 80–82 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.47–2.56 (t, 4H, $J = 4.8$ Hz, $N^4(CH_2)_2$); 3.13–3.18 (t, 4H, $J = 4.8$ Hz, $N^1(CH_2)_2$); 3.68 (s, 3H, OCH_3); 5.26 (s, 1H, NH); 7.63–8.07 (m, 4H, Ar–H). IR (KBr, *v*) cm^{-1}: 3343 (NH stretch); 3057, 3024 (aromatic C–H stretch), 2875, 2855 (aliphatic C–H stretch); 1652, 1608 (aromatic C=C stretch); 1589 (C=N ring stretch); 1060 (C–O stretch); 740 (ortho substituted). HRMS (ESI) calcd for $C_{13}H_{16}N_4O$ $[M + H]^+$: 244.1337; found: 244.1329. Anal. calculated for $C_{13}H_{16}N_4O$: C 63.91, H 6.60, N 22.93; found: C 63.76, H 6.48, N 22.76.

*Syntheses of (**10a–g**; **11a–g**; **12a–g**)*: The procedure described by Lowe III *et al.*, (1991) was adapted for this preparation. In a 10 ml round bottom flask equipped with a reflux condenser and N_2 inlet, equimolar amounts (0.05 mmol) of 2-chloro-3-piperazinylquinoxaline (**4**), 2-methoxy-3-piperazinylquinoxaline (**6**) or 2-piperazinylquinoxaline (**9**) and respective chloroethylphenylthiazole (**1a–g**); and sodium carbonate (0.1174 g, 1.11 mmol) and potassium iodide (2 mg) in 2 ml of DMF were placed. The reaction mixture was refluxed for 48 h. Once the reaction showed completion on TLC (9:1 $CHCl_3$, MeOH as mobile phase), the cooled reaction mixture was poured into ice-water mixture and the precipitate was filtered, washed with water, and recrystallised in suitable solvents to afford the pure final compounds **10a–g**; **11a–d** and **g**; **12a–d** and **g**. For compounds **11e**, **11f**, **12e**, and **12f**, once the reaction showed completion on TLC (9:1 $CHCl_3$, MeOH as mobile phase), the cooled reaction mixture was poured into ice-water mixture and the compound was extracted using ethylacetate (3 × 5 mL). Combined organic layers were washed with saturated aqueous brine solution (5 mL) and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure using rotary evaporator and the resultant residue was chromatographed on silica gel (230–400 mesh) using 3 % MeOH in $CHCl_3$ as eluent to afford oily title compound (**11e**, **11f**, **12e**, and **12f**).

*{4-[2-(4-(2-chloroquinoxalin-3-yl)piperazin-1-yl]ethyl)phenyl}-thiazol-2-amine (**10a**)*

Recrystallisation Solvent: Ethanol. % Yield: 77 % (0.174 g); mp: 162–164 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.59–2.63 (t, 4H, $J = 4.8$ Hz, $N^4(CH_2)_2$); 2.65–2.69 (m, 4H, $(CH_2)_2$); 3.16–3.19 (t, 4H, $J = 4.8$ Hz, $N^1(CH_2)_2$); 3.84 (s, 2H, NH_2); 6.95 (s, 1H, thiazole); 7.18–8.07 (m, 8H, Ar–H). IR (KBr, *v*) cm^{-1}: 3440, 3410 (NH stretch); 3065, 3027 (aromatic C–H stretch); 2825, 2758 (aliphatic C–H stretch); 1638 (C=N ring stretch); 1608, 1596 (aromatic C=C stretch); 1259 (aliphatic C–N stretch), 810 (para disubstituted benzene); 770 (C–Cl stretch), 708 (aromatic C–H bending). HRMS (ESI) calcd for $C_{23}H_{23}ClN_6S$ $[M + H]^+$: 450.1426; found: 450.1417; Anal. calculated for $C_{23}H_{23}ClN_6S$: C 61.25, H 5.14, N 18.63, S 7.11; found: C 61.11, H 5.19, N 18.45, S 7.05.

*4-{4-[2-(4-(2-chloroquinoxalin-3-yl)piperazin-1-yl)ethyl]phenyl}-N-methylthiazol-2-amine (**10b**)*

Recrystallisation Solvent: Methanol. % Yield: 79 % (0.181 g); mp: 140–142 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.49 (s, 3H, NHC$\underline{H}_3$); 2.53–2.62 (t, 4H, $J = 4.9$ Hz, $N^4(CH_2)_2$); 2.67–2.72 (m, 4H, $(CH_2)_2$); 3.11–3.17 (t, 4H, $J = 4.9$ Hz, $N^1(CH_2)_2$); 4.02 (s, 1H, N$\underline{H}$CH$_3$); 6.61 (s, 1H, thiazole); 7.21-8.16 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3335 (NH stretch); 3054, 3015 (aromatic C–H stretch); 2856, 2745 (aliphatic C–H stretch); 1632 (C–S stretch); 1605, 1575 (aromatic C=C stretch); 1257 (aliphatic C–N stretch); 815 (para disubstituted benzene); 758 (C–Cl stretch), 705 (aromatic C–H bending). HRMS (ESI) calcd for $C_{24}H_{25}ClN_6S$ $[M + H]^+$: 464.1322; found: 464.1318; Anal. calculated for $C_{24}H_{25}ClN_6S$: C 61.99, H 5.42, N 18.07, S 6.90; found: C 61.91, H 5.41, N 18.05, S 6.85.

