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Synthesis and pharmacological evaluation of piperidine (piperazine)-amide substituted derivatives as multi-target antipsychotics

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ABSTRACT

We report the optimisation of a series of novel amide-piperidine (piperazine) derivatives using the multiple ligand approach with dopamine and serotonin receptors. Of the derivatives, compound **11** exhibited high affinity for the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors, but low affinity for the 5-HT_{2C} and histamine H_1 receptors and human ether-a-go-go-related gene (hERG) channels. *In vivo*, compound **11** reduced apomorphine-induced climbing, MK-801-induced hyperactivity and DOI-induced head twitching without observable catalepsy, even at the highest dose tested. In addition, it exhibited suppression in a CAR test. Furthermore, in a novel object recognition task, it displayed procognition properties. Therefore, compound **11** is a promising candidate multi-target antipsychotic.

Schizophrenia is a severe mental illness with a lifetime prevalence of up to 1% worldwide. The clinical picture of schizophrenia is characterised by positive symptoms, such as delusions and hallucinations; negative symptoms, including asociality, apathy, and anhedonia; and cognitive deficits, such as memory and learning impairment or attention deficit disorder.[1] Most available antipsychotics, such as the typical antipsychotic haloperidol (Fig. 1), suppress the dopaminergic system by blocking dopamine (DA) receptors, particularly the D_2 subtype.[2,3] Although these drugs control positive symptoms, they do not prevent negative symptoms or improve cognitive dysfunction, and cause several common adverse effects, such as extrapyramidal syndrome (EPS).[4,5]

The majority of atypical antipsychotics, including clozapine, olanzapine, and risperidone, block dopamine (D_1, D_2, D_3, or D_4), serotonin (5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}) and other (histamine and adrenergic) receptors (Fig. 1).[6,7] Atypical antipsychotics can control the positive symptoms of schizophrenia, and reduce EPS.[8] However, they have adverse events such as significant weight gain,.[9] hyperglycaemia,[10,11] and metabolic dysfunction,[12] caused by high-affinity binding to off-target receptors, such as the H_1.[13–15] and 5-HT_{2C}.[16,17] receptors, Hence, there is a need for new antipsychotics with greater efficacy and tolerability, particularly for treating negative symptoms and cognitive deficit of schizophrenia.

Aripiprazole (Fig. 1) is a new third-generation atypical antipsychotic.[18] Unlike clozapine and risperidone, aripiprazole is an agonist of 5-HT_{1A} and D_2 receptors, and an antagonist of 5-HT_{2A} receptors.[19,20] It is also a dopamine system stabiliser. Similarly, cariprazine (Fig. 1) is a partial agonist of the D_2, D_3, and serotonin 5-HT_{1A} receptors, but shows low affinity for the 5-HT_{2C}, 5-HT_7, and H_1 receptors. Thus, cariprazine has a lower risk for EPS, tardive dyskinesia, and prolactin abnormality.[21] In addition, it has advantages for treating mood symptoms and cognitive deficits related to schizophrenia and bipolar mania.[22]

Most atypical and third-generation antipsychotics are heterocyclic aryl-piperazine (piperidines) derivatives that act on multiple targets, such as D_2, 5-HT, 5-HT_{1A}, and 5-HT_{2A} receptors. The 5-HT_{1A} receptor plays a crucial role in multiple physiological functions, and by acting on postsynaptic 5-HT_{1A} receptors promotes dopamine release in the frontal cortex.[23] 5-HT_{2A} receptor antagonism diminishes the EPS side effect, which is caused by excessive D_2 receptor blockade.[24] In addition, regulation of 5-HT receptors can improve schizophrenia.[25]

To develop more effective antipsychotic drugs with minimal or no side effects, the multi-receptor affinity profile has been used. Our research group[26,27] aims to discover novel antipsychotics with high affinity for dopamine D_2, 5-HT_{1A}, and 5-HT_{2A} receptors, but low affinity for the off-target H_1, alpha-1, and 5-HT_{2C} receptors, which are associated with weight gain.[28–30] In addition, blocking of alpha-2 receptor promotes cortical glutamatergic transmission and reverses cognitive impairment in rats,[31] and the serotonin 5-HT_6 receptor is important in drug discovery because it modulates multiple neurotransmitter

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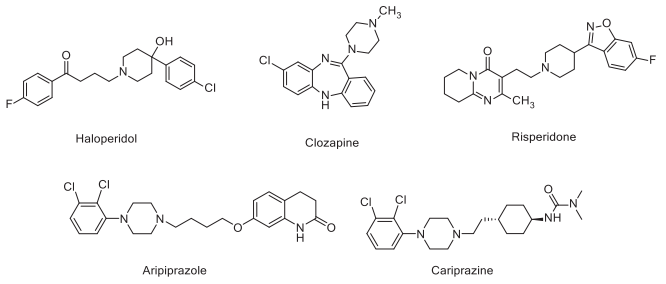


