Design, Synthesis, and Antidepressant Activity Study of Novel Aryl Piperazines Targeting Both 5-HT$_{1A}$ and Sigma-1 Receptors

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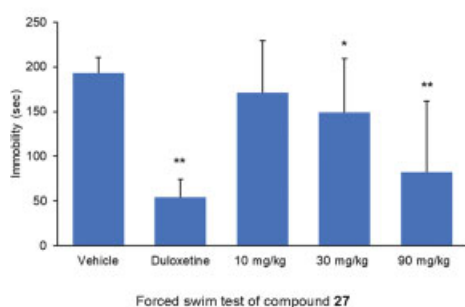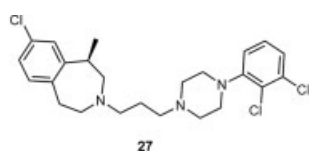
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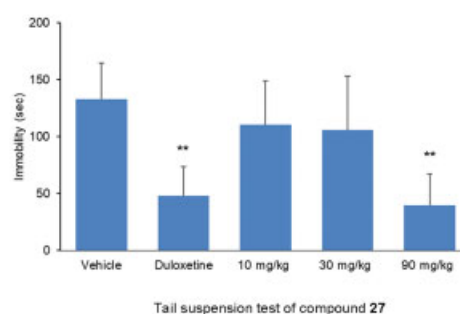
Tail suspension test of compound 27

Abstract

A total of 20 novel aryl piperazine derivatives were designed and synthesized, and their structures were confirmed by mass spectrometry and nuclear magnetic resonance analyses. Their 5-HT$_{1A}$ and sigma-1 receptor affinities were determined, and six of them showed high affinities ($K_i < 20$ nmol/L) to both 5-HT$_{1A}$ and sigma-1 targets. Then, metabolic stability ($T_{1/2}$) tests of six compounds in rat and human liver microsomes were performed. Our data indicated that compound **27** has both high affinity for 5-HT$_{1A}$ and sigma-1 receptors (5-HT$_{1A}$: $K_i = 0.44$ nmol/L; sigma-1: $K_i = 0.27$ nmol/L), and good metabolic stability ($T_{1/2}$ values are 21.7 and 24.6 minutes, respectively). Interestingly, results from the forced swimming test, mouse tail suspension test, and preliminary pharmacokinetic test suggested the marked antidepressant activity, good pharmacokinetic characteristics, and low toxicity of compound **27** in the two models. In conclusion, compound **27** has great value of further study as an active molecule of antidepressant drugs.

Keywords
► 5-HT$_{1A}$ receptor
► sigma-1 receptor
► high affinity
► antidepressant

Introduction

Depression, the third biggest health problem in the world, is estimated to become the second biggest health burden in the world by 2030.[1] Depression therapy is mainly focused on antidepressants in clinics, which are often associated with slow effect and severe side effects, such as sexual dysfunction, nausea, insomnia, or weight gain, as well as loss of cognitive ability.[2–4] The choice of treatment for depression is still limited. Therefore, it is very important to develop new antidepressants with rapid onset, low side effects, and improved cognitive function. Among which the research and development of new dual- or multi-target antidepressants is an important direction in the field.

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter distributed in the central and peripheral nervous systems. 5-HT$_{1A}$ receptor (5-HT$_{1A}$R) is the first isolated and fully sequenced subtype of the 5-HTR$_S$ (5-HT receptor) family, and is widely considered as a target for the treatment of anxiety, depression, schizophrenia, and neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease.[5–7] 5-HT$_{1A}$R partial agonist vilazodone (5-HT$_{1A}$, K_i = 1.50 nmol/L) is a good antidepressant drug that has been successfully marketed (►Fig. 1).[8,9]

Sigma-1 (σ1) receptor is a nonopioid receptor and widely distributed in the central nervous system. σ1 receptor plays an important role in regulating a variety of neural activities. Several small molecules with good affinity for σ1 receptor have been applied to the pathological study of pain, depression, schizophrenia, etc.[10–12] Evidence suggested that Jo-1784 (σ1, K_i = 75 nmol/L)[13] delivered "antidepressant-like" effects in animal behavioral models of depression in forced swimming test (FST), tail suspension test (TST), and clinical trials (►Fig. 1).[14] Fluvoxamine, usually considered as a serotonin reuptake inhibitor actually, has high affinity for σ1 receptor, and it is believed that its clinical effect of improving cognition and alleviating anxiety is mainly attributed to σ1 receptor agonism.[15]

Early studies by Skuza and Rogóz showed that in the FST of rats, the combined use of 5-HT$_{1A}$ and σ1 receptor agonists could dose-dependently reduce the interaction of immobility duration.[16] Otsuka Pharmaceutical company developed the antidepressant OPC (OPC-14523), which exhibits high *in vitro* affinities for 5-HT$_{1A}$R, σ1 receptor, and serotonin transporter (►Fig. 1). Compared with other selective serotonin reuptake inhibitors, OPC-14523 has significantly shorter onset time and significantly improved cognitive ability.[17,18] Therefore, exploring the compounds acting on both 5-HT$_{1A}$ and σ1 receptors as new potential antidepressant active molecules has scientific basis and feasibility.

Research studies have revealed that *N*-alkylated tetrahydroisoquinoline (TIQ) derivatives could produce slight affinity differences for the binding of subtypes of 5-HT receptor family, with medium to good selectivity.[19,20] Besides, aryl piperazine derivatives, especially compounds with long carbon chains connected to the N atom of dichlorophenylpiperazines, can be used clinically to treat central nervous system diseases, such as listed drugs aripiprazole, brilaroxazine, and cariprazine (►Fig. 2).[21,22]