*2-{4-[2-(4-(2-chloroquinoxalin-3-yl)piperazin-1-yl)ethyl]phenyl}-5-methylthiazol-2-amine (**10c**)*

Recrystallisation Solvent: Ethanol. % Yield: 79 % (0.183 g); mp: 158–160 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.35 (s, 3H, CH_3); 2.48–2.56 (t, 4H, $J = 4.9$ Hz, $N^4(CH_2)_2$); 2.61-2.67 (m, 4H, $(CH_2)_2$); 3.09-3.15 (t, 4H, $J = 4.9$ Hz, $N^1(CH_2)_2$); 3.77 (s, 2H, NH_2); 7.19–8.05 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3428, 3407 (NH stretch), 3020, 2895 (aromatic C–H stretch); 2810 (aliphatic C–H stretch); 1640, 1602 (aromatic C=C stretch); 1260 (aliphatic C–N stretch), 817 (para disubstituted benzene); 766 (C–Cl stretch), 711 (aromatic C–H bending). HRMS (ESI) calcd for $C_{24}H_{25}ClN_6S$ $[M + H]^+$: 464.1486; found: 464.1480; Anal. calculated for $C_{24}H_{25}ClN_6S$: C 61.99, H 5.42, N 18.07, S 6.90; found: C 61.89, H 5.38, N 18.03, S 6.88.

*4-{4-[2-(4-(2-chloroquinoxalin-3-yl)piperazin-1-yl)ethyl]phenyl}-thiazol-2-ol (**10d**)*

Recrystallisation Solvent: Ethanol. % Yield: 78 % (0.175 g); mp: 192–194 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.49–2.58 (t, 4H, $J = 4.7$ Hz, $N^4(CH_2)_2$); 2.62–2.67 (m, 4H, $(CH_2)_2$); 3.13–3.17 (t, 4H, $J = 4.7$ Hz, $N^1(CH_2)_2$); 5.38 (br s, 1H, OH); 7.07 (s, 1H, thiazole); 7.14–8.01 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3555 (OH stretch); 3071, 3045 (aromatic C–H stretch); 2829, 2749 (aliphatic C–H stretch); 1637, 1606 (aromatic C=C stretch); 1582 (C=N ring stretch); 1248 (aliphatic C–N stretch); 817 (para disubstituted benzene); 762 (C–Cl stretch), 708 (aromatic C–H bending). HRMS (ESI) calcd for $C_{23}H_{22}ClN_5OS$ $[M + H]^+$: 451.1307; found: 451.1303; Anal. calculated for $C_{23}H_{22}ClN_5OS$: C 61.12, H 4.91, N 15.50, S 7.09; found: C 61.09, H 4.86, N 15.43, S 7.05.

*2-{4-[4-(2,5-dimethylthiazol-4-yl)phenethyl]piperazin-1-yl}-3-chloroquinoxaline (**10e**)*

Recrystallisation Solvent: Ethanol–water. % Yield: 52 % (0.12 g); mp: 90–92 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.39 (s, 3H, 5-CH_3); 2.52–2.58 (m, 4H, $(CH_2)_2$); 2.61–2.66 (t, 4H, $J = 4.8$ Hz, $N^4(CH_2)_2$); 2.76 (s, 3H, 2-CH_3); 3.18–3.24 (t, 4H, $J = 4.8$ Hz, $N^1(CH_2)_2$); 7.25–8.20 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3065, 3027 (aromatic C–H stretch); 2842, 2753 (aliphatic C–H stretch); 1647 (C–S stretch); 1603, 1590 (aromatic C=C stretch); 1261 (aliphatic C–N stretch); 823 (para disubstituted benzene); 759 (C–Cl stretch), 705 (aromatic C–H bending). HRMS (ESI) calcd for $C_{25}H_{26}ClN_5S$ $[M + H]^+$: 463.1256; found: 463.1249; Anal. calculated for $C_{25}H_{26}ClN_5S$: C 64.71, H 5.65, N 15.09, S 6.91; found: C 64.65, H 5.56, N 14.99, S 6.85.