Fig. 1. First-generation and Atypical antipsychotics.

systems,[32] for example, disinhibition of GABAergic neurons in the frontal cortex, regulating the cholinergic and/or glutamatergic systems. Blocking of the 5-HT_6 receptor increases dopamine release in the prefrontal cortex, which is critical in cognition and learning and in neuropsychological and neuropsychiatric disorders, such as schizophrenia and AD.[33–35] Therefore, effects on the a_2 and 5-HT_6 receptors must also be taken into account.

Heterocyclic and arylpiperazine (piperidine) fragments were selected as the base moieties based on their preferential binding to dopamine and serotonin receptors. Next, hybridisation with amine moieties fragments which were developed by open the amide ring of aripiprazole and introduction of the different amine moieties based on cariprazine (Fig. 2), and the two pharmacophores connected via flexible spacer, finally a new class of compounds with heterocyclic or aryl-piperazines (piperidines) pharmacophores linked to the modifiable amide was designed **6–24** (Schemes 1 and 2).

To determine the affinities of the new compounds (**6–24**) for D_2, 5-HT_{1A}, 5-HT_{2A}, H_1, 5-HT_{2C}, 5-HT_6, noradrenergic α_1 and α_2 receptors, a preliminary pharmacological evaluation was conducted. Among these derivatives, compound **11** exhibited high affinity for the D_2, 5-HT_{1A}, 5-HT_{2A}, 5-HT_6, and α_2 receptors, and low affinity for the 5-HT_{2C}, H_1, and α_1 receptors and hERG channels. In the behaviour study, compound **11** suppressed apomorphine-induced climbing and MK-801-induced hypermobility, significantly reduced 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) induced head twitching and had a high threshold for induction of catalepsy. In addition, compound **11** exhibited dose-dependent suppression the CRA test. Moreover, compound **11** induced cognitive improvement in a novel object recognition task.

The general strategy used to prepare the target compounds **6–24** is outlined in Schemes 1–2. As shown in scheme 1compounds **3a-3 g** were synthesised from compounds **1a-1e** with acyl chlorides **2a-2c**. Compounds **4a-4 g** were prepared by hydrolysis of compounds **3a-3 g** with sodium hydroxide. Compounds **5a-5 g** were prepared from intermediates **4a-4 g** by substitution with 1,3-dibromopropane (1,2-dibromoethane or 1,4-dibromobutane) in acetone. Finally, compounds **5a-5 g** were reacted with a heterocyclic arylpiperazine (piperidine) in the presence of K_2CO_3 and a catalytic amount of KI to afford compounds **6–22** at a high yield (Tables 1 and 2). As shown in Scheme 2 compound **7** reacted with 2-(chloromethyl) oxirane to afford compound **23**, which was reacted with (6-fluorobenzo[*d*]isoxazol-3-yl) piperidine to obtain compound **24** (Table 2).

We investigated the affinities of heterocyclic or arylpiperazine (piperidine) and their derivatives for the D_2, 5-HT_{1A} and 5-HT_{2A} receptors (compounds **6–13;** Table 1). Compound **6** (2,3-dichlorophenylpiperazine) exhibited moderate affinity for the D_2 and 5-HT_{2A} receptors. When the amine moieties were substituted with 3-trifluoromethyl phenylpiperazine, (pyridin-2-yl)piperazine, 2-methoxyphenylpiperazine and 2-(piperazin-1-yl) pyrimidine, the resulting compounds **7–10** demonstrated lower affinities for the three receptors. In addition, the (6-fluorobenzo[*d*]isoxazol-3-yl) piperidine derivative **11** exhibited high affinities for the three receptors (D_2, K_i = 2.1 nM; 5-HT_{1A}, K_i = 3.5 nM; 5-HT_{2A}, K_i = 7.8 nM, respectively). Replacement of the (6-fluorobenzo[*d*]isoxazol-3-yl) piperidine with a (benzo[*d*]isothiazol-3-yl)piperazine (compound **12**) or (benzo[*b*]thiophen-7-yl)piperazine (compound **13**) reduced the affinities for the three receptors. Therefore, (6-fluorobenzo[*d*]isoxazol-3-yl) piperidine had greater affinity for the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors than the other heterocyclic arylpiperazine (piperidine).

