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Synthesis and Biological Evaluation of Five-Atom-Linker-Based Arylpiperazine Derivatives with an Atypical Antipsychotic Profile

Chunhui Wu,[a, c] Yu Wang,[a, b] Feipu Yang,[b] Wenqiang Shi,[b] Zhen Wang,[b] Ling He,*[a] Yang He,*[b] and Jingshan Shen[b]

Herein we describe a focused set of new arylpiperazine derivatives as potential broad-spectrum antipsychotics. The general structure contains a quinolinone-like moiety, an arylpiperazine moiety, and a five-atom linker. Among them, 7-(5-(4-(benzo[*d*]isothiazol-4-yl)piperazin-1-yl)pentyl)quinolin-2(1*H*)-one (**S6**) shows a promising preclinical profile. Compound **S6**, characterized by partial D_2R agonism, 5-$HT_{1A}R$ agonism, 5-$HT_{2A}R$ antagonism, and blockade of SERT activities, was found to decrease psychosis- and depressive-like symptoms in rodents. The polypharmacological profile of **S6** could provide opportunities for the treatment of various other central nervous system disorders such as anxiety, depression, and psychoses associated with dementia. Furthermore, **S6** demonstrated acceptable safety, toxicology, and pharmacokinetic profiles, and has been selected as a preclinical candidate for further evaluation in schizophrenia.

Introduction

Schizophrenia is a complex psychological disorder of unclear etiology characterized by the coexistence of positive, negative and cognitive symptoms.[1,2] Although the emergence of antipsychotics brought enormous progress to the treatment of schizophrenia, there are still huge unmet clinical needs that exist owing to its complicated pathophysiology.[3,4]

In the field of drug discovery, the "one-target, one-drug" paradigm has been the mainstream over the past years. However, this strategy seems to be unsuitable for complex psychiatric diseases such as schizophrenia. In clinical practice, atypical antipsychotics are often used together with antidepressants for schizophrenia to get maximum efficacy.[5] Patients often take several single drugs with different bioavailability, pharmacokinetics, and metabolism profiles. This therapeutic regimen often leads to drug-drug interactions, particularly in patients with psychiatric comorbidity. Literature data suggest that the above drawbacks could be avoided by designing a molecule with a "selective" multireceptor profile which simultaneously modulates several specific targets to get better safety and efficacy for the treatment of schizophrenia.[6–8] From the target's perspective, treatment with D_2 receptor partial agonists represented by Aripiprazole and Brexpiprazole is regarded as the best approach to modulate dopaminergic function because of their excellent effectiveness and tolerability.[9–11] Besides dopamine D_2 receptors, various serotonin receptors are also important targets for schizophrenia. A wealth of preclinical and clinical evidence strongly supports the relevance of 5-HT_{1A} receptor activation and 5-HT_{2A} receptor inhibition for the treatment of schizophrenia.[12–14] Furthermore, designing a molecule with serotonin (5-HT) transporter (SERT) inhibition function is beneficial to the treatment of schizophrenia and both the efficacy and safety of selective serotonin reuptake inhibitors (SSRIs) as augmentation therapy for schizophrenia have been proven clinically.[15] Although the antipsychotic drug ziprasidone, introduced in 2000, possessed 5-$HT_{2A}R$ antagonism, 5-$HT_{1A}R$ agonism, and SERT blockade activities, however, it is a full antagonist for D_2R. Thus, our work aimed to search for versatile molecules that combine D_2 receptor partial agonism and serotonin reuptake inhibition with functional action on various 5-HT receptors, especially 5-HT_{1A} receptors. We expected that compounds with such a multifunctional profile would be more effective and better tolerated than currently-used antipsychotics.

In this paper, we described a series of five-atom-linker-based multireceptor acting compounds that possess antipsychotic-like activity. The design concept of new compounds was shown in Figure 1. The general structure contains a quinolinone-like moiety, an arylpiperazine moiety, and a five-atom linker. We select the dihydroquinolinone fragment of Aripiprazole and Brexpiprazole or its bioisostere on the basis of their weak to moderate serotonin reuptake inhibition activities.[16,17] The choice of arylpiperazines originates from potent fragments reported by literature as well as our own experience.[18,19] As our

[a] Dr. C. Wu, Dr. Y. Wang, Prof. L. He
Department of Pharmacology
China Pharmaceutical University
Nanjing 210009 (China)
E-mail :
E-mail: heling92@hotmail.com
[b] Dr. Y. Wang, Dr. F. Yang, Dr. W. Shi, Prof. Z. Wang, Dr. Y. He, Prof. J. Shen
CAS Key Laboratory of Receptor Research
Drug Discovery and Design Center
Shanghai Institute of Materia Medica, Chinese Academy of Sciences (CAS)
Shanghai 201203 (China)
E-mail: heyang@simm.ac.cn
[c] Dr. C. Wu
Department of Druggability Evaluation
Topharman Shanghai Co. Ltd.
Shanghai 201203 (China)