*4-{4-[2-(4-(2-chloroquinoxalin-3-yl)piperazin-1-yl)ethyl]phenyl}-N,5-dimethylthiazol-2-amine (**10f**)*

Recrystallisation Solvent: Ethanol. % Yield: 45 % (0.11 g); mp: 134–136 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.31 (s, 3H,CH_3); 2.51 (s, 3H, NHC$\underline{H}_3$); 2.59-2.63 (t, 4H, $J = 4.9$ Hz, $N^4(CH_2)_2$); 2.65–2.69 (m, 4H, $(CH_2)_2$); 3.16–3.19 (t, 4H, $J = 4.9$ Hz, $N^1(CH_2)_2$); 4.18 (s, 1H, N$\underline{H}$CH$_3$); 7.18–7.97 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3410 (NH stretch); 3065, 3027 (aromatic C–H stretch); 2847, 2743 (aliphatic C–H stretch); 1644 (C–S stretch); 1608, 1596 (aromatic C=C stretch); 1263 (aliphatic C–N stretch); 810 (para disubstituted benzene); 761 (C–Cl stretch), 707 (aromatic C–H bending). HRMS (ESI) calcd for $C_{25}H_{27}ClN_6S$ $[M + H]^+$: 478.1961; found: 478.1957; Anal. calculated for $C_{25}H_{27}ClN_6S$: C 62.65, H 5.68, N 17.54, S 6.69; found: C 62.56, H 5.59, N 17.45, S 6.54.

*2-{4-[4-(2-methylthiazol-4-yl)phenethyl]piperazin-1-yl}-3-chloroquinoxaline (**10g**)*

Recrystallisation Solvent: Ethanol- water. % Yield: 63 % (0.142 g); mp: 86–88 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.49–2.55 (t, 4H, $J = 4.7$ Hz, $N^4(CH_2)_2$); 2.64–2.71 (m, 4H, $(CH_2)_2$); 2.75 (s, 3H, CH_3); 3.17–3.22 (t, 4H, $J = 4.7$ Hz, $N^1(CH_2)_2$); 7.15 (s, 1H, thiazole); 7.21–8.09 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3045, 3032 (aromatic C–H stretch); 2828, 2763 (aliphatic C–H stretch); 1639 (C–S stretch); 1636, 1602 (aromatic C=C stretch); 1262 (aliphatic C–N stretch); 809 (para disubstituted benzene); 765 (C–Cl stretch), 709 (aromatic C–H bending). HRMS (ESI) calcd for $C_{24}H_{24}ClN_5S$ $[M + H]^+$: 449.1342; found: 449.1337; Anal. calculated for $C_{24}H_{24}ClN_5S$: C 64.06, H 5.38, N 15.56, S 7.13; found: C 63.99, H 5.29, N 15.45, S 7.04.

*4-{4-[2-(4-(2-methoxyquinoxalin-3-yl)piperazin-1-yl)ethyl]phenyl}-thiazol-2-amine (**11a**)*

Recrystallisation Solvent: Ethanol. % Yield: 66 % (0.223 g); mp: 96–98 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.49–2.53 (t, 4H, $J = 4.8$ Hz, $N^4(CH_2)_2$); 2.57–2.76 (m, 4H, $(CH_2)_2$); 3.27–3.32 (t, 4H, $J = 4.8$ Hz, $N^1(CH_2)_2$); 3.72 (s, 3H, OCH_3); 3.84 (s, 2H, NH_2); 6.88 (s, 1H, thiazole); 7.23–8.00 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3348, 3439 (NH stretch); 3065, 3027 (aromatic C–H stretch); 2828, 2763 (aliphatic C–H stretch); 1635, 1616 (aromatic C=C stretch); 1556 (C=N ring stretch); 1255 (aliphatic C–N stretch); 1118 (C–O stretch); 820 (para disubstituted benzene); 709 (aromatic C–H bending). HRMS (ESI) calcd for $C_{24}H_{26}N_6OS$ $[M + H]^+$: 446.2148; found: 446.2137; Anal. calculated for $C_{24}H_{26}N_6OS$: C 64.55, H 5.87, N 18.82, S 7.18; found: C 64.49, H 5.69, N 18.84, S 7.14.

*4-{4-[2-(4-(2-methoxyquinoxalin-3-yl)piperazin-1-yl)ethyl]phenyl}-N-ethylthiazol-2-amine (**11b**)*

Recrystallisation Solvent: Ether. % Yield: 83 % (0.292 g); mp: 114–116 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.46–2.51 (t, 4H, $J = 4.7$ Hz, $N^4(CH_2)_2$); 2.57 (s, 3H, $NHC\underline{H}_3$); 2.65–2.72 (m, 4H, $(CH_2)_2$); 3.29-3.34 (t, 4H, $J = 4.7$ Hz, $N^1(CH_2)_2$); 3.68 (s, 3H, OCH_3); 4.11 (s, 1H, $N\underline{H}CH_3$); 6.71 (s, 1H, thiazole); 7.35–8.04 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3350 (NH stretch); 3058, 3009 (aromatic C–H stretch); 2817, 2760 (aliphatic C–H stretch); 1644, 1609 (aromatic C=C stretch); 1587 (C=N ring stretch); 1260 (aliphatic C–N stretch); 1079 (C–O stretch); 812 (para disubstituted benzene); 712 (aromatic C–H bending). HRMS (ESI) calcd for $C_{25}H_{28}N_6OS$ $[M + H]^+$: 460.1836; found: 460.1827; Anal. calculated for $C_{25}H_{28}N_6OS$: C 65.19, H 6.13, N 18.25, S 6.96; found: C 65.08, H 6.06, N 18.15, S 6.88.