To assess the SARs of the compounds, the effects of different substituent group on amide were evaluated by replacing methyl, ethyl or phenyl on the R_2. Compound **14** (ethyl) showed moderate affinity for 5-HT_{1A} receptor but not the D_2 and 5-HT_{2A} receptors (Table 2). Moreover, compound **15** (phenyl) exhibited lower affinities for all three receptors.

Replacement of **R** with a methyl or fluorine group yielded the fluorine derivative compound **16**, which had moderate affinity for the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors. Substitution of a methyl (compound **17**) on the R of the benzene ring had similar effects on the D_2 and 5-HT_{2A} receptors and a lesser effect on the 5-HT_{1A} receptor.

Substitution of the methylene group between the benzene ring and the amino group (compound **18**) dramatically decreased the affinity for all three receptors compared to compound **11** (Table 2). Specifically, introduce methyl groups the nitrogen atoms of the amide, compound **19** exhibited good affinities for the three receptors (D_2, K_i = 20.6 nM; 5-HT_{1A}, K_i = 21.3 nM; 5-HT_{2A}, K_i = 12.7 nM, respectively).

Changes in the length of the linker between the benzene ring and the piperidine ring (Table 2) chain shortening (compound **21**) and lengthening (compound **22**) lead to loss of affinity for D_2, 5-HT_{1A}, and 5-HT_{2A} receptors. Introduction of OH to the carbon chain of compound **24** resulted in moderate affinity for the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors. Hence, chain length is a determinant of binding affinities for the three receptors. The derivative with a three-carbon chain (compound **11**) showed optimum activity. Finally, when the amide was moved from the 4-position (compound **11**) to the 3-position (compound **22**), activity was unaffected.

The SAR analyses indicated that the binding affinities of these compounds depend on several factors. First, substitution with a 6-fluorobenzo[*d*]isoxazol-3-yl)-piperidine group increases affinity for D_2, 5-$HT_{1A,}$ and 5-HT_{2A} receptors compared to other aryl piperazines. Second, substitutions on benzene ring reduce affinity for those receptors (H > F > CH_3). Third, introduction of a methylene group

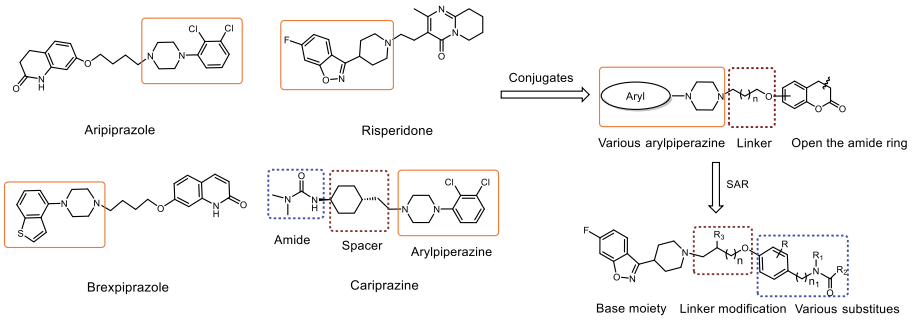
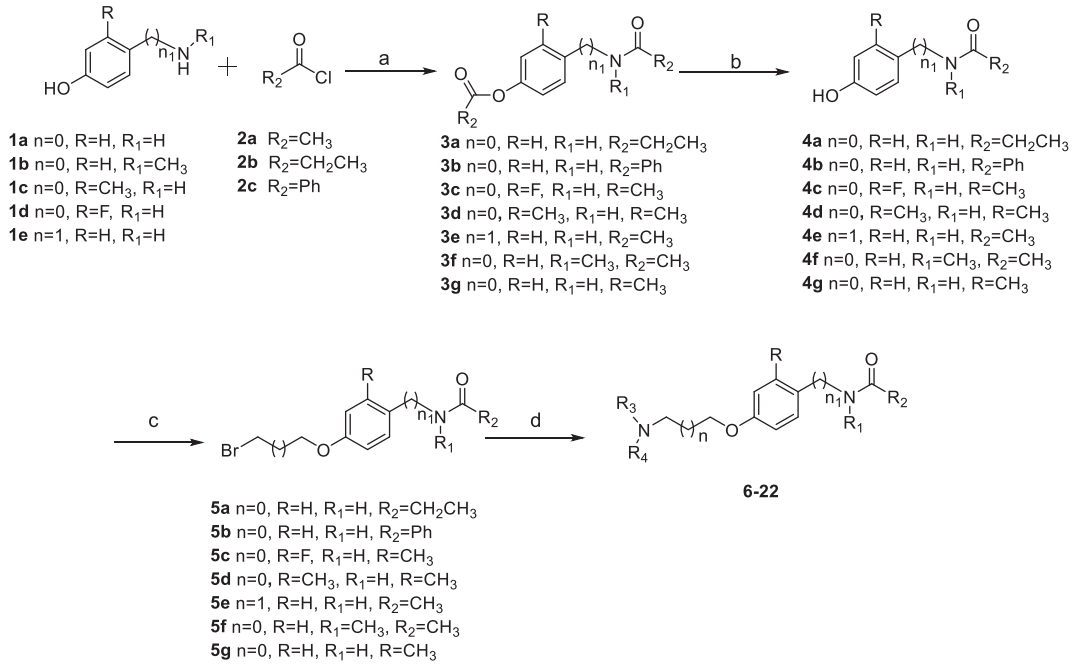