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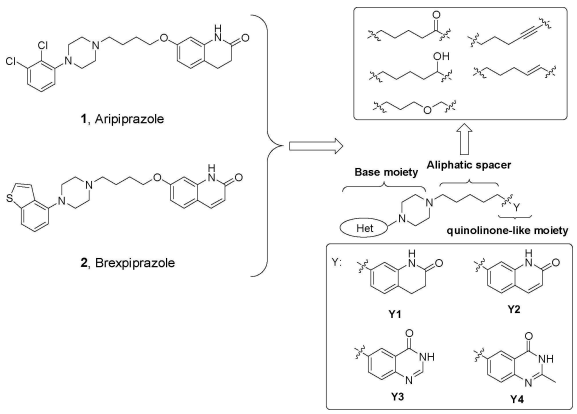
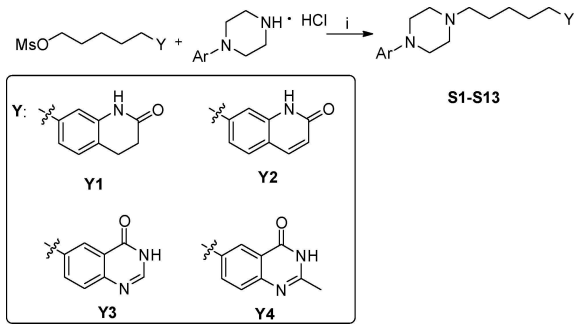
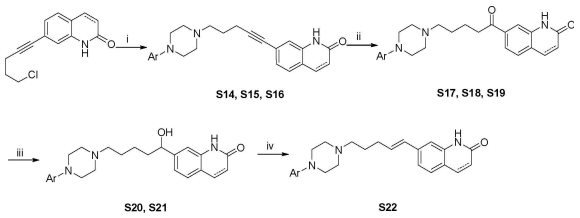


Figure 1. Design of new five-atom-linker-based arylpiperazine derivatives.

previous SAR studies on antipsychotic drugs indicated that an appropriate linker is of great importance for desired multi-receptor activity, we also explored the influence of linker flexibility of the new derivatives on receptor function profiles.[18] Among the derivatives prepared, compound **S6** manifested a unique polypharmacological antipsychotic profile. It displayed much higher potency for the desired targets (D_2, 5-HT_{1A}, 5-HT_{2A}, and SERT) than other off-target receptors (α_{1A}, H_1, 5-HT_{2C}, M_3, hERG). Thus, compound **S6** was developed as an atypical antipsychotic candidate to treat schizophrenia based on the D_2R, 5-HT_{1A}R, 5-HT_{2A}R and SERT multi-target profile.



Scheme 1. Reagents and conditions: (i) K_2CO_3, CH_3CN, reflux, 7 h.

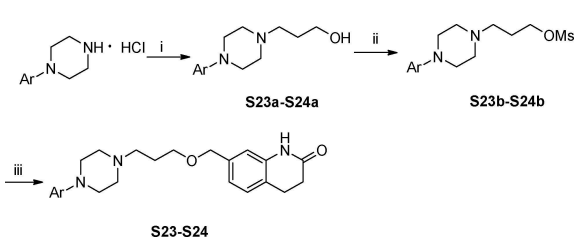


Scheme 2. Reagents and conditions: (i) NaI, K_2CO_3, CH_3CN, reflux, 24 h; (ii) **S14** to **S17** or **S15** to **S18** or **S16** to **S19**, 4% H_2SO_4, $HgSO_4$, MeOH, 50 °C, 40 h; (iii) **S17** to **S20** or **S18** to **S21**, $NaBH_4$, DCM/MeOH, rt, 0.5 h; (iv) **S21** to **S22**, 6 N HCl, MeOH, reflux, 12 h.