*4-{4-[2-(4-(2-methoxyquinoxalin-3-yl)piperazin-1-yl)ethyl]phenyl}-5-methylthiazol-2-amine (**11c**)*

Recrystallisation Solvent: Ether. % Yield: 70 % (0.244 g); mp: 68–70 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.35 (s, 3H, CH_3); 2.51–2.56 (t, 4H, $J = 4.9$ Hz, $N^4(CH_2)_2$); 2.59–2.76 (m, 4H, $(CH_2)_2$); 3.25–3.34 (t, 4H, $J = 4.9$ Hz, $N^1(CH_2)_2$); 3.69 (s, 3H, OCH_3); 3.89 (s, 2H, NH_2); 7.18–7.95 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3440, 3428 (NH stretch); 3058, 3009 (aromatic C–H stretch); 2817, 2775 (aliphatic C–H stretch); 1642, 1608 (aromatic C=C stretch); 1545 (C=N ring stretch); 1261 (aliphatic C–N stretch), 1107 (C–O stretch); 831 (para disubstituted benzene); 711 (aromatic C–H bending). HRMS (ESI) calcd for $C_{25}H_{28}N_6OS$ $[M + H]^+$: 460.1786; found: 460.1782; Anal. calculated for $C_{25}H_{28}N_6OS$: C 65.19, H 6.13, N 18.25, S 6.96; found: C 65.08, H 6.06, N 18.15, S 6.88.

*4-{4-[2-(4-(2-methoxyquinoxalin-3-yl)piperazin-1-yl)ethyl]phenyl}thiazol-2-ol (**11d**)*

Recrystallisation Solvent: Acetone. % Yield: 78 % (0.263 g); mp: 122–124 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.45-2.52 (t, 4H, $J = 4.7$ Hz, $N^4(CH_2)_2$); 2.66–2.78 (m, 4H, $(CH_2)_2$); 3.21–3.29 (t, 4H, $J = 4.7$ Hz, $N^1(CH_2)_2$); 3.73 (s, 3H, OCH_3); 4.74 (s, 1H, thiazole); 5.42 (br s, 1H, OH); 7.25–8.01 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3558 (OH stretch); 3062, 3027 (aromatic C–H stretch); 2832, 2787 (aliphatic C–H stretch); 1647, 1615 (aromatic C=C stretch); 1590 (C=N ring stretch); 1262 (aliphatic C–N stretch); 1077 (C–O stretch); 819 (para disubstituted benzene). 704 (aromatic C–H bending). HRMS (ESI) calcd for $C_{24}H_{25}N_5O_2S$ $[M + H]^+$: 447.1677; found: 447.1674; Anal. calculated for $C_{24}H_{25}N_5O_2S$: C 64.41, H 5.63, N 15.65, S 7.16; found: C 64.26, H 5.60, N 15.51, S 7.08.

*4-{4-[2-(4-(2-methoxyquinoxalin-3-yl)piperazin-1-yl)ethyl]phenyl}-5-methyl thiazol-2-amine (**11e**)*

% Yield: 42% (0.147 g, oil). ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.35 (s, 3H, 5-CH_3); 2.46–2.53 (t, 4H, $J = 4.7$ Hz, $N^4(CH_2)_2$); 2.58–2.72(m, 4H, $(CH_2)_2$); 2.76 (s, 3H, 2-CH_3); 3.23-3.29 (t, 4H, $J = 4.7$ Hz, $N^1(CH_2)_2$); 3.79 (s, 3H, OCH_3); 7.39-8.25 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3044, 3026 (aromatic C–H stretch); 2832, 2758 (aliphatic C–H stretch); 1640, 1604 (aromatic C=C stretch); 1580 (C=N ring stretch); 1266 (aliphatic C–N stretch); 1112 (C–O stretch); 809 (para disubstituted benzene), 708 (aromatic C–H bending). HRMS (ESI) calcd for $C_{26}H_{29}N_5OS$ $[M + H]^+$: 459.2126; found: 459.2118; Anal. calculated for $C_{26}H_{29}N_5OS$: C 67.94, H 6.36, N 15.24, S 6.98; found: C 67.86, H 6.32, N 15.21, S 6.93.

*4-{4-[2-(4-(2-methoxyquinoxalin-3-yl)piperazin-1-ylethyl]phenyl}-N,5-dimethyl thiazol-2-amine (**11f**)*

% Yield: 48% (0.173 g, oil). ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.36 (s, 3H,CH_3); 2.49–2.56 (t, 4H, $J = 4.8$ Hz, $N^4(CH_2)_2$); 2.60 (s, 3H, $NHC\underline{H}_3$); 2.63–2.79 (m, 4H, $(CH_2)_2$); 3.26–3.36 (t, 4H, $J = 4.8$ Hz, $N^1(CH_2)_2$); 3.68 (s, 3H, OCH_3); 4.28 (s, 1H, $N\underline{H}CH_3$); 7.12–7.88 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3478 (NH stretch); 3047, 3115 (aromatic C–H stretch); 2832, 2758 (aliphatic C–H stretch); 1646, 1613 (aromatic C=C stretch); 1587 (C=N ring stretch); 1258 (aliphatic C–N stretch); 1115 (C–O stretch); 818 (para disubstituted benzene), 703 (aromatic C–H bending). HRMS (ESI) calcd for $C_{26}H_{30}N_6OS$ $[M + H]^+$: 474.2335; found: 474.2328; Anal. calculated

for $C_{26}H_{30}N_6OS$: C 65.80, H 6.37, N 17.71, S 6.76; found: C 65.76, H 6.32, N 17.71, S 6.73.