Inspired by the above research, arylalkyl piperazine derivatives obtained by carbon chain fusion of TIQ and its electronic, isosteric, and arylpiperazine parts may have the synergistic effect to target 5-HT$_{1A}$ and σ1 receptors at the same time. Herein, we designed four classes of dual-target agonist, TIQ phenylpiperazine derivatives (class A compounds), thiophene tetrahydropyridine phenylpiperazine derivatives (class B compounds), dihydroindole phenylpiperazine derivatives (class C compounds), and benzonitrogen seven-membered heterocyclic phenylpiperazine derivatives (class D compounds) as shown in ►Fig. 3. All the four classes of compounds are subject to the affinity test of 5-HT$_{1A}$ and σ1 receptors. Compounds with a high affinity of 5-HT$_{1A}$ and σ1 receptors are further examined for their *in vitro* liver microsomal stability test, yielding optimal compounds. On this basis, the antidepressant and preliminary pharmacokinetic (PK) studies of the optimal compounds are performed to find
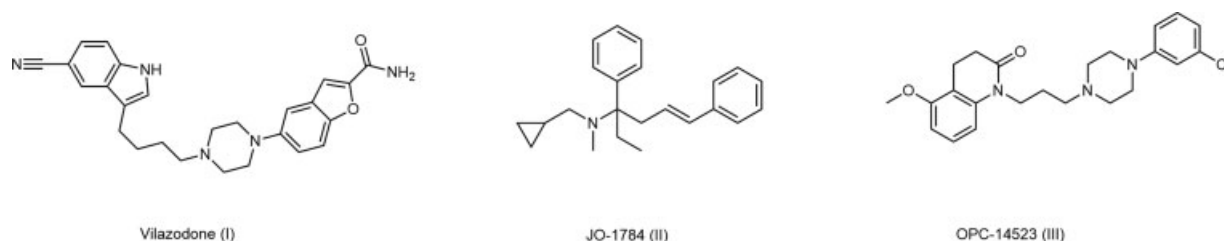
Fig. 1 Representatives of 5-HT$_{1A}$ or sigma-1 agonist.
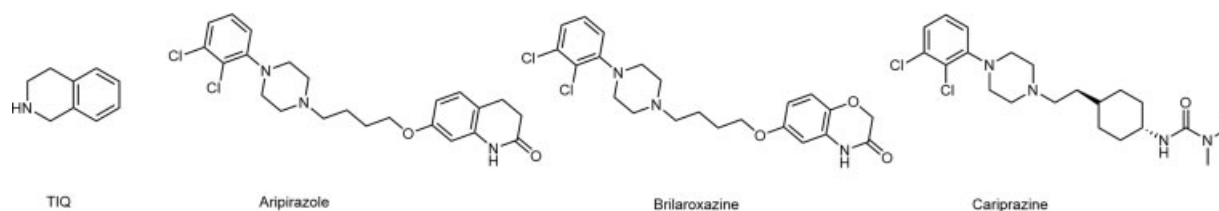
Fig. 2 TIQ and aryl piperazine derivatives. TIQ, tetrahydroisoquinoline.
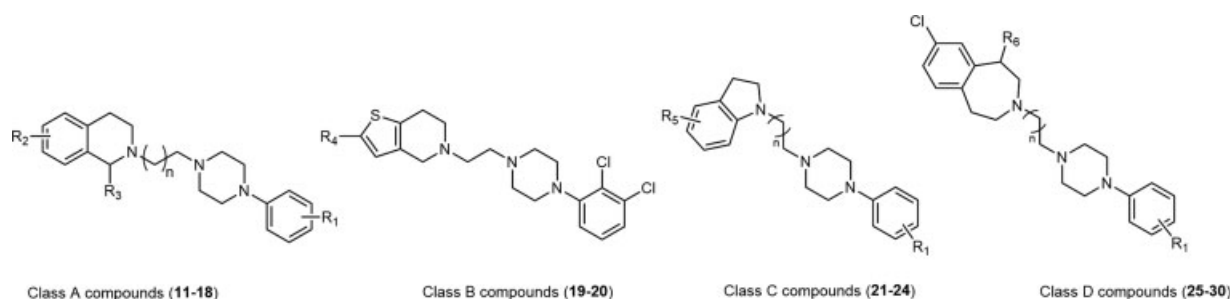
Fig. 3 General structural formula of classes (A)–(D) compounds.

the bioactive and druggable compounds. At the same time, the structure–activity relationship analysis is performed to guide the discovery of better antidepressant compounds targeting 5-HT$_{1A}$ and σ1 receptors.

Results and Discussion

Structure, *In Vitro* Activity, and Synthesis of the Compounds

Through replacing 3,4-dihydroquinolinone of the lead compound OPC-14523 with 1,2,3,4-tetrahydroisoquinolines, class A compounds **11–18** were obtained. ►**Table 1** lists the derivatives' structures and target binding affinities. Our data indicated that the compounds obtained by replacing 3,4-dihydroquinolinone of OPC-14523 with TIQ derivatives have high affinity for 5-HT$_{1A}$ and σ1 receptors, such as compounds **17** and **18**.

To explore influences of different nitrogen-containing aromatic heterocycles on the affinity of 5-HT$_{1A}$ and σ1 receptors, the electronic isosteres of TIQ were designed. By replacing TIQ in the above-mentioned type A compounds with tetrahydropyridine, dihydroindole, and benzoazepine seven-membered heterocyclic ring, 12 compounds (**19–30**) of type B, C, and D were prepared. Their structures and target binding affinities are determined and shown in ►**Table 2**. The results exhibited that compounds **19**, **20**, and **27** had high affinity for the two targets, suggesting that the substitution of thiophene tetrahydropyridine and (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo [*D*] azo group for TIQ could obtain a highly active dual-target action compound.

The above compounds (**11–30**) were synthesized by a two-step synthesis route (**Scheme 1**). Briefly, the substituted phenylpiperazines (commercially available) were reacted with 1-bromo-2-chloroethane or 1-bromo-3-chloropropane in the presence of potassium carbonate to obtain intermediates **5–10**, which were condensed with different substituted aromatic nitrogen-containing heterocycles under the action of potassium carbonate and potassium iodide to obtain target compounds **11–30**, respectively.

Preliminary Structure–Activity Relationship Analysis

Results from the preliminary structure–activity relationship analysis showed that:

- When the length of carbon chain between TIQ and phenyl-piperazine is 2, the affinity of compounds for two targets

was significantly better than three-carbon compounds, such as compound **15** (4.0 nmol/L, 11.1 nmol/L) > compound **11** (484.1 nmol/L, 59.4 nmol/L), compound **16** > compound **12**.
- When there were substitutions on the TIQ ring, the affinity activity for two targets was significantly better than that of unsubstituted compounds on the ring, such as compounds **17** and **18** > compound **15**.
- The affinity of phenylpiperazine compounds with two chlorine substituents to σ1 receptor was significantly higher than that with two methyl substituents, such as compound **15** > **16**.
- When TIQ of A compounds was replaced by a tetrahy-drothiophenopyridine ring, their affinity for two targets was significantly improved, such as compounds **19** and **20** > compound **15**.
- Compounds containing dihydroindole with CN at C-3 have a strong affinity for 5-HT$_{1A}$ but a weak affinity for σ1 receptor, such as compounds **22** and **24**. If CN was substituted at C-4, the affinity for both receptors was lost, such as compounds **21** and **23**.
- Among the benzodiazepine seven-membered heterocyclic compounds, the activity of methyl compound **27** with *R* configuration to both targets (0.44 and 0.27 nmol/L) was significantly better than compound **28** with *S* configuration.
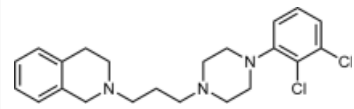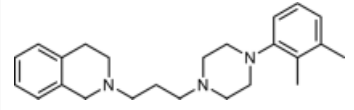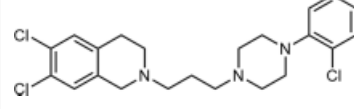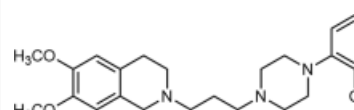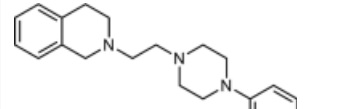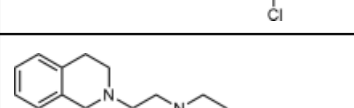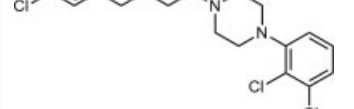
In Vitro Liver Microsomal Stability Test

Compounds **15**, **17**, **18**, **19**, **20**, and **27** with good affinities ($K_i < 20$ nmol/L) for 5-HT$_{1A}$ and σ1 receptors were selected for liver microsomal stability test. The results showed that compound **27** had a long half-life and good metabolic stability in human and rat liver microsomes (HLM and RLM) with HLM $T_{1/2}$ and RLM $T_{1/2}$ being 24.6 and 21.7 minutes, respectively, as shown in ►**Table 3**.