Results and Discussion

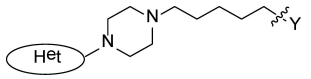
Synthesis of these new arylpiperazine derivatives was performed as exemplified in Schemes 1–3. Pentyl methanesulfonates substituted with quinolinone-like moieties were coupled with various arylpiperazine moieties to produce **S1**–**S13**. Target compounds **S14**–**S16** were synthesized via N-alkylation of the appropriate chloride intermediates with corresponding arylpiperazine moieties as outlined in Scheme 2. Treatment of **S14**–**S16** with a 4% H_2SO_4 solution in the presence of $HgSO_4$ to affect the hydration of the alkyne functionality to afford aryl ketone derivatives **S17**–**S19**. The reduction of the carbonyl groups of **S17** and **S18** with $NaBH_4$ in the DCM/MeOH system gave alcohol derivatives **S20** and **S21** respectively in a quantitative yield. Alcohol **S21** was dehydrated under acidic conditions to give compound **S22**. The synthesis of benzyl ether derivatives **S23**–**S24** was shown in Scheme 3. Firstly, intermediate mesylates **S23b**–**S24b** was obtained through initial alkylation of corresponding arylpiperazine moieties with 3-bromo-1-propanol to alcohols **S23a**–**S24a** followed by reaction with methanesulfonyl chloride. Then **S23b**–**S24b** were condensed with 7-(hydroxymethyl)-3,4-dihydroquinolin-2(1*H*)-one in the presence of NaH to give **S23**–**S24**.

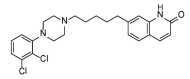
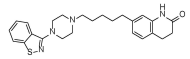
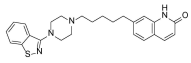
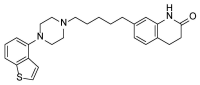
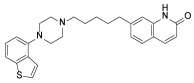
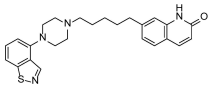
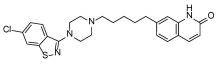
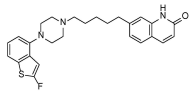
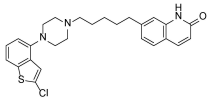
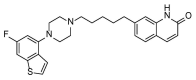
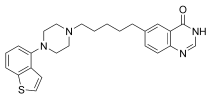
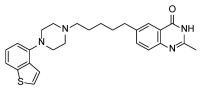
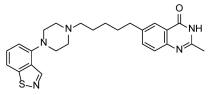
Taking Aripiprazole and Brexpiprazole as lead compounds, our work started from the synthesis of **S1**–**S13**. As shown in Table 1, compound **S1** behaved like a low potency ligand for all three receptors, especially for 5-HT_{1A}R and 5-HT_{2A}R. Compounds **S2** and **S3** owning a 1-(benzo[*d*]isothiazole-3-yl)piperazine fragment exhibited good activities for all the three receptors. In light of the crucial role of 5-HT_{2A}R in the action of antipsychotics such as the alleviation of the negative symptoms of schizophrenia,[20] we emphasized the antipsychotic potential displayed by compound **S3** with high potency at the 5-HT_{2A}R (IC_{50} = 61.2 nM), greater than that displayed for reference drug Brexpiprazole. Compounds **S4** and **S5** possessing a 1-(benzo[b]thiophen-4-yl)piperazine fragment displayed similar strong activities for all the three receptors, which is consistent with **S2** and **S3**. This result points out that changing the 3,4-dihydroquinolin-2(1*H*)-one moiety with quinolin-2(1*H*)-one moiety made little difference in receptor function profiles. Furthermore, the 3-(piperazin-1-yl)benzo[*d*]isothiazole moiety seemed to be superior to the 1-(benzo[b]thiophen-4-yl)piperazine moiety in terms of 5-HT_{2A}R potency (**S2** vs **S4**, **S3** vs **S5**). Replacement of the 1-(benzo[b]thiophen-4-yl)piperazine moiety of **S5** with its bioisostere 1-(benzo[*d*]isothiazole-4-yl)piperazine had almost no



Scheme 3. Reagents and conditions: (i) K_2CO_3, 3-bromo-1-propanol, CH_3CN, reflux, 5 h; (ii) MsCl, Et_3N, DCM, rt, 0.5 h; (iii) 7-(hydroxymethyl)-3,4-dihydroquinolin-2(1*H*)-one, NaH, THF, reflux, 8 h.

Table 1. Functional activities of **S1**–**S13** on main targets.