*2-{4-[4-(2-methylthiazol-4-yl)phenethyl]piperazin-1-yl}-3-methoxyquinoxaline (**11g**)*

Recrystallisation Solvent: Acetone. % Yield: 47% (0.16 g); mp: 88–90 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.47–2.54 (t, 4H, $J = 4.9$ Hz, $N^4(CH_2)_2$); 2.57–2.67 (m, 4H, $(CH_2)_2$); 2.76 (s, 3H, CH_3); 3.24–3.33 (t, 4H, $J = 4.9$ Hz, $N^1(CH_2)_2$); 3.75 (s, 3H, OCH_3); 7.42 (s, 1H, thiazole); 7.54–8.31 (m, 8H, Ar–H). IR (KBr, ν) cm^{-1}: 3040, 3025 (aromatic C–H stretch); 2835, 2750 (aliphatic C–H stretch); 1645, 1604 (aromatic C=C stretch); 1585 (C=N ring stretch); 1269 (aliphatic C–N stretch); 1118 (C–O stretch); 825 (para disubstituted benzene), 710 (aromatic C–H bending). HRMS (ESI) calcd for $C_{25}H_{27}N_5OS$ $[M + H]^+$: 445.1722; found: 445.1718; Anal. calculated for $C_{25}H_{27}N_5OS$: C 67.39, H 6.11, N 15.72, S 7.20; found: C 67.31, H 6.07, N 15.66, S 7.13.

*4-{4-[2-(4-(quinoxalin-2-yl)piperazin-1-yl)ethyl]phenyl}thiazol-2-amine (**12a**)*

Recrystallisation Solvent: *n*-Hexane. % Yield: 68% (0.142 g); mp: 110–112 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.55–2.62 (t, 4H, $J = 4.8$ Hz, $N^4(CH_2)_2$); 2.75–2.88 (m, 4H, $(CH_2)_2$); 3.17–3.23 (t, 4H, $J = 4.8$ Hz, $N^1(CH_2)_2$); 3.86 (s, 2H, NH_2); 6.78 (s, 1H, thiazole); 7.28–8.25 (m, 9H, Ar–H). IR (KBr, ν) cm^{-1}: 3445, 3423 (NH stretch); 3056, 3035 (aromatic C–H stretch); 2845, 2757 (aliphatic C–H stretch); 1634, 1610 (aromatic C=C stretch); 1576 (C=N ring stretch); 1260 (aliphatic C–N stretch); 829 (para disubstituted benzene), 710 (aromatic C–H bending). HRMS (ESI) calcd for $C_{23}H_{24}N_6S$ $[M + H]^+$: 416.1688; found: 416.1681; Anal. calculated for $C_{23}H_{24}N_6S$: C 66.32, H 5.81, N 20.18, S 7.70; found: C 66.24, H 5.74, N 20.06, S 7.63.

*N–methyl-4-{4-[2-(4-(quinoxalin-2-yl)piperazin-1-yl)ethyl]phenyl}thiazol-2-amine (**12b**)*

Recrystallisation Solvent: Ethanol. % Yield: 56% (0.121 g); mp: 152–154 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.34–2.49 (m, 4H, $(CH_2)_2$); 2.59–2.63 (t, 4H, $J = 4.8$ Hz, $N^4(CH_2)_2$); 2.93 (s, 3H, $NHC\underline{H}_3$); 4.12 (s, 1H, $N\underline{H}CH_3$); 3.11–3.18 (t, 4H, $J = 4.8$ Hz, $N^1(CH_2)_2$); 6.92 (s, 1H, thiazole); 7.39–8.32 (m, 9H, Ar–H). IR (KBr, ν) cm^{-1}: 3445 (NH stretch); 3056, 3035 (aromatic C–H stretch); 2845, 2757 (aliphatic C–H stretch); 1640, 1608 (aromatic C=C stretch); 1588 (C=N ring stretch); 1262(aliphatic C–N stretch); 826 (para disubstituted benzene), 712 (aromatic C–H bending). HRMS (ESI) calcd for $C_{24}H_{26}N_6S$ $[M + H]^+$: 430.1920; found: 430.1915; Anal. calculated for $C_{24}H_{26}N_6S$: C 66.95, H 6.09, N 19.52, S 7.45; found: C 66.84, H 5.94, N 19.46, S 7.43.