In vivo Pharmacokinetic Test of Compound 27

In vivo PK evaluation of compound **27** was performed in rats. Our data showed that intravenous administration of **27** (5 mg/kg) produced detectable plasma levels of the compound with a half-life ($T_{1/2}$) of 18.39 hours. Besides, the $T_{1/2}$ values of the oral administration of the compound for 30 and 100 mg/kg doses were 24.07 and 39.49 hours, respectively, and the bioavailability values were 5.90 and 10.40%, suggesting that compound **27** had good PK characteristics (►**Table 4**).

Table 1 Biophysical evaluation of compounds 11–18 against 5-HT$_{1A}$ and sigma-1 receptors

Compd.	Structure	5-HT$_{1A}$ (K_i, nmol/L)	Sigma-1 (K_i, nmol/L)
11		484.1	59.4
12		244.9	863.9
13		0.7	278
14		>1,000	0.33
15		4	11.1
16		3.9	158.6
17		2.3	3.5
18		3	0.46

Study on the Antidepressant-Like Activity of Compound 27

Forced Swim Test
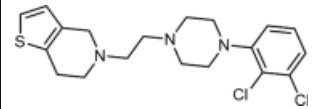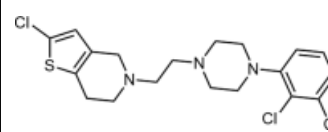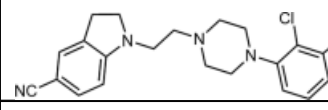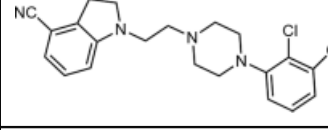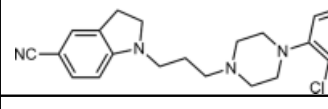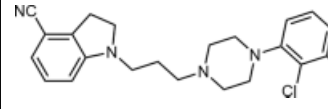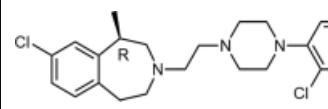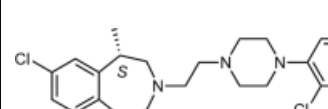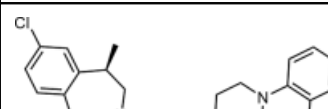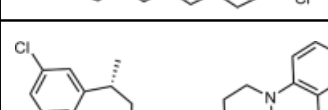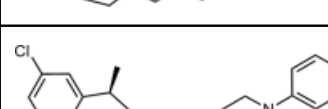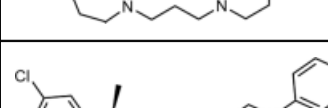
ICR (Institute of Cancer Research) male mice were randomly divided into five groups, and then intragastrically administered with different doses of compound **27** (10, 30, and 90 mg/kg) and positive drug duloxetine (20 mg/kg/d) for 7 consecutive days. Our data indicated that **27** dose-depen-

dently decreased the immobility time by 12, 23, and 58% when compared with the negative control. The antidepressant-like effect of **27** was statistically significant at a high dose (90 mg/kg), as shown in ►**Fig. 4**.

Mouse Tail Suspension Test

Compound **27** was intragastrically administered at 10, 30, and 90 mg/kg/d (po) for 7 consecutive days to three of five groups of randomly assigned ICR male mice, and duloxetine

Table 2 Biophysical evaluation of compound 19–30 against 5-HT$_{1A}$ and sigma-1 receptors

Compd.	Structure	5-HT$_{1A}$ (K_i, nmol/L)	Sigma-1 (K_i, nmol/L)
19		0.18	0.08
20		0.21	0.08
21		>1,000	>1,000
22		2.3	>1,000
23		>1,000	>1,000
24		43.4	608
25		>1,000	1.1
26		519.8	2.0
27		0.44	0.27
28		>1,000	1.55
29		289.6	9.7
30		660.2	112.0
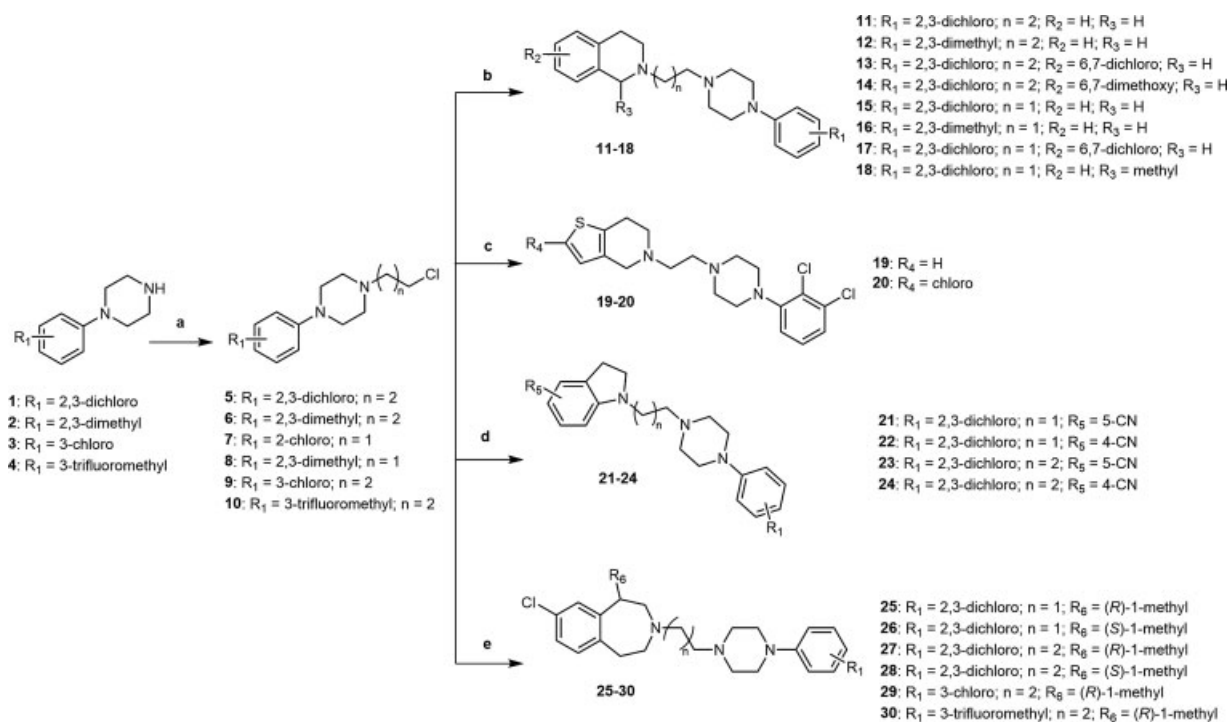
Scheme 1 Synthesis of compounds **11–30**. Reagents and conditions: (a) 1-bromo-2-chloroethane (or 1-bromo-3-chloro-propane), K_2CO_3, acetone, 60°C; (b) 1,2,3,4-tetrahydroisoquinoline and its derivatives, K_2CO_3, CH_3CN, 82°C; (c) 4,5,6,7-tetrahydrothienopyridine and its derivatives, K_2CO_3, CH_3CN, 82°C; (d) indoline derivatives, K_2CO_3, CH_3CN, 82°C; (e) 2,3,4,5-tetrahydro-1H-benzo[d]azepine, K_2CO_3, CH_3CN, 82°C.