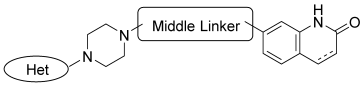
Compd	Structure	D_2R IC_{50} [nM]	5-$HT_{1A}R$ EC_{50} [nM]	5-$HT_{2A}R$ IC_{50} [nM]
S1		83.0	1260	8070
S2		6.8	12.2	157
S3		10.1	14.6	61.2
S4		10.1	9.9	203
S5		10.2	9.2	209
S6		8.5	9.9	358
S7		36.8	>10000	394
S8		4.8	21.8	1020
S9		22.3	13.0	2980
S10		1.5	>10000	974
S11		324	54.0	201
S12		50.7	25.9	781
S13		4.9	26.5	630
BRE[a]	–	4.8	66.8	320

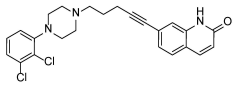
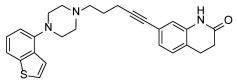
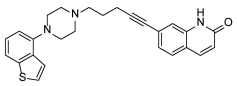
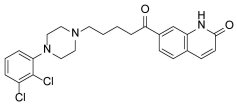
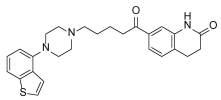
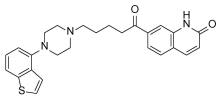
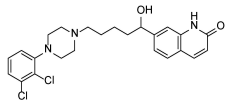
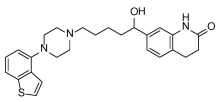
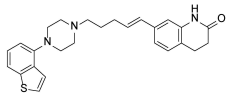
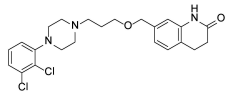
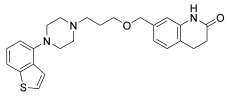
[a] Brexpiprazole.

effect on the D_2R and 5-$HT_{1A}R$ activities, however, this could slightly decrease the 5-$HT_{2A}R$ antagonistic activity (**S6** vs **S5**). It is worth to note that compounds **S2**–**S6** presented a favorable balance between functional activities at D_2 and 5-HT_{1A} receptors ($0.5 < IC_{50}$ (D_2R) : EC_{50} (5-$HT_{1A}R$) < 2). Introduction of a chlorine atom at 6-position of benzo[*d*]isothiazole fragment brought about remarkably reduced activities for the main targets (**S7** vs **S3**). Specifically, **S7** was completely devoid of agonistic activity for 5-$HT_{1A}R$. For the 2-position of benzothiophene part, the introduction of a fluorine or chlorine atom induced comparable activities for D_2R and 5-$HT_{1A}R$ while sharply reduced potency for 5-$HT_{2A}R$ (**S8** and **S9** vs **S5**). In contrast, compound **S10** with a fluorine atom at 6-position of benzothiophene part showed increased potency for D_2R but the effect on 5-$HT_{1A}R$ and 5-$HT_{2A}R$ was significantly decreased (**S10** vs **S5**). These outcomes suggested that the substitution of electron-withdrawing groups on benzothiophene or benzo[*d*]isothiazole ring was detrimental for 5-$HT_{2A}R$ potency. Compounds **S11** and **S12** were bioisosteric analogs of compound **S5** and both of them exhibited lower activities for D_2 and 5-HT_{1A} receptors than **S5**. Additionally, the introduction of a methyl group to the quinazolin-4(3H)-one moiety of compound **S11** was harmful to 5-$HT_{2A}R$ potency whereas beneficial for D_2 and 5-$HT_{1A}R$ potency (**S12** vs **S11**). Compound **S13** as a bioisosteric analog of compound **S6** displayed comparable potency for D_2 receptor while reduced potency for 5-$HT_{1A}R$ and 5-$HT_{2A}R$ (**S13** vs **S6**). These data supported the contention that the quinolin-2(1*H*)-one moiety is superior to the quinazolin-4(3H)-one moiety.