*5-methyl-4-{4-[2-(4-(quinoxalin-2-yl)piperazin-1-yl)ethyl]phenyl}thiazol-2-amine (**12c**)*

Recrystallisation Solvent: Methanol. % Yield: 78% (0.167 g); mp: 108–110 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.41 (s, 3H, CH_3); 2.55–2.61 (t, 4H, $J = 4.9$ Hz, $N^4(CH_2)_2$); 2.68–2.77 (m, 4H, $(CH_2)_2$); 3.21–3.27 (t, 4H, $J = 4.9$ Hz, $N^1(CH_2)_2$); 3.92 (s, 2H, NH_2); 7.14–8.16 (m, 9H, Ar–H). IR (KBr, ν) cm^{-1}: 3340, 3345 (NH stretch); 3056, 3035 (aromatic C–H stretch); 2845, 2750 (aliphatic C–H stretch); 1646, 1606 (aromatic C=C stretch); 1590 (C=N ring stretch); 1256 (aliphatic C–N stretch); 821 (para disubstituted benzene), 708 (aromatic C–H bending). HRMS (ESI) calcd for $C_{24}H_{26}N_6S$ $[M + H]^+$: 430.1858; found: 430.1851; Anal. calculated for $C_{24}H_{26}N_6S$: C 66.95, H 6.09, N 19.52, S 7.45; found: C 66.91, H 6.04, N 19.41, S 7.38.

*4-{4-[2-(4-(quinoxalin-2-yl)piperazin-1-yl)ethyl]phenyl}thiazol-2-ol (**12d**)*

Recrystallisation Solvent: Ethanol. % Yield: 71% (0.147 g); mp: 142–144 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.59–2.63 (t, 4H, $J = 4.8$ Hz, $N^4(CH_2)_2$); 2.70–2.88 (m, 4H, $(CH_2)_2$); 3.16–3.19 (t, 4H, $J = 4.8$ Hz, $N^1(CH_2)_2$); 5.58 (br s, 1H, OH); 6.89 (s, 1H, thiazole); 7.10–7.97 (m, 9H, Ar–H). IR (KBr, ν) cm^{-1}: 3610 (OH stretch); 3049, 3015 (aromatic C–H stretch); 2862, 2798 (aliphatic C–H stretch); 1638, 1614 (aromatic C=C stretch); 1578 (C=N ring stretch); 1260 (aliphatic C–N stretch); 825 (para disubstituted benzene), 702 (aromatic C–H bending). HRMS (ESI) calcd for $C_{23}H_{23}N_5OS$ $[M + H]^+$: 417.1889; found: 417.1887 Anal. calculated for $C_{23}H_{23}N_5OS$: C 66.16, H 5.55, N 16.77, S 7.68; found: C 66.11, H 5.44, N 16.691, S 7.62.

*2-{4-[4-(2,5-dimethylthiazol-4-yl)phenethyl]piperazin-1-yl}quinoxaline (**12e**)*

% Yield: 70% (0.15 g, oil). ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.28 (s, 3H, 5-CH_3); 2.54–2.59 (t, 4H, $J = 4.9$ Hz, $N^4(CH_2)_2$); 2.61–2.78 (m, 4H, $(CH_2)_2$); 2.76 (s, 3H, 2-CH_3); 3.18–3.24 (t, 4H, $J = 4.9$ Hz, $N^1(CH_2)_2$); 7.22–8.11 (m, 9H, Ar–H). IR (Neat) cm^{-1}: 3060, 3039 (aromatic C–H stretch); 2845, 2757, 1369 (aliphatic C–H stretch); 1632, 1616 (aromatic C=C stretch); 1577 (C=N ring stretch); 1268 (aliphatic C–N stretch); 825 (para disubstituted benzene), 706 (aromatic C–H bending). HRMS (ESI) calcd for $C_{25}H_{27}N_5S$ $[M + H]^+$: 429.2127;

found: 429.2123. Anal. calculated for $C_{25}H_{27}N_5S$: C 69.90, H 6.34, N 16.30, S 7.46; found: C 69.82, H 6.28, N 16.22, S 7.42.

*N,5-dimethyl-4-{4-[2-(4-(quinoxalin-2-yl)piperazin-1-yl)ethyl]phenyl}thiazol–2-amine (**12f**)*

% Yield: 69% (0.17 g, oil). ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.33 (s, 3H,CH_3); 2.42–2.54 (m, 4H, $(CH_2)_2$); 2.59–2.67 (t, 4H, $J = 4.8$ Hz, $N^4(CH_2)_2$); 2.77 (s, 3H, NHC$\underline{H}_3$); 3.14–3.17 (t, 4H, $J = 4.8$ Hz, $N^1(CH_2)_2$); 4.42 (s, 1H, N$\underline{H}$CH_3); 7.22–8.18 (m, 9H, Ar–H). IR (Neat) cm^{-1}: 3445 (NH stretch); 3072, 3045 (aromatic C–H stretch); 2852, 2748 (aliphatic C–H stretch); 1644, 1612 (aromatic C=C stretch); 1576 (C=N ring stretch); 1261 (aliphatic C–N stretch); 824 (para disubstituted benzene), 710 (aromatic C–H bending). HRMS (ESI) calcd for $C_{25}H_{28}N_6S$ $[M + H]^+$: 444.2336; found: 444.2335. Anal. calculated for $C_{25}H_{28}N_6S$: C 67.54, H 6.35, N 18.90, S 7.21; found: C 67.42, H 6.28, N 18.82, S 7.19.