Table 3 Metabolic stability study in liver microsomes

Compd.	RLM $T_{1/2}$ (min)	HLM $T_{1/2}$ (min)
15	1.7	8.7
17	2.6	7.2
18	1.6	5.0
19	1.9	1.7
20	3.5	21.6
27	21.7	24.6

Abbreviations: HLM, human liver microsome; RLM, rat liver microsome.

served as the positive control (20 mg/kg/d, po). Results from the TST showed that in comparison to the excipient group, the immobility time of compound **27** was apparently reduced by 17, 20, and 70%, and the reduction of immobility time was statistically significant at the dose of 90 mg/kg. The results are shown in ►**Fig. 5**.

Acute Toxicity Test of Compound 27

The experimental method of single gavage in mice was used. The results showed that the LD_{50} and maximum tolerable dose (MTD) of compound **27** were 1,600 and 1,000 mg/kg, respectively, and the MTD of the positive control drug vortioxetine was 300 mg/kg, indicating that the acute toxicity of compound **27** was low and well tolerated.

Conclusion

OPC-14523 was used as the lead compound. In this study, the 3,4-dihydroquinolinone of OPC-14523 was replaced by 1,2,3,4-tetrahydroisoquinoline to obtain class A compounds, then nitrogen-containing aromatic heterocycles were substituted for the TIQ structure of class A compounds to give a total of 20 new arylalkyl piperazine compounds (compounds **11–30**). The affinity test of 5-$HT_{1A}R$ and σ1 receptor indicated that compounds **15**, **17**, **18**, **19**, **20**, and **27** had high affinities ($K_i < 20$ nmol/L) for the two targets; next the stability ($T_{1/2}$) tests of the six compounds in RLM and HLM were performed. The results revealed that compound **27**

Table 4 PK profiles of compound 27 in rats

Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	CL (L/h/kg)	$T_{1/2}$ (h)	AUC_{0-t} (ug/L × h)	AUC_{0-inf} (ug/L × h)	F (%)
5 (iv)	501	0.08	2.79	18.39	1,254	1900	
30 (po)	116	0.83	33.79	24.07	438	901	5.90
100 (po)	115	2.83	25.76	39.49	1,305	5141	10.40

Abbreviation: PK, pharmacokinetics.
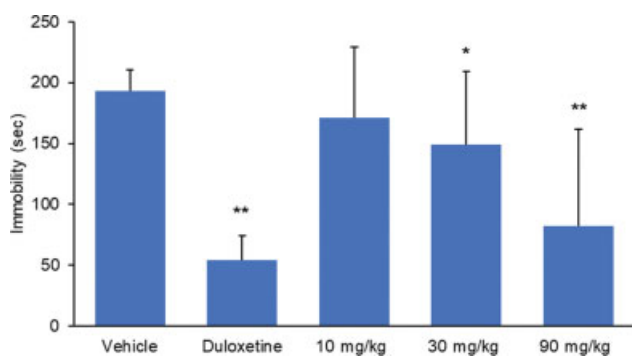
Fig. 4 Pharmacodynamics study of compound **27** at graded doses on the immobility time of mice in FST. Results are represented as mean ± SEM with n = 8 in each group. Values are significant at $^*p < 0.05$, $^{**}p < 0.01$ when compared with the vehicle group. FST, forced swim test; SEM, standard error of the mean.
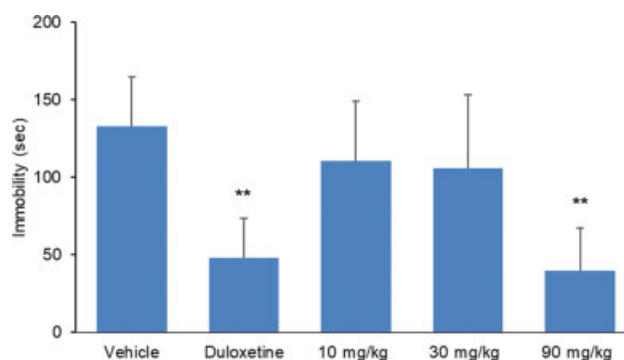
Fig. 5 Pharmacodynamics study of **27** on the immobility time of mice in TST. Results are represented as mean ± SEM (n = 8). $^*p < 0.05$, $^{**}p < 0.01$ versus the vehicle group. TST, tail suspension test; SEM, standard error of the mean.

showed high affinity for 5-HT$_{1A}$ and σ1 receptors (5-HT$_{1A}$: $K_i = 0.44$ nmol/L; σ1: $K_i = 0.27$ nmol/L) and had good metabolic stability ($T_{1/2}$ values are 21.7 and 24.6 minutes, respectively). FST, TST, and preliminary PK test of compound **27** showed that **27** exhibited good antidepressant activity in both models, and had good PK characteristics and low acute toxicity. Compound **27** is a promising active molecule of antidepressants. Our study provides a useful reference for the design and synthesis of new multi-target antidepressant compounds with higher activity, lower side effects, and good druggability.

Experimental Section

General Synthetic Procedure of 11–18

The substituted phenylpiperazine (10 mmol), 1-bromo-3-chloropropane (20 mmol), and potassium carbonate (24 mmol) were dissolved in 80 mL acetone. The mixture was stirred at 60°C for 8 hours. The reaction mixture was rotary-evaporated to remove acetone, added dichloromethane (80 mL) and water (80 mL) for extraction. The organic phase was separated, dried with anhydrous Na$_2$SO$_4$, and concentrated to obtain the crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a white solid (**5**).

1-(3-Chloropropyl)-4-(2,3-dimethylphenyl)piperazine (compound **5**, 4.8 mmol), TIQ (4.8 mmol), potassium carbonate (14.4 mmol), and potassium iodide (4.8 mmol) were dissolved in 50 mL of acetonitrile. The mixture was stirred at 82°C for 7 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. The residue was diluted with 50 mL of water and 30 mL of dichloromethane for extraction. The organic phase was separated, dried with anhydrous Na$_2$SO$_4$, and concentrated to obtain a residue, which was purified by column chromatography to give a white solid.

The above solid was dissolved in 30 mL ethyl acetate, then 2 mol/L hydrogen chloride–ethyl acetate solution was slowly added to adjust the pH to the desired value (pH 2–3). During the addition, a solid was precipitated, filtered, and then dried under vacuum to give the target product (**11**; white solid; yield: 18.3%).

2-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt (11): white solid; yield: 18.3%. ESI-MS (*m/z*): calcd. for C$_{22}$H$_{28}$Cl$_2$N$_3$$^+$ [M + H]$^+$ 404.1655; found 404.1. ^{1}H NMR (400 MHz, DMSO) δ 11.56 (s, 1H), 11.33 (s, 1H), 7.42–7.34 (m, 2H), 7.30–7.19 (m, 5H), 4.60 (d, *J* = 15.6 Hz, 1H), 4.31 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.78–3.60 (m, 3H), 3.49–3.41 (m, 2H), 3.37–3.20 (m, 10H), 3.04 (m, 1H), 2.45–2.32 (m, 2H).