To examine the effects of the central linker on functional activities, we also designed the compounds outlined in Table 2, which contain substituted or conformationally constrained five-atom linkers. The alkynyl containing compound **S14** showed enhanced activities for D_2 and 5-$HT_{2A}R$ compared with **S1** while retained medium activity for 5-$HT_{1A}R$. In contrast, the alkynyl containing compound **S15** displayed reduced activities for D_2 and 5-$HT_{1A}R$ compared with **S4** while comparable activity for 5-$HT_{2A}R$. With respected to **S16**, it exhibited reduced activities for D_2, 5-$HT_{1A}R$, and 5-$HT_{2A}R$ compared with **S5**. Substituent modification on the pentyl linker seems to be beneficial for functional activities at D_2R and 5-$HT_{2A}R$. Replacement of the methylene adjacent to quinolin-2(1*H*)-one moiety with a carbonyl group resulted in improved potency for all three receptors (**S17** vs **S1**). Similarly, compound **S18** as well as **S19** retained high potency for D_2R, and 5-$HT_{2A}R$ while their effect on 5-$HT_{1A}R$ was slightly reduced (**S18** vs **S4**, **S19** vs **S5**). Introducing a hydroxy group to the pentyl linker at the carbon atom adjacent to quinolin-2(1*H*)-one moiety elicited considerably enhanced activities for the main targets (**S20** vs **S1**). Notably, **S20** with the privileged structure of Aripiprazole had the strongest activity for the D_2 receptor ($IC_{50} = 1.3$ nM), even higher than that of Brexpiprazole. Unlike **S20**, **S21** with a hydroxy substitution on the pentyl linker is more potent at D_2R and 5-$HT_{2A}R$ but slightly less potent at 5-$HT_{1A}R$ than **S4**. Interestingly, the alkenyl-containing compound **S22** retained high potency for D_2R but the effect on 5-$HT_{1A}R$ and 5-$HT_{2A}R$ was weakened (**S22** vs **S4**). The benzyl ethers **S23** and **S24** manifested moderate to weak activities for D_2R, 5-$HT_{1A}R$, and 5-$HT_{2A}R$, which suggested the significance of the presence of O atom in the linker in modulating dopaminergic and serotonergic function (**S24** vs **S4**). Furthermore, compared with the pentyl linker, the less lipophilic nature of the propyloxymethyl linker will decrease lipid solubility of compounds (See Supplemental Table S1), thus reducing the blood–brain barrier penetration of the molecular which will result in insufficient drug concentration to achieve efficacy. We can see that unlike 1-(benzo[*b*]thiophen-4-yl) piperazine and 1-(benzo[*d*]isothiazole-3-yl)piperazine moieties, 1-(2,3-dichlorophenyl)piperazine fragment makes compounds lack appreciable activity for 5-$HT_{2A}R$ (**S14**, **S17**, **S20**), which was

Table 2. Functional activities of **S14**–**S24** on main targets.



Compd	Structure	D_2R IC_{50} [nM]	5-$HT_{1A}R$ EC_{50} [nM]	5-$HT_{2A}R$ IC_{50} [nM]
S14		30.6	1265	2214
S15		51.9	22.6	210
S16		22.8	47.6	782
S17		3.0	380	3840
S18		6.2	31.1	285
S19		3.8	19.8	138
S20		1.3	238	754
S21		4.5	15.7	108
S22		9.0	97.5	502
S23		76.7	121	1390
S24		121	44.7	525
BRE[a]	–	4.8	66.8	320

[a] Brexpiprazole.

consistent with SAR of compounds discussed in our previous study.[19] These relationships are summarized in Figure 2.

In our examination of novel five-atom-linker-based arylpiperazine derivatives as potential antipsychotic agents, we have attempted to balance the D_2R and 5-$HT_{1A}R$ potency ratio on the hypothesis that the desired ratio might be a key to drug's atypical nature. For further characterization, we set two compounds selection criteria: (a) IC_{50} (D_2R), EC_{50} (5-$HT_{1A}R$) <30 nM, IC_{50} (5-$HT_{2A}R$) <500 nM; (b) the potency ratio between D_2R and 5-$HT_{1A}R$ should be no greater than 5. Then compounds **S2**–**S6** and **S21** were chosen to test their intrinsic activities for

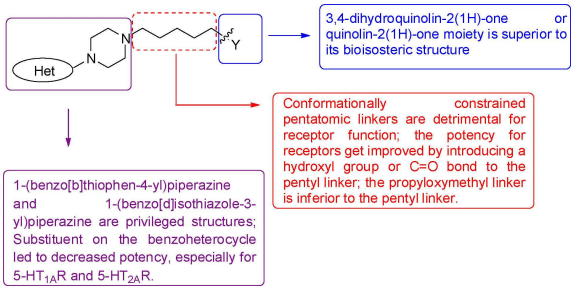


Figure 2. Summary of the SAR studies on different regions of the five-atom-linker-based arylpiperazine derivatives.

the D_2 receptor further. Our design assumptions prompt us to select compounds with D_2 partial activity. For D_2R partial agonists, too high or low D_2 intrinsic activity is unsuitable, as high D_2 intrinsic activity will not produce robust antipsychotic activity while low D_2 intrinsic activity will result in elevated prolactin secretion and risk of EPS.[21] As shown in Table 3, compounds **S2**–**S4** and **S21** were devoid of D_2 receptor agonistic activity, indicating that they were full antagonists at the D_2 receptor. Both **S3** and **S6** displayed significant partial agonistic activity at D_2 receptor, comparable to that of Brexpiprazole in terms of E_{max} value. Furthermore, **S6** is a more potent D_2 receptor agonist than **S5** and Brexpiprazole in terms of EC_{50} value. Compound **S6** possesses a relatively low D_2 intrinsic activity and high 5-$HT_{1A/2A}$ receptors activity, which will lead to minimal side effects and produce beneficial antipsychotic effects.[22,23]

SERT is closely involved in psychiatric diseases. We used a fluorescence-based assay to measure the SERT uptake activity of **S6**.[24] As shown in Table 4, compound **S6** showed potency stronger than that of Brexpiprazole while slightly weaker than that of Citalopram at SERT. This pharmacological characteristic may contribute to the alleviation of the comorbid depressive symptoms in schizophrenia.