Fig. 2. Design of amide derivatives.



Scheme 1. Reagents and conditions: (a) Triethylamine, CH_2Cl_2, rt, 6 h; (b) CH_3OH, NaOH, 50℃, 24 h (c) $Br(CH_2)_{3\ or\ 4}Br$, K_2CO_3, acetone, reflux; (d) CH_3CN, K_2CO_3, KI, reflux.

between the benzene ring and the amino group significantly decreased the affinity for all three receptors (n_1, 0 > 1). The nitrogen atom of the amide with unsubstituted preferred activity [please clarify] (R_1, H > CH_3). Substitution of (R_2) with methyl was favoured (CH_3 > CH_2CH_3 > Ph). Finally, the straight three-carbon chain alkyl was preferred over other alkyl linkers (n, 3 > 4 > 1), and introducing substituents into the flexible chain also slightly reduced the affinity to all three receptors.

The above SAR studies have shown that the tested compounds (**11**, **20**) display high affinities for the D_2, 5-HT_{1A} and 5-HT_{2A} receptors, as do multi-target antipsychotics. Thus, compounds **11** and **20** were screened for further evaluation.

The α_2 and 5-HT_6 receptors were also assessed. As shown in Table 3, compound **11** showed a higher affinity for α_2 receptor (K_i = 16.3 nM) than did risperidone (K_i = 28.2 nM) and compound **20** (K_i = 193 nM), and a higher affinity (K_i = 12.9 nM) for the 5-HT_6 receptor compared to risperidone (Ki = 1190 nM) and compound **20** (K_i = 765 nM). Therefore, compound **11** may enhance cognitive performance but exhibited only moderate binding affinity to the two targets.

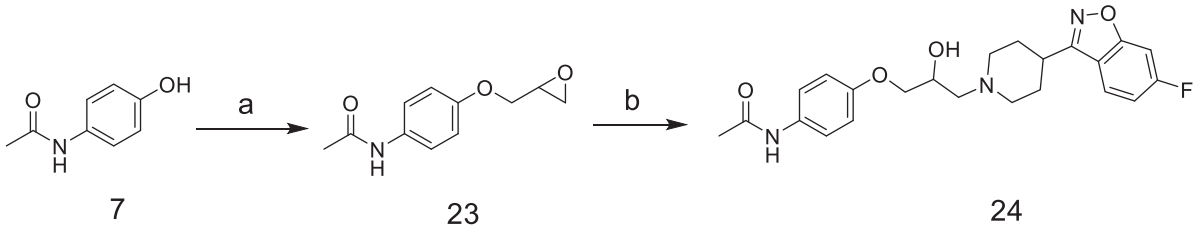
Assays of the H_1, 5-HT_{2C}, and alpha-1 receptors were also conducted.[36] Compound **11** had a lower affinity (K_i = 2143 nM) for the H_1 receptor than risperidone (K_i = 49.3 nM) and compound **20** (K_i = 54.2 nM), a lower affinity for the 5-HT_{2C} receptor (K_i = 1987 nM) than risperidone (K_i = 39.1 nM) and compound **20** (K_i = 186 nM; Table 3), and a lower affinity (K_i = 3296 nM) for the alpha-1 receptor than risperidone (K_i = 21.9 nM) and compound **20** (K_i = 195 nM; Table 3). Therefore, compound **11** has a lower rate of orthostatic hypotension than risperidone and a low probability of weight gain.

Cardiotoxicity is a significant side effect for drug discovery,[37] and is often caused by blockade of the hERG channel. Therefore, hERG channel blockade is an important indicator of cardiotoxicity.

In this study, compound **11** was evaluated for its ability to block hERG channels by the patch-clamp technique. Compound **11** (IC_{50} = 2.98 μM) showed lesser hERG inhibition than compound **20** (IC_{50} = 369.1 nM). In addition, the acute toxicities of compounds **11** and **20** were investigated in terms of the LD_{50} values (po, compound **11**, LD_{50} > 2000 mg/kg; compound **20**, LD_{50} = 369.1 mg/kg).