2-(3-(4-(2,3-Dimethylphenyl)piperazin-1-yl)propyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt (12): white solid; yield: 85%. ESI-MS (*m/z*): calcd. for C$_{24}$H$_{34}$N$_3$$^+$ [M + H]$^+$ 364.2747; found 364.2. ^{1}H NMR (400 MHz, DMSO) δ 11.36 (s, 2H), 7.32–7.18 (m, 4H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 4.60 (d, *J* = 14.8 Hz, 1H), 4.31 (dd, *J* = 15.4, 8.0 Hz, 1H), 3.90–3.70 (m, 8H), 3.68–3.50 (m, 2H), 3.41–3.32 (m, 4H), 3.28–3.01 (m, 2H), 2.45–2.30 (m, 2H), 2.23 (s, 3H), 2.18 (s, 3H).

6,7-Dichloro-2-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt (13): white solid; yield: 25.1%. ESI-MS (*m/z*): calcd. for C$_{22}$H$_{26}$Cl$_4$N$_3$$^+$ [M + H]$^+$ 472.0875; found 472.2. ^{1}H NMR (400 MHz, DMSO) δ 11.32 (s, 1H), 11.30 (s,1H), 7.62 (s, 1H), 7.56 (s, 1H), 7.39 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 7.6, 2.0 Hz, 1H), 4.60 (d, *J* = 14.8 Hz, 1H), 4.41–4.29 (m, 1H), 3.80–3.69 (m, 1H), 3.68–3.55 (m, 2H), 3.54–3.39 (m, 6H), 3.37–3.12 (m, 6H), 3.11–3.01 (m, 1H), 2.42–2.25 (m, 2H).

2-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt (14): white solid; yield: 34%. ESI-MS (*m/z*): calcd. for C$_{24}$H$_{32}$Cl$_2$N$_3$O$_2$$^+$ [M + H]$^+$ 464.1866; found 464.3. ^{1}H NMR (400 MHz, DMSO) δ 11.13 (s, 1H), 10.74 (s, 1H), 7.43–7.33 (m, 2H), 7.26–7.20 (m, 1H), 6.84 (s, 1H), 6.78 (s, 1H), 4.48 (d, *J* = 15.2 Hz, 1H), 4.20 (dd, *J* = 15.3, 7.3 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.69 (m, 1H), 3.63 (d, *J* = 8.3 Hz, 2H), 3.47 (d, *J* = 9.5 Hz, 2H), 3.35–3.25 (m, 4H), 3.24 (d, *J* = 9.0 Hz, 6H), 2.95 (d, *J* = 16.8 Hz, 1H), 2.32 (m, 2H).

2-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt (15): white solid; yield: 11.6%. ESI-MS (*m/z*): calcd. for C$_{21}$H$_{26}$Cl$_2$N$_3$$^+$ [M + H]$^+$ 390.1498; found 390.1. ^{1}H NMR

(400 MHz, DMSO) δ 10.89 (s, 2H), 7.34–7.27 (m, 2H), 7.22 (d, $J = 5.9$ Hz, 2H), 7.15 (dd, $J = 12.8$, 6.8 Hz, 1H), 6.98 (dd, $J = 13.5$, 7.7 Hz, 2H), 3.93–3.65 (m, 4H), 3.38 (m, 10H), 3.2 (d, $J = 23.6$ Hz, 4H).

2-(2-(4-(2,3-Dimethylphenyl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt (16):

white solid; yield: 27%. ESI-MS (m/z): calcd. for $C_{23}H_{32}N_3^+$ [M + H]$^+$ 350.2591; found 350.2. ^{1}H NMR (400 MHz, DMSO) δ 11.06 (s, 2H), 7.29 (d, $J = 6.3$ Hz, 2H), 7.20 (d, $J = 5.9$ Hz, 2H), 7.08 (t, $J = 7.7$ Hz, 1H), 6.93 (dd, $J = 13.5$, 7.7 Hz, 2H), 4.80–4.60 (m, 1H), 4.49–4.25 (m, 1H), 3.95–3.65 (m, 6H), 3.40–3.00 (m, 10H), 2.23 (s, 3H), 2.19 (s, 3H).

6,7-Dichloro-2-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt (17):

white solid; yield: 48.3%. ESI-MS (m/z): calcd. for $C_{21}H_{24}Cl_4N_3^+$ [M + H]$^+$ 458.0719; found 458.1. ^{1}H NMR (400 MHz, DMSO) δ 11.19 (s, 2H), 7.62 (s, 1H), 7.55 (s, 1H), 7.39 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.36 (t, $J = 8.4$ Hz, 1H), 7.23 (dd, $J = 7.6$, 2.0 Hz, 1H), 4.70–4.56 (m, 1H), 4.45–4.24 (m, 1H), 4.05–2.96 (m, 16H).

2-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride salt (18):

white solid; yield: 50%. ESI-MS (m/z): calcd. for $C_{22}H_{28}Cl_2N_3^+$ [M + H]$^+$ 404.1655; found 404.2. ^{1}H NMR (400 MHz, DMSO) δ 11.54–11.16 (m, 2H), 7.42–7.33 (m, 2H), 7.33–7.20 (m, 5H), 4.82 (m, 1H), 3.82–3.51 (m, 10H), 3.34–3.25 (m, 6H), 3.07 (d, $J = 17.6$ Hz, 1H), 2.09–1.56 (m, 2H).

General Synthetic Procedure of 19–20

The substituted phenylpiperazine (10 mmol), 1-bromo-2-chloroethane (20 mmol), and potassium carbonate (24 mmol) were dissolved in acetone (80 mL). The mixture was stirred at 60°C for 8 hours. The reaction mixture was rotary-evaporated to remove acetone, and diluted with dichloromethane (80 mL) and water (80 mL) for extraction. The organic phase was separated, dried with anhydrous Na$_2$SO$_4$, and concentrated to obtain the crude product, which was purified by column chromatography (petroleum ether: ethyl acetate = 5:1) to give a white solid (8).

1-(2-Chloroethyl)-4-(2,3-dichlorophenyl)piperazine (compound **8**, 5 mmol), 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (5 mmol), potassium carbonate (15 mmol), and potassium iodide (5 mmol) were dissolved in acetonitrile (60 mL). The mixture was stirred at 82°C for 7 hours. After the completion of the reaction, the solvent was distilled off under reduced pressure. The residue was diluted with water (50 mL) and dichloromethane (40 mL) for extraction. The organic phase was separated, dried with anhydrous Na$_2$SO$_4$, and concentrated to obtain a residue, which was purified by column chromatography (petroleum ether:ethyl acetate = 3:1) to give a light yellow oily liquid.

The above light yellow oily liquid was dissolved in 30 mL ethyl acetate, then 2 mol/L hydrogen chloride–ethyl acetate solution was slowly added to adjust the pH to the desired value (pH 2–3). Solid was precipitated, filtered, and then dried in a vacuum to give the target product (**19**; white solid; yield: 74%).

5-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine dihydrochloride salt (19):

white solid; yield: 74%. ESI-MS (m/z): calcd. for $C_{19}H_{24}Cl_2N_3S^+$ [M + H]$^+$ 396.1063; found 396.1. ^{1}H NMR (400 MHz, DMSO) δ 11.14 (s, 1H), 10.94 (s, 1H), 7.33–7.27 (m, 2H), 7.25 (d, $J = 5.1$ Hz, 1H), 7.14 (dd, $J = 6.6$, 3.0 Hz, 1H), 6.78 (d, $J = 5.1$ Hz, 1H), 3.52–3.50 (m, 2H), 3.00–2.95 (m, 4H), 2.78–2.74 (m, 4H), 2.67–2.53 (m, 8H).