*2-{4-[4-(2-methylthiazol-4-yl)phenethyl]piperazin-1-yl}quinoxaline (**12g**)*

Recrystallisation Solvent: Ether. % Yield: 69% (0.143 g); mp: 128–130 °C. ^{1}H NMR (DMSO-d_6) (δ) ppm: 2.42–2.55 (m, 4H, $(CH_2)_2$); 2.60–2.66 (t, 4H, $J = 4.8$ Hz, $N^4(CH_2)_2$); 2.86 (s, 3H, CH_3); 3.21–3.29 (t, 4H, $J = 4.8$ Hz, $N^1(CH_2)_2$); 7.14 (s, 1H, thiazole); 7.19–8.35 (m, 9H, Ar–H). IR (KBr, ν) cm^{-1}: 3057, 3036 (aromatic C–H stretch); 2854, 2741 (aliphatic C–H stretch); 1648, 1629 (aromatic C=C stretch); 1586 (C=N ring stretch); 1263 (aliphatic C–N stretch); 822 (para disubstituted benzene), 711 (aromatic C–H bending). HRMS (ESI) calcd for $C_{24}H_{25}N_5S$ $[M + H]^+$: 415.1624; found: 415.1619. Anal. calculated for $C_{24}H_{25}N_5S$: C 69.37, H 6.06, N 16.85, S 7.72; found: C 69.29, H 6.01; N 16.82, S 7.59.

Pharmacology

In vitro radioligand displacement studies

The affinity and specificity of the NCEs were estimated in radioligand displacement studies on rat 5-HT_{2A} and D_2 receptors obtained from rat cortical (5-HT receptors) and striatal (D_2 receptors) membrane preparations. Test compounds were dissolved in DMSO (10 mM stock solution), aliquoted, and stored at −25 °C. For competitive binding experiments, the membrane preparations were thawed, diluted with assay buffer, 50 mM TRIS–HCl, at pH 7.4, and washed twice. The particular receptor preparation was incubated with the respective radioligand (5-HT_{2A}: [^{3}H]ketanserine, Perkin Elmer, A_{spec}: 67 Ci/mmol; D_2: [^{3}H]spiperone, Amersham GE, A_{spec}: 101 Ci/mmol) and up to six concentrations of the NCEs. Dilutions of the NCEs were made with assay buffer. Nonspecific binding of the radioligands was determined with 100 μM mianserin for the 5-HT_{2A} ligand [^{3}H]ketanserine and 100 μM haloperidol for D_2 ligand [^{3}H]spiperone. To block the 5-HT affinity of the D_2 radioligand [^{3}H]spiperone, 10 μM ketanserin was added to the respective assays. The assay samples were incubated at ambient temperature for 60 min (D_2) or 90 min (5-HT_{2A}), rapidly filtered through Whatman GF/B glass-fiber filters, and washed four times with ice-cold assay buffer. Filter-bound radioactivity was determined by liquid scintillation counting. All test compounds were assayed in at least three independent experiments. The IC_{50} values were estimated using iterative nonlinear curve fitting.

In vivo pharmacological studies

The Institutional Animal Ethics Committee of the Birla Institute of Technology and Science, Pilani, Rajasthan, India, approved experimentation on animals (Protocol No. IAEC/RES/11/2). *Swiss albino* mice (25–30 g) of either sex obtained from Hissar Agricultural University, Hissar, Haryana, India were used for the pharmacological studies. Pharmacokinetic studies carried out showed that the exposure at 10 mg/kg dose was similar to the exposure of several atypical antipsychotics at therapeutically relevant doses, and hence this dose was chosen to carry out the in vivo pharmacological tests. Statistical analysis was done using GraphPad InStat software.

D_2 receptor antagonism studies in nigrostriatal pathway (climbing mouse assay)

Apomorphine hydrochloride (1 mg/kg) solution (as per the base calculations) was prepared in triple-distilled water containing 0.1 % w/v sodium metabisulphite and was injected *s.c.* 1 h before testing.

Risperidone (0.6 mg/kg) and NCEs (10 mg/kg) were prepared as suspension in 0.25% w/v sodium carboxymethylcellulose in triple-distilled water and were injected *i.p.* 30 min before testing.

Inhibition or reversal of Apomorphine-induced cage-climbing behavior in mice by a test molecule is an indication of mesolimbic dopaminergic D_2 receptor antagonism (Costall *et al.*, 1978). During the experimentation, mice were placed individually in separate aluminum cages, measuring 20 × 15 × 15 cm^3, with walls lined with 1 cm^2 aluminum wire mesh (diameter 2 mm). They were placed in the above cages for 30 min for adaptation before the experiment. Groups of mice (eight per group) were

administered with either the test molecule (10 mg/kg) or vehicle or Risperidone *i.p.* 1 h prior to the apomorphine challenge (1 mg/kg, *s.c.*). Mice were then observed for the climbing behavior after 10, 20, and 30 min and the scoring was done as below.