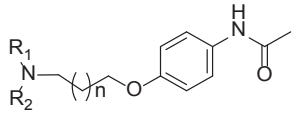
Animal models of complex neuropsychiatric disorders can predict the reliability, toxicity and effectiveness of drugs. The apomorphine-induced climbing model was used to simulate the positive symptoms of schizophrenia.[38] Compound **11** (0.01–1.0 mg/kg, po) significantly suppressed apomorphine-induced climbing in mice (ED_{50} 0.28 mg/kg), while the ED_{50} values of the control groups (risperidone and haloperidol) were 0.025 and 0.53 mg/kg, respectively (Table 4). The DOI-induced head twitch mouse model was used to assess antagonism of 5-HT_{2A} receptors. DOI is a non-subtype-selective 5-HT_2 agonist and suppressed the stereotypic head twitch induced by selective 5-HT_{2A} receptor antagonists.[39] Compound **11** (0.01–1.0 mg/kg, po) significantly and dose-dependently attenuated DOI-elicited head twitching (ED_{50} 0.22 mg/kg) (Table 4).

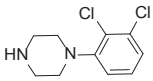
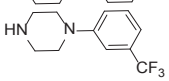
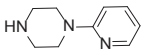
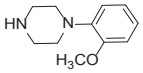
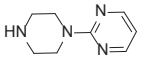
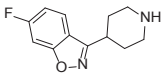
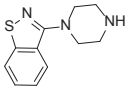
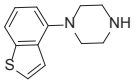
Phencyclidine (PCP) and Dizocilpine (MK-801) can induce schizophrenic symptoms (negative and cognitive symptoms) in healthy mice by noncompetitive antagonism of the NMDA receptor[40–42] but those symptoms are alleviated significantly by antipsychotics. Hence, the MK801-induced hyperactivity model was used to predict the efficacy of



Scheme 2. Reagents and conditions: (a) 2-(chloromethyl) oxirane, K_2CO_3, Acetone, Reflux; (b) CH_3CN, K_2CO_3, KI, reflux.

Table 1
Binding Affinities for D_2, 5-HT_{1A} and 5-HT_{2A} receptors of compounds 6–13.[a]



Compound	NR_1R_2	n	Receptor affinity K_i ± SEM (nM)		
			D_2	5-HT_{1A}	5-HT_{2A}
6		1	167.2 ± 21.2	> 10,000[b]	288.9 ± 31.2
7		1	> 10,000[b]	> 10,000[b]	447.9 ± 50.9
8		1	> 10,000[b]	1988 ± 243	2341 ± 401
9		1	467.3 ± 38.3	> 10,000[b]	> 10,000[b]
10		1	498.2 ± 50.1	> 10,000[b]	> 10,000[b]
11		1	2.1 ± 0.3	3.5 ± 0.3	7.8 ± 0.9
12		1	79.1 ± 9.1	69.7 ± 8.8	116.9 ± 27.8
13		1	16.3 ± 3.5	258 ± 36	109 ± 17
risperidone	–	–	3.8 ± 0.3	271 ± 29	0.39 ± 0.03

[a] K_i values are taken from three experiments, expressed as means ± SEM.
[b] The K_i values were not calculated because the inhibition percentages at 10 μM were too low.

novel antischizophrenics.[43] Compound **11** (0.01–1.0 mg/kg, po) significantly decreased the enhanced locomotor activity induced by MK-801 with an ED_{50} of 0.19 mg/kg (Table 4). The ED_{50} values of the control groups treated with risperidone and haloperidol were 0.011 and 0.16 mg/kg, respectively. Therefore, compound **11** improved the negative and cognitive symptoms of schizophrenia.

Catalepsy is a significant predictor of the incidence of extrapyramidal motor disorder.[44,45] Hence, compound **11** was subjected to the vertical grid and elevated bar tests in mice. Haloperidol and risperidone induced significant catalepsy (ED_{50} 3.6 and 1.2 mg/kg, respectively). Compound **11** showed a high threshold for the induction of catalepsy (ED_{50} 25.2 mg/kg, Table 4). The therapeutic index (90, based on the efficacy of apomorphine and MK-801 models) was higher than risperidone (therapeutic index, 48) and haloperidol (therapeutic index, 6.8). The high threshold for catalepsy suggests compound **11** to have a low risk for EPS.[46]

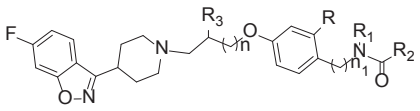
The conditioned avoidance response (CAR) test is an assay of antipsychotic activity and affinity for DA receptors.[47,48] Compound **11** and risperidone inhibited the avoidance response in rat (Fig. 3). Compound **11** suppressed CAR behaviour (ED_{50} 0.28 mg/kg), while the ED_{50} value for risperidone was 0.49 mg/kg, indicating compound **11** to have an antipsychotic effect (Table 4).