2-Chloro-5-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine dihydrochloride salt (20):

white solid; yield: 14%. ESI-MS (m/z): calcd. for $C_{19}H_{23}Cl_3N_3S^+$ [M + H]$^+$ 430.0673; found 430.0. ^{1}H NMR (400 MHz, DMSO) δ 11.29 (s, 2H), 7.33–7.26 (m, 2H), 7.14 (dd, $J = 6.6$, 3.1 Hz, 1H), 6.81 (s, 1H), 3.49–3.40 (m, 2H), 2.99–2.95 (m, 4H), 2.75 (dd, $J = 7.0$, 4.7 Hz, 2H), 2.72–2.68 (m, 2H), 2.65–2.52 (m, 8H).

General Synthetic Procedure for 21–24

The substituted phenylpiperazine (10 mmol), 1-bromo-2-chloroethane (20 mmol), and potassium carbonate (24 mmol) were dissolved in acetone (80 mL). The mixture was stirred at 60°C for 8 hours. The resulting mixture was rotary-evaporated to remove acetone, and diluted with dichloromethane (80 mL) and water (80 mL) for extraction. The organic phase was separated, dried with anhydrous Na$_2$SO$_4$, and then concentrated to obtain the crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give a white solid (**8**).

1-(2-Chloroethyl)-4-(2,3-dichlorophenyl)piperazine (compound **8**, 5 mmol), indoline-5-carbonitrile (5 mmol), potassium carbonate (15 mmol), and potassium iodide (5 mmol) were dissolved in acetonitrile (60 mL), and the mixture was stirred at 82°C for 7 hours. The solvent was distilled off under reduced pressure. And then 50 mL of water and 40 mL of dichloromethane were added for extraction. The organic phase was separated, dried with anhydrous Na$_2$SO$_4$, and concentrated to give a residue.

The residue was dissolved in 30 mL ethyl acetate, and then 2 mol/L hydrogen chloride–ethyl acetate solution was slowly added to adjust to pH to the desired value (pH 2–3). During the addition, solids are precipitated, filtered, recrystallized using ethanol to obtain the target product (**21**; white solid; yield: 30.7%).

1-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)indoline-5-carbonitrile hydrochloride salt (21):

white solid; yield: 30.7%. ESI-MS (m/z): calcd. for $C_{21}H_{23}Cl_2N_4^+$ [M + H]$^+$ 401.1294; found 401.2. ^{1}H NMR (400 MHz, CDCl$_3$) δ 13.44 (s, 1H), 7.43 (d, $J = 7.9$ Hz, 1H), 7.33–7.24 (m, 2H), 7.21 (t, $J = 8.0$ Hz, 1H), 7.03 (d, $J = 7.7$ Hz, 1H), 6.81 (d, $J = 8.2$ Hz, 1H), 3.97 (s, 2H), 3.66 (dt, $J = 16.9$, 9.7 Hz, 6H), 3.39 (d, $J = 12.3$ Hz, 2H), 3.23 (m, 4H), 3.09 (t, $J = 8.1$ Hz, 2H).

1-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)ethyl)indoline-4-carbonitrile hydrochloride salt (22):

white solid; yield: 38.3%. ESI-MS (m/z): calcd. for $C_{21}H_{23}Cl_2N_4^+$ [M + H]$^+$ 401.1294; found 401.1. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.39 (s, 1H), 7.44–7.30 (m, 2H), 7.22 (dd, $J = 10.5$, 5.1 Hz, 2H), 7.01 (dd, $J = 17.6$, 7.8 Hz, 2H), 3.75–3.59 (m, 4H), 3.55 (t, $J = 8.4$ Hz, 2H), 3.43 (d, $J = 10.5$ Hz, 4H), 3.27 (m, 4H), 3.13 (t, $J = 8.4$ Hz, 2H).

1-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl) indoline-5-carbonitrile hydrochloride salt (23): white solid; yield: 34.7%. ESI-MS (*m/z*): calcd. for $C_{22}H_{25}Cl_2N_4^+$ [M + H]$^+$ 415.1451; found 415.3. ^{1}H NMR (400 MHz, CDCl$_3$) δ 13.09 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.32–7.24 (m, 2H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 6.7 Hz, 1H), 6.47 (d, *J* = 8.3 Hz, 1H), 3.80–3.50 (m, 6H), 3.48–3.25 (m, 4H), 3.08 (t, *J* = 8.5 Hz, 6H), 2.40 (s, 2H).

1-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)propyl) indoline-4-carbonitrile hydrochloride salt (24): white solid; yield: 37.6%. ESI-MS (*m/z*): calcd. for $C_{22}H_{25}Cl_2N_4$ [M + H]$^+$ 415.1451; found 415.2. ^{1}H NMR (400 MHz, CDCl$_3$) δ 13.03 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 13.6, 9.6 Hz, 2H), 7.01 (dd, *J* = 13.9, 7.8 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 3.67 (t, *J* = 12.0 Hz, 4H), 3.59 (t, *J* = 8.2 Hz, 2H), 3.47–3.28 (m, 4H), 3.22 (t, *J* = 8.0 Hz, 2H), 3.10 (t, *J* = 6.5 Hz, 2H), 2.97 (t, *J* = 7.4 Hz, 2H), 2.40 (t, *J* = 7.5 Hz, 2H).

General Synthetic Procedure for 25–30

The substituted phenylpiperazine (10 mmol), 1-bromo-2-chloroethane (20 mmol), and potassium carbonate (24 mmol) were dissolved in 80 mL acetone. The mixture was stirred at 60°C for 8 hours. The resulting mixture was rotary-evaporated to remove acetone. The residue was diluted with dichloromethane (80 mL) and water (80 mL) for extraction. The organic phase was separated, dried with anhydrous Na$_2$SO$_4$, and concentrated to obtain the crude product, which was purified by column chromatography (petroleum ether: ethyl acetate = 5:1) to give a white solid (**8**).

1-(2-Chloroethyl)-4-(2,3-dichlorophenyl)piperazine (compound **8**, 5.1 mmol) and (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (5.1 mmol), potassium carbonate (15.4 mmol), and potassium iodide (5.1 mmol) were dissolved in 60 mL acetonitrile. The mixture was stirred at 82°C for 7 hours. The solvent was distilled off under reduced pressure. The residue was diluted with 50 mL of water and 40 mL of dichloromethane for extraction. The organic phase was separated, dried with anhydrous Na$_2$SO$_4$, and purified with column chromatography (petroleum ether:ethyl acetate = 20:1 - 3:1) to give an oily liquid.

The above oily liquid was dissolved in 30 mL ethyl acetate, and 2 mol/L hydrogen chloride–ethyl acetate solution was slowly added to adjust the pH to the desired value (pH 2–3). During the addition, solids were precipitated, which were filtered and dried under vacuum to obtain the target product (**25**; white solid; yield: 82.0%).