Table 3. Agonistic activities of selected compounds on D_2R.

Compd	D_2R EC_{50} [nM][a]	E_{max} [%][b]
S2	N.A.	<20
S3	N.A.	<20
S4	N.A.	<20
S5	2.0	23
S6	0.3	27
S21	N.A.	<20
Brexpiprazole	6.3	29

[a] N.A.: not active. [b] Expressed as percentage of the effect of 10 μM dopamine.

Table 4. SERT uptake activity of **S6** and reference drugs.

Compd	SERT IC_{50} [nM]
S6	39.7
Brexpiprazole	176.3
Citalopram	8.3

The atypical antipsychotics can trigger many adverse events and several off-target receptors are reported to contribute to these side effects.[25–27] Therefore, further *in vitro* pharmacological characterization of **S6** is essential. Schizophrenia patients treated with antipsychotic medication often suffer from orthostatic hypotension, due to the blockade of the α_{1A}-adrenoceptor.[28,29] Unlike Risperidone, compounds **S6** and Brexpiprazole showed moderate α_{1A} adrenoreceptor antagonistic activity, this means that they will not elicit orthostatic hypotension (Table 5). Antagonism of histamine H_1 receptor and serotonin 5-HT_{2C} receptor has been identified as the main cause of antipsychotic-induced weight gain.[30–33] Concerning H_1R, all tested compounds displayed mild-to-moderate potency. Furthermore, compound **S6** was devoid of 5-HT_{2C} receptor antagonistic activity. Based on the above results, compound **S6** exhibited a low propensity to cause drug-induced weight gain. Pancreatic M_3 cholinergic receptor is involved in antipsychotics-induced hyperglycemia and type II diabetes mellitus.[34] Potent M_3 receptor antagonists olanzapine and clozapine caused a higher incidence of diabetes than other antipsychotics in clinical practice. Like Risperidone and Brexpiprazole, **S6** had no antagonistic activity against the M_3 receptor, suggesting it will not cause hyperglycemia. Moreover, **S6**, as well as Risperidone and Brexpiprazole, may have a low ability to cause QT interval prolongation due to their weak potency on hERG.[35]

The possible drug-induced hepatotoxicity, as well as nephrotoxicity of compound **S6**, was examined and the results were shown in Table 6. **S6** exhibited lower cell toxicities against Chang Liver cells than Risperidone and Brexpiprazole. Besides, both compound **S6** and Risperidone displayed low cell toxicities against HEK 293 cells ($>600\ \mu g\,mL^{-1}$). These results indicated that compound **S6** was almost nontoxic and suitable for further *in vivo* exploration.

The hyperactivity induced by NMDA receptor antagonists such as MK-801, Phencyclidine (PCP) or ketamine is often used as a rodent model of psychoses.[36] Thus agents normalizing hyperactivity demonstrate antipsychotic-like properties.[37] In this model, compound **S6** reversed the PCP-induced hyperactivity dose-dependently ($ED_{50} = 3.08\ mg\,kg^{-1}$, Figure 3), which

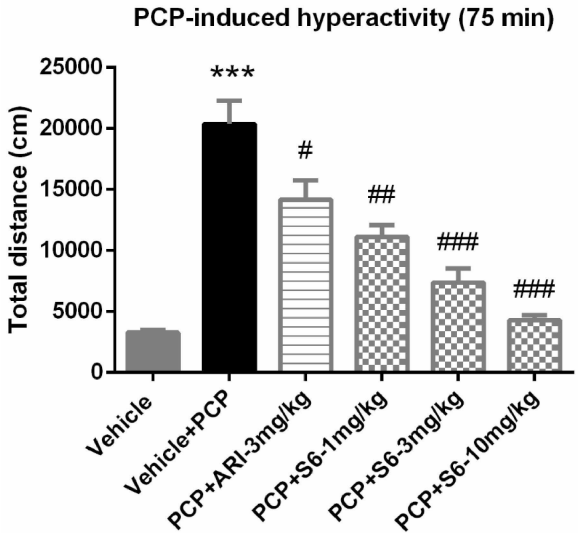


Figure 3. Effect of all doses of compound **S6** (po, 1 $mg\,kg^{-1}$, 3 $mg\,kg^{-1}$ and 10 $mg\,kg^{-1}$) and Aripiprazole (ARI, 3 $mg\,kg^{-1}$) on ICR mouse model (PCP-induced hyperactivity; PCP: 7 $mg\,kg^{-1}$, ip). Data are presented as means ± SEM with $N = 8$ in each group. The one-way ANOVA followed by Dunnett's post-hoc test was performed. ***$p < 0.001$ versus vehicle treatment; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ and $^{\#\#\#}p < 0.001$ versus PCP treatment.