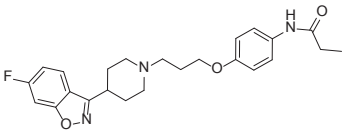
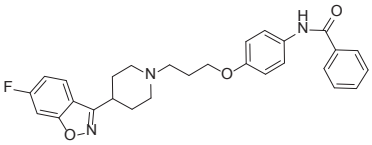
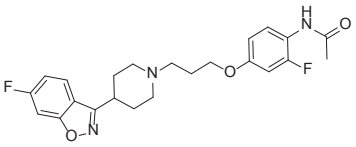
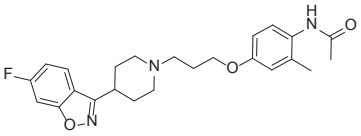
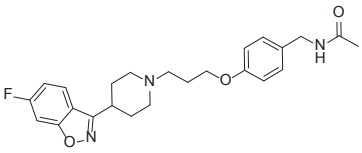
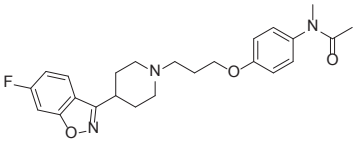
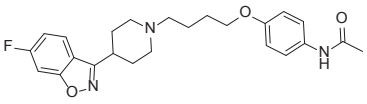
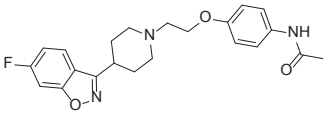
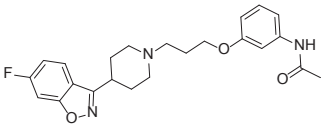
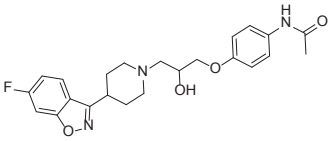
To validate the effects of compound **11** on cognitive improvement, a novel object recognition (NOR) test was performed to investigate visual recognition memory; this test is commonly used to evaluate the effectiveness of candidate antipsychotics.[49] In this study, there were acquisition and retention trials. In the acquisition trial, the rats were trained to recognise two identical objects, and after an interval, memory performance was evaluated by testing the exploration times for a familiar and a novel object. The rats will preferentially explore the novel object if the memory of the acquisition trial is preserved. During this session, the rats are administered a memory-enhancing drug. Therefore, the exploration time for the novel object will be greater than that for the familiar object.

In the acquisition trial, the four groups were given oral vehicle, compound **11**, rivastigmine, and risperidone before training, and presented with two identical objects to explore. In this model, compound 11 was orally administered 1 h prior to the acquisition trial, and the exploration times for the two identical objects were recorded (Fig. 4A). After a 24 h acquisition trial, one of the familiar objects was replaced with a novel object, the time spent investigating each of the objects was recorded (Fig. 4B). There was no marked difference in exploration time among the blank, experiment, and control groups in the acquisition trial (Fig. 4A). In the retention trial, the rats given rivastigmine and compound **11** showed enhanced recognition memory at 0.1 and 0.3 mg/kg, the rats used longer time exploring the novel object, particularly with the dose of 0.3 mg/kg, suggesting the memory for the familiar object preserved and enhanced with the increasing doses compound **11**. By contrast, vehicle and 0.01 mg/kg compound **11** and 0.1 mg/kg risperidone did not influence the total exploration time (Fig. 4B). Therefore, compound **11** has potential cognitive-enhancement activity.

The pharmacokinetics of compound **11** was measured in rats (Table 5). Oral (10.0 mg/kg) and intravenous (3.0 mg/kg) administration yielded similar half-lives ($t_{1/2}$), 3.34 and 3.68 h, respectively. Compound **11** showed an intravenous AUC (area under the curve) of 9492.03 ng·h/mL and an oral AUC of 878.74 ng·h/mL. After oral

Table 2
Binding Affinities for D_2, 5-HT_{1A} and 5-HT_{2A} receptors of compounds **14–24**.[a]