"0," when all the four feet were placed on the cage floor,
"1," when three feet were placed on the cage floor,
"2," when two feet were placed on the cage floor,
"3," when one foot was placed on the cage floor, and
"4," when all the four feet were off the cage floor.

The percentage inhibition or reversal of climbing behavior of Apomorphine hydrochloride was calculated by the difference from the score of treated subjects to the score of control animals and referring it to score of control group set to 100 %. Haloperidol (1.0 mg/kg, *i.p.*) was used as control as it completely inhibited the climbing induced by apomorphine.

5-HT_{2A} receptor antagonism studies (quipazine-induced head twitches)

Quipazine maleate (5 mg/kg) solution (as per the base calculations) was prepared in triple-distilled water containing 0.1 % w/v sodium metabisulphite and was injected *i.p.* 30 min before testing. Risperidone (0.6 mg/kg) and NCEs (10 mg/kg) were prepared as suspension in 0.25 % w/v sodium carboxymethylcellulose in distilled water and were also injected *i.p.* 30 min before testing.

Inhibition or reversal of quipazine-induced head twitches in mice by the test molecule is an indication of central serotonergic 5-HT_{2A} receptor antagonism (Malick *et al.*, 1977). During the experimentation, mice were placed individually in separate plastic translucent cages, measuring 20 × 15 × 15 cm^3. They were placed in the above cages for 30 min for adaptation before the experiment. Groups of mice (eight per group) were administered *i.p.* with either the test molecule (10 mg/kg) or vehicle or Risperidone 1 h prior to the quipazine maleate challenge (5 mg/kg, *i.p.*). Risperidone (0.6 mg/kg, *i.p*) was used as control as it completely inhibits quipazine-induced head twitches in mice. The head twitches were then counted between 30 and 40 min. The percentage inhibition or reversal of head twitches was calculated by the difference from the count of treated subjects to the count of control animals and referring it to count of control group set to 100 %.

D_2 receptor antagonism studies in nigrostriatal pathway (catalepsy test)

NCEs (10 mg/kg) were prepared as suspension in 0.25 % w/v sodium carboxymethylcellulose in triple-distilled water and were injected *i.p.* 30 min before testing.

Induction of catalepsy by the test molecules is an indication of antagonism at nigrostriatal dopaminergic D_2 receptors leading to EPS (Malick *et al.*, 1977). During the experimentation, mice were placed individually in separate plastic translucent cages, measuring 20 × 15 × 15 cm^3. They were placed in the above cages for 30 min for adaptation before the experiment. Groups of mice (eight per group) were administered *i.p.* with either the test molecule (10 mg/kg) or vehicle. The mice were then tested for catalepsy by placing both the front paws on a 4 cm high wooden block (6 × 4 × 4 cm^3) and measuring the time taken for it to come back to the normal posture. The scoring was done in accordance with literature (Lumma Jr. *et al.*, 1981). If the animal maintained the imposed posture for at least 20 s, then it was said to be cataleptic and given one point. For every further 20 s it continued to maintain the imposed posture, an extra point was given, thus the animal was given a score of 2 points if it maintained the posture for 40 s, 3 points for 60 s, and so on. The mice were tested for cataleptic behavior 1.0, 2.0, 3.0, 4.0, and 5 h after treatment with the test molecule. Average cataleptic times and scores are calculated at each time of measurement of cataleptic behavior per molecule. The maximum of all average cataleptic scores/times are noted per molecule and then conclusions are drawn with respect to which test molecule is cataleptic and the degree of catalepsy.

Conclusion

A series of 4-{4-[2-(4-(2-substitutedquinoxalin-3-yl) piperazin-1-yl)ethyl]phenyl} thiazole derivatives were synthesized and evaluated in vitro for their affinity for the dopamine D_2 and serotonin 5-HT_{2A} receptors (Table 1). All the final compounds were evaluated for the atypical antipsychotic activity in animal models. The overall results are summarized in Table 3. Compound **12d** is the most active among the synthesized compounds with 5-HT_{2A}/D_2 ratio of 1.23077 followed by **11f** and **10a** with 5-HT_{2A}/D_2 ratios of 1.14286 and 1.12857, respectively. All the above three compounds are more active than the standard drug risperidone (5-HT_{2A}/D_2 ratio of 1.0989) as they exhibited higher 5-HT_{2A}/D_2 ratio than risperidone. None of the above compounds exhibited catalepsy. Hence, these compounds satisfy all the criteria required for a molecule to be an atypical antipsychotic according to Meltzer's classification (Meltzer *et al.*, 1989; Roth *et al.*, 1998). Further studies in transforming these agents into clinically useful agents are in progress in our laboratory.

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Conflict of interest The authors declare no conflict of interest.

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