is in line with its strong activity for D_2R *in vitro*. Besides, it is worth to note that Aripiprazole produced less potent efficacy than **S6** at 3 $mg\,kg^{-1}$.

The head twitch responses (HTR) in rodents elicited by Quipazine, a serotonin receptor agonist, is a specific behavior relative to the activation of 5-HT_{2A}R.[38] Consistent with its strong activity for 5-HT_{2A}R *in vitro,* **S6** inhibited head twitches dose-dependently (Table 7). Furthermore, **S6** expressed a potent inhibitory action on the HTR comparable to that of Brexpiprazole at 1 $mg\,kg^{-1}$. Additionally, Aripiprazole had a much higher occupancy at D_2R than at 5-HT_{2A}R,[16] whereas compound **S6** may have comparable occupancy at D_2R and 5-HT_{2A}R at the same dosage. This characteristic of **S6** may bring clinical benefits. The high potency of **S6** for 5-HT_{2A}R *in vitro* is supported by *in vivo* data displaying strong inhibition of Quipazine-induced HTR in mice. 5-HT_{2A}R antagonism may be the main mechanism involved in the drug-induced reduction of HTR, but 5-HT_{1A}R agonists are also inhibitory.[39] Therefore, the

Table 5. Functional activities of compound **S6** and reference antipsychotics on several off-target receptors.

Compd	IC_{50} [nM] α_{1A}	H_1	5-HT_{2C}	M_3	hERG
S6	391	194	>10000	>10000	1020
RIS[a]	10	454	7	>10000	1330
BRE[b]	202	349	69.5	>10000	1260

[a] Risperidone. [b] Brexpiprazole.

Table 6. Cell viability of compound **S6** and reference antipsychotics.

Compd	Hepatotoxicity IC_{50} [$\mu g\,mL^{-1}$]	Nephrotoxicity IC_{50} [$\mu g\,mL^{-1}$]
S6	>600	>600
Risperidone	238.8	>600
Brexpiprazole	44.2	19.1

Table 7. Effect of **S6** on ICR mice model of quipazine-induced head twitches response.

Treatment	Dose [$mg\,kg^{-1}$]	Head twitches [number of episodes][a]	HTR reduction [%]
Vehicle	0	14.8 ± 1.07	
S6	1	6.4 ± 0.75***	56.76
	3	3.2 ± 1.24***	78.38
Brexpiprazole	1	3.8 ± 0.86***	74.32
Aripiprazole	3	5.0 ± 1.38***	66.21

[a] Data are presented as means ± SEM with $N = 5$ in each group. The one-way ANOVA followed by Dunnett's post-hoc test was performed. *** $p <$ 0.001 versus Quipazine-treated group.

detailed mechanism involved in the effect of **S6** is unclear and further research is needed.

The antidepressant potential of compound **S6** was investigated in the forced swim test (FST) in mice. Neither Aripiprazole nor Brexpiprazole, only compound **S6** was effective at the dose of 0.1 mg kg^{-1} (Figure 4), which is in line with its strong inhibition on SERT. At 0.3 mg kg^{-1}, the partial agonist **S6** may behave as an antagonist for D_2R *in vivo* and would influence the motor function of mice, which led to the ineffectiveness of **S6** in the FST at this dosage.[40] Besides, Fluoxetine at the dose of 10 mg kg^{-1} caused a statistically significant decrease in immobility time. Aripiprazole lacks antidepressant-like activity in FST (data not shown), which is consistent with results reported by Bourin et al.[41] Moreover, as the spontaneous locomotor activity of mice after administration of **S6** or Fluoxetine at effective doses was not influenced (data not shown), their antidepressant-like effects should be specific.