Compound	Structure	Receptor affinity K_i ± SEM (nM)		
		D_2	5-HT_{1A}	5-HT_{2A}
14		> 10,000[b]	76.3 ± 2.9	> 10,000
15		> 10,000[b]	> 10,000[b]	> 10,000[b]
16		148.3 ± 171	122.1 ± 14.2	41.8 ± 6.5
17		150.3 ± 22.1	> 10,000[b]	135.2 ± 14.3
18		1589 ± 171	2142 ± 248	141.1 ± 16.8
19		20.6 ± 3.6	21.3 ± 2.6	12.7 ± 0.6
20		1143 ± 157	1232 ± 396	223.7 ± 33.4
21		> 10,000[b]	> 10,000[b]	> 10,000[b]
22		> 10,000[b]	> 10,000[b]	> 10,000[b]
24		119.2 ± 12.5	155.6 ± 22.9	72.2 ± 8.9

[a] K_i values are taken from three experiments, expressed as means ± SEM.
[b] The K_i values were not calculated because the inhibition percentages at 10 μM were too low.

Table 3
Binding affinities for the 5-HT_6, H_1, 5-HT_{2C}, alpha 1, and alpha 2 receptors (K_i nM ± SEM) of compounds 11, 22 and a reference antipsychotic.[a]

Compound	Receptor affinity K_i ± SEM (nM)[a]				
	5-HT_6	alpha 2	H_1	5-HT_{2C}	alpha 1
ripersidone	1190 ± 139	28.2 ± 4.1	49.3 ± 6.8	39.1 ± 4.9	21.9 ± 3.8
11	**12.9 ± 2.5**	**16.3 ± 2.1**	**2143 ± 308**	**1987 ± 212**	**3296 ± 418**
20	765 ± 89	193 ± 20	54.2 ± 6.2	186 ± 19	195 ± 30

[a] K_i values are taken from three experiments, expressed as means ± SEM.

Table 4
In vivo pharmacological profile of compound **11**. Inhibition of different behavioral responses after oral administration of the test and reference compounds in mice.

Compd	APO[a] ED_{50}	DOI[b] ED_{50}	CAR[e]ED_{50}	CAT[c] ED_{50}	MK-801[d] ED_{50}	CAT/APO	CAT/MK-801
risperidone	0.025 (0.016–0.037) [f]	0.019 (0.013–0.024)	0.49	1.2	0.011 (0.003–0.051)	48	109.1
haloperidol	0.53 (0.01–1.47)	0.92 (0.40–1.372)		3.6	0.16 (0.064–0.37)	6.8	22.5
11	**0.28** (0.22–0.31)	**0.22** (0.082–0.35)	**0.28**	**25.2**	**0.19**	**90**	**132.6**

Vehicle: 30% PEG 400; [a]APO: apomorphine (1.0 mg/kg, sc)-induced climbing (po, 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg, 30% PEG 400); [b]DOI: DOI-induced (1.0 mg/kg, ip) head twitch (po, 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg, 30% PEG 400); [c]CAT: catalepsy (po, 1, 5, 15, 45, and 100 mg/kg, 30% PEG 400); [d]MK-801:MK-801-induced (0.3 mg/kg, sc) hyperactivity (po, 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg, 30% PEG 400); CAR[e]: Conditioned avoidance Response (po, 0.05, 0.15, 0.45 and 1.35 mg/kg,); [f]95% Confidence limits given in parentheses.

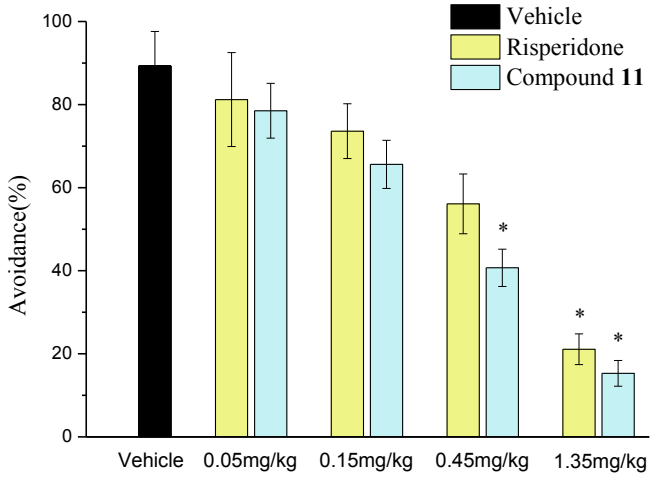


Fig. 3. Effect of risperidone (n = 10) and compound **11** (n = 10, 0.05, 0.15, 0.45 and 1.35 mg/kg, po, 30% PEG 400) on the performance of conditioned avoidance response in rats 90 min after single oral administration. Data was expressed as Mean ± SEM (n = 10). *, P < 0.05 versus vehicle treated control group.

administration, the clearance of compound **11** was 10.4 mL/h/kg, the T_{max} was 7 h, and the peak serum concentration (C_{max}) was 754.41 ng/mL. After intravenous administration, the clearance was 3.22 mL/h/kg. In general, compound **11** showed drug-like pharmacokinetic properties and favourable oral bioavailability (F = 31.04%).