(*R*)-8-Chloro-3-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine dihydrochloride salt (25): white solid; yield: 82.0%. ESI-MS (*m/z*): calcd. for $C_{23}H_{29}Cl_3N_3^+$ [M + H]$^+$ 452.1422; found 452.0. ^{1}H NMR (400 MHz, DMSO) δ 11.18 (s, 1H), 10.68 (s, 1H), 7.31–7.26 (m, 2H), 7.13–7.09 (m, 4H), 3.08 (t, *J* = 7.4 Hz, 1H), 3.00–2.78 (m, 6H), 2.70–2.61 (m, 2H), 2.60–2.56 (m, 4H), 2.56–2.42 (m, 5H), 2.41–2.31 (m, 1H), 1.25 (d, *J* = 7.2 Hz, 3H).

(*S*)-8-Chloro-3-(2-(4-(2,3-dichlorophenyl)piperazin-1-yl)ethyl)-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine dihydrochloride salt (26): white solid; yield: 79.3%.

ESI-MS (*m/z*): calcd. for $C_{23}H_{29}Cl_3N_3^+$ [M + H]$^+$ 452.1422; found 452.3. ^{1}H NMR (400 MHz, DMSO) δ 11.32 (s, 1H), 10.65 (s, 1H), 7.31–7.22 (m, 2H), 7.15–7.04 (m, 4H), 3.05 (t, *J* = 7.3 Hz, 1H), 2.97–2.74 (m, 6H), 2.70–2.30 (m, 12H), 1.23 (d, *J* = 7.2 Hz, 3H).

(*R*)-8-Chloro-3-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine dihydrochloride salt (27): white solid; yield: 59%. ESI-MS (*m/z*): calcd. for $C_{24}H_{31}Cl_3N_3^+$ [M + H]$^+$ 466.1578; found 466.2. ^{1}H NMR (400 MHz, DMSO) δ 11.51 (s, 1H), 11.43 (s, 1H), 7.42–7.34 (m, 2H), 7.30 (t, *J* = 1.3 Hz, 2H), 7.26–7.19 (m, 2H), 3.81–3.68 (m, 2H), 3.61 (d, *J* = 11.0 Hz, 2H), 3.55–3.40 (m, 4H), 3.23 (dd, *J* = 15.5, 7.9 Hz, 8H), 3.02 (dd, *J* = 15.9, 6.0 Hz, 1H), 2.96–2.78 (m, 2H), 2.39–2.19 (m, 2H), 1.41 (m, 3H).

(*S*)-8-Chloro-3-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine dihydrochloride salt (28): white solid; yield: 59.2%. ESI-MS (*m/z*): calcd. for $C_{24}H_{31}Cl_3N_3^+$ [M + H]$^+$ $C_{24}H_{31}Cl_3N_3^+$ 466.1578; found 466.3. ^{1}H NMR (400 MHz, DMSO) δ 11.35 (s, 1H), 11.29 (s, 1H), 7.44–7.14 (m, 6H), 3.73 (t, *J* = 7.8 Hz, 2H), 3.61 (d, *J* = 10.1 Hz, 2H), 3.52–3.39 (m, 4H), 3.31–3.13 (m, 8H), 3.02 (dd, *J* = 15.9, 6.0 Hz, 1H), 2.96–2.79 (m, 2H), 3.33–3.25 (m, 2H), 1.42 (dd, *J* = 12.5, 6.9 Hz, 3H).

(*R*)-8-Chloro-3-(3-(4-(3-chlorophenyl)piperazin-1-yl)propyl)-1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine dihydrochloride salt (29): white solid; yield: 89%. ESI-MS (*m/z*): calcd. for $C_{24}H_{32}Cl_2N_3^+$ [M + H]$^+$ 432.1968; found 432.3. ^{1}H NMR (400 MHz, DMSO) δ 11.47 (s, 1H), 11.25 (s, 1H), 7.33–7.22 (m, 4H), 7.07 (t, *J* = 2.2 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.88 (dd, *J* = 7.8, 1.9 Hz, 1H), 3.91 (d, *J* = 13.1 Hz, 2H), 3.73 (dd, *J* = 15.9, 9.0 Hz, 2H), 3.57 (d, *J* = 11.8 Hz, 2H), 3.47 (dd, *J* = 18.6, 14.2 Hz, 2H), 3.27–3.08 (m, 8H), 3.01 (dd, *J* = 15.9, 5.9 Hz, 1H), 2.89 (m, 2H), 2.31–2.24 (m, 2H), 1.41 (dd, *J* = 14.1, 6.9 Hz, 3H).

(*R*)-8-Chloro-1-methyl-3-(3-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propyl)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine dihydrochloride salt (30): white solid; yield: 74%. ESI-MS (*m/z*): calcd. for $C_{25}H_{32}ClF_3N_3^+$ [M + H]$^+$ 466.2231; found 466.4. ^{1}H NMR (400 MHz, DMSO) δ 11.34 (s, 1H), 11.16 (s, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.35–7.26 (m, 4H), 7.25 (s, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 3.98 (d, *J* = 13.0 Hz, 2H), 3.77–3.67 (m, 2H), 3.60 (d, *J* = 11.6 Hz, 2H), 3.45 (d, *J* = 11.0 Hz, 2H), 3.28–3.09 (m, 8H), 3.02 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.94–2.84 (m, 2H), 2.33–2.25 (m, 2H), 1.41 (dd, *J* = 12.3, 7.0 Hz, 3H).

Receptor Binding Assay

The binding affinity for 5-HT$_{1A}$R was performed by incubating the displacement of [^{3}H]-8-OH-DPAT to HEK-293 cell membrane homogenates at 37°C for 10 minutes, in Tris/HCl buffer (50 mmol/L, pH 7.7). The σ1 receptor binding assay was determined by Jurkat cell membranes with [^{3}H](+)-pentazocine at 37°C for 2 hours, in 5 mmol/L Tris/HCl buffer (pH 7.4). The K_i values for 5-HT$_{1A}$ and σ1 were calculated from the corresponding IC$_{50}$ values according to the method of Cheng–Prusoff. The binding affinity results were expressed as means of at least three separate experiments.

Method for Studying the Stability of Liver Microsomes

To a solution of 20 μL 10 μmol/L standard working solution (substrate reaction concentration: 1 μmol/L) was added 140 μL 5.7 mmol/L cold $MgCl_2$ solution. After well mixing, RLM and HLM proteins (cold; 20 μL, 5 g/L; reaction concentration: 0.5 g/L) were supplemented. The solution was pre-incubated at 37°C in a water bath for 5 minutes, then added 20 μL 10 mmol/L NADPH (reaction concentration: 1.0 mmol/L) for the same preincubation for 5 minutes. The reaction was conducted in a 37°C water bath for 0, 5, 10, 20, 30, and 60 minutes, and terminated with 400 μL ice methanol. The resulting solution was vortexed for 3 minutes, and centrifuged at 12,000 rpm at 4°C for 10 minutes. The concentration of the target compounds in the supernatant was detected at each incubation time point using the established liquid chromatography–mass spectrometry (LC-MS) method. The mobile phase was acetonitrile–10 mmol/L ammonium acetate with 0.02% formic acid being added. By comparing with the concentration of the 0 hour sample, the metabolic rates of the target compounds were measured after incubation with RLM and HLM.