In summary, a series of novel heterocyclic aryl piperidine (piperazine)-amide substituted derivatives were designed and synthesized, and their biological activities and SAR were evaluated *in vitro* and *in vivo*. Multiple factors, such as aryl piperazines, substituents on the amide and flexible chains, and chain length, influenced affinity for the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors, both individually and collectively. Among those compounds, compound **11** showed high affinities for the D_2, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_6 receptors. In addition, compound **11** exhibited desirable selectivity affinities for other receptors relevant to side effects of conventional treatment, including the 5-HT_{2C}, H_1, and α_1 receptors. In addition, compound **11** showed low hERG inhibitory activity and a high threshold for inducing catalepsy. Furthermore, compound **11** significantly inhibited apomorphine-induced climbing behaviour, MK-801 induced hyperactivity, and DOI-induced head twitching.

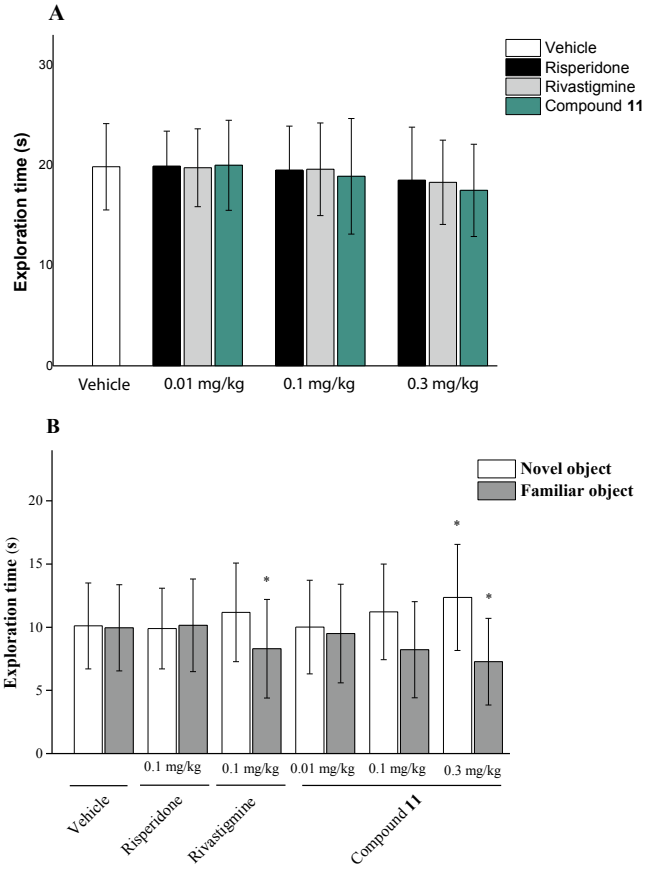


Fig. 4. Effects of compound **11** on novel object recognition test in rats (n = 10). Rats treated with vehicle (30% PEG 400), risperidone (0.1 mg/kg), rivastigmine (0.1 mg/kg) and compound **11** (0.01, 0.1, and 0.3 mg/kg) orally (dissolved in 30% PEG 400) 1 h before the acquisition trials. (A) Exploration times in the acquisition trial and (B) The time spent in exploring a familiar and novel object during acquisition trials (after 24 h training) were scored. Data are presented as the mean ± SEM, *, p < 0.05 versus the vehicle by post-hoc Student's *t*-test.

Moreover, compound **11** produced a dose-dependent suppression in a CRA test and improved learning and memory. In summary, compound **11** has several advantages over the commonly used atypical

Table 5
Pharmacokinetic Profile of Compound 11 in Rats (Male, n = 6/Group).

Dose mg/kg	C_{max}(ng/ml)	T_{max}(h)	$t_{1/2}$(h)	AUC_{0-t} (ng*h/ml)	$AUC_{0-\infty}$ (ng*h/ml)	CL/F (mL/h)	F(%)
10(op)[a]	745.41	7	3.34	9492.03	9638.27	10.4	31.04
3(iv)[b]			3.68	878.74	931.48	3.22	

[a] suspension in 0.5% Sodium ethyl cellulose.
[b] 100% saline.

antipsychotic risperidone and may facilitate the discovery of novel antischizophrenics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Financial disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

The synthesis of the novel compounds; Receptors Binding Affinities; hERG, Behavioral Research, Pharmacokinetics Study, The Spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS) of the novel compounds and HPLC of compound **11**. Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2020.127506.

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