Chromatographic conditions of six compounds are as follows: the chromatographic column is Agilent extended C18 column (150 mm × 4.6 mm, 5 μm, Agilent, United States); the precolumn is C18 protective column (4 mm × 3.0 mm, 5 μm, Phenomenex, United States); the flow rate is 1.0 mL/min; the column temperature is 30°C. Mass spectrometric conditions: the ionization mode is electrospray ionization; the temperature is 350°C; selective ion monitoring, positive ion detection; the dryer temperature is 350°C; the fragmentation voltage is 70 V; the atomizer pressure (psi) is 35; the dry air velocity is 8 L/min; and the high vacuum is 1.3E-005Torr.

In Vivo Pharmacokinetic Test

Eighteen healthy male Sprague-Dawley rats were randomly divided into three groups. Rats in the three groups were given **27** by tail vein (5.0 mg/kg), gavage (30 mg/kg), and gavage (100 mg/kg), respectively. After administration, rat blood was collected from orbit at different time points. Drug concentration in the plasma was measured by LC-MS. The PK parameters and absolute bioavailability were calculated by DAS2.0 software.

For the detail, the methods can be described as follows: (1) intravenous administration group: six Sprague-Dawley male rats were fasted for 12 hours with water access freely prior to drug dosing. The rats were given **27** solution (1.0 mg/mL in glucose injection) by tail vein injection at the dose of 5.0 mg/kg. Then 0.3 mL blood was collected from fundus venous plexus before and after drug administration at 5, 15, 30, and 60 minutes, as well as 2, 4, 7, 10, and 24 hours, respectively, and centrifuged at 4,000 rpm for 10 minutes. The plasma was stored at −20°C in a refrigerator for further study. (2) Intragastric administration group: six Sprague-Dawley male rats were fasted for 12 hours with water access freely prior to drug dosing. The rats were given 3 and 10 mg/mL **27** solution by gavage at the dose of 30 and 100 mg/kg. Then 0.3 mL blood was collected from fundus

venous plexus before and after drug administration at 10, 20, 30, and 60 minutes, and 2, 4, 7, 10, and 24 hours, respectively, and then centrifuged at 4,000 rpm for 10 minutes. The plasma was stored at −20°C in a refrigerator for further study.

FST Assay

ICR male mice were randomly divided into five groups. Compound **27** were intragastrically administered at doses of 10, 30, and 90 mg/kg and duloxetine (20 mg/kg/d) for 7 consecutive days. The drug was administered 1 hour before each experiment. In the test, the mice were placed in a water pool (15 cm depth with water temperature of 23–25°C) in a transparent glass cylinder for 6 minutes, and at the same time, videotaped for 6 minutes. Then the immobility time of mice during swimming was recorded and analyzed.

TST Assay

ICR male mice were given vehicle, duloxetine (control drug, 20 mg/kg/d, po) as well as **27** (10, 30, and 90 mg/kg, po) for 7 consecutive days. The drug was administered 1 hour before each experiment. In the TST, the mice were pasted with adhesive tape 1 cm away from its tail tip, and hung for 6 minutes for video recording. Then, the immobility time of the mice during the tail suspension period was analyzed.

Ethics Statement

The present study was approved by the animal ethics committee and abides by the relevant agreements of the Jiangsu Enhua Pharmaceutical Co., Ltd., Jiangsu, People's Republic of China.

Conflict of Interest

None.

References

1 GBD 2016 SDG Collaborators. Measuring progress and projecting attainment on the basis of past trends of the health-related Sustainable Development Goals in 188 countries: an analysis from the Global Burden of Disease Study 2016. Lancet 2017; 390(10100):1423–1459

2 Hindmarch I, Hashimoto K. Cognition and depression: the effects of fluvoxamine, a sigma-1 receptor agonist, reconsidered. Hum Psychopharmacol 2010;25(03):193–200

3 Kulkarni SK, Dhir A. Current investigational drugs for major depression. Expert Opin Investig Drugs 2009;18(06):767–788

4 Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA 2010;303(01):47–53

5 Delgado M, Caicoya AG, Greciano V, et al. Anxiolytic-like effect of a serotonergic ligand with high affinity for 5-HT1A, 5-HT2A and 5-HT3 receptors. Eur J Pharmacol 2005;511(01):9–19

6 McCreary AC, Jones CA. Antipsychotic medication: the potential role of 5-HT(1A) receptor agonism. Curr Pharm Des 2010;16(05):516–521

7 López JF, Chalmers DT, Little KY, Watson SJAE. A.E. Bennett Research Award. Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. Biol Psychiatry 1998;43(08):547–573

8 McCormack PL. Vilazodone: a review in major depressive disorder in adults. Drugs 2015;75(16):1915–1923

9 Bang-Andersen B, Ruhland T, Jørgensen M, et al. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. J Med Chem 2011;54(09):3206–3221

10 Narita N, Hashimoto K, Tomitaka S, Minabe Y. Interactions of selective serotonin reuptake inhibitors with subtypes of sigma receptors in rat brain. Eur J Pharmacol 1996;307(01):117–119

11 Bermack JE, Debonnel G. The role of sigma receptors in depression. J Pharmacol Sci 2005;97(03):317–336

12 Uchida N, Ujike H, Tanaka Y, et al. A variant of the sigma receptor type-1 gene is a protective factor for Alzheimer disease. Am J Geriatr Psychiatry 2005;13(12):1062–1066

13 Junien JL, Roman F, Defaux JP, et al. JO-1784, a new selective ligand for sigma-1 sites-characteristics and functional-activity. Eur J Pharmacol 1990;183:2145–2145

14 Villard V, Meunier J, Chevallier N, Maurice T. Pharmacological interaction with the sigma1 (σ1)-receptor in the acute behavioral effects of antidepressants. J Pharmacol Sci 2011;115(03):279–292

15 Hayashi T, Su TP. Sigma-1 receptor ligands: potential in the treatment of neuropsychiatric disorders. CNS Drugs 2004;18(05):269–284

16 Skuza G, Rogóz Z. Antidepressant-like effect of combined treatment with selective sigma receptor agonists and a 5-HT1A receptor agonist in the forced swimming test in rats. Pharmacol Rep 2007;59(06):773–777

17 Bermack JE, Debonnel G. Effects of OPC-14523, a combined sigma and 5-HT1a ligand, on pre- and post-synaptic 5-HT1a receptors. J Psychopharmacol 2007;21(01):85–92

18 Bermack JE, Haddjeri N, Debonnel G. Effects of the potential antidepressant OPC-14523 [1-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-methoxy-3,4-dihydro-2-quinolinone monomethanesulfonate] a combined sigma and 5-HT1A ligand: modulation of neuronal activity in the dorsal raphe nucleus. J Pharmacol Exp Ther 2004;310(02):578–583

19 Możdżeń E, Papp M, Gruca P, et al. 1,2,3,4-Tetrahydroisoquinoline produces an antidepressant-like effect in the forced swim test and chronic mild stress model of depression in the rat: Neurochemical correlates. Eur J Pharmacol 2014;729:107–115

20 Chodkowski A, Wróbel MZ, Turło J, et al. Novel 4-aryl-pyrido[1,2-c]pyrimidines with dual SSRI and 5-HT1A activity. Part 4. Eur J Med Chem 2015;90:21–32

21 Kiss B, Horváth A, Némethy Z, et al. Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. J Pharmacol Exp Ther 2010;333(01):328–340

22 Frankel JS, Schwartz TL. Brexpiprazole and cariprazine: distinguishing two new atypical antipsychotics from the original dopamine stabilizer aripiprazole. Ther Adv Psychopharmacol 2017;7(01):29–41