Catalepsy in rodents is a model predictive of EPS in humans.[42] As shown in Table 8, **S6** displayed a low probability for inducing catalepsy (CAT/PCP = 19.59), better than that of Risperidone and Aripiprazole. The high threshold for catalepsy of **S6** might translate into low clinical EPS liability. As 5-HT_{1A} agonists could alleviate antipsychotic-induced extrapyramidal symptoms (EPS), the good performance of **S6** in the catalepsy test may be partly attributed to its high potency for 5-HT_{1A}R.[43,44] Additionally, **S6** also has excellent performance in the muscle relaxation test in mice as it did not elicit muscle relaxation at the maximum dosage of 30 mg kg^{-1}.

Compound **S6** with excellent *in vivo* activity drew our attention. Then we evaluated the *in vivo* pharmacokinetic profile of **S6** in rats. **S6** reached maximum blood concentration at 0.83h post oral administration (AUC $_{(0-24h)}$ = 1485.58 ng × h mL^{-1}). Other pharmacokinetic parameters were shown in Table 9. The acceptable bioavailability of **S6** (F = 35.5 %) recommends further drug development of these novel antipsychotic agents.

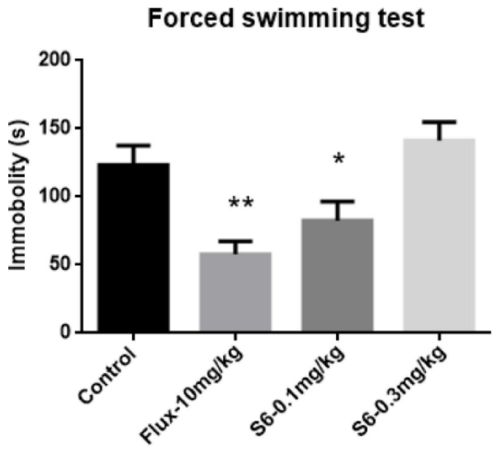


Figure 4. Effect of compounds Flux (Fluoxetine, 10 mg kg^{-1}) and **S6** administered ip in the forced swim test in C57 mice. Data are presented as means ± SEM with $N = 8$ in each group. The one-way ANOVA followed by Dunnett's post-hoc test was performed. *$p < 0.05$ and **$p < 0.01$ versus vehicle treatment.

Conclusions

Our endeavor in the synthesis and biological investigation of novel five-atom-linker-based arylpiperazine derivatives have facilitated the discovery of compound **S6** with excellent antipsychotic profile, combining partial agonistic activity for D_2R, agonistic activity for 5-HT_{1A}R as well as antagonistic activity for 5-HT_{2A}R and SERT. The polypharmacology profile of **S6** makes it have opportunities to treat diverse CNS diseases. Besides, **S6** demonstrated no appreciable action on targets associated with side effects. In rodents, **S6** displayed antipsychotic and antidepressant potential with a high threshold for inducing catalepsy or muscle relaxation. Finally, **S6** manifested an acceptable pharmacokinetic profile in rats. Based on the pleasing preclinical findings, we suggest that **S6** for the treatment of schizophrenia deserves further development.

Experimental Section

General Procedures

Reaction solvents were purchased and used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded on Varian Mercury Plus-300 (300 MHz for ^{1}H NMR), Bruker AVANCE III 400 (400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR) or Bruker AVANCE III 500 (500 MHz for ^{1}H NMR) spectrometer with TMS in DMSO-d_6 or $CDCl_3$ solution as an internal standard. Chemical shifts were given in d values (ppm) and coupling constants (J) were given in Hz. Signal multiplicities were characterized as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). ESIMS were performed on a Finnigan MAT95 mass spectrometer.

Procedures for the Synthesis of Compounds S1–S24

7-(5-(4-(2,3-dichlorophenyl)piperazin-1-yl)pentyl)quinolin-2(1*H*)-one (S1). 5-(2-oxo-1,2-dihydroquinolin-7-yl)pentyl methanesulfonate (220 mg, 0.71 mmol), 1-(2,3-dichlorophenyl)piperazine

Table 8. Pharmacological profile of **S6** in vivo.

Compd	PCP[a]	CAT[b]	CAT/PCP
S6	3.08	60.33	19.59
Aripiprazole	2.93[45]	7.13[45]	2.43[45]
Risperidone	0.03[45]	0.30[45]	10[45]

[a] PCP: phencyclidine-induced hyperactivity (ED_{50}, mg kg^{-1}, po). [b] CAT: catalepsy (ED_{50}, mg kg^{-1}, po).

Table 9. Sprague–Dawley rat PK profile of **S6**.

Parameters	po [10 mg kg^{-1}]	iv [5 mg kg^{-1}]
C_{max} [ng mL^{-1}]	170.20	1646.71
T_{max} [h]	0.83	0.083
$t_{1/2}$ [h]	4.54	5.72
AUC_{0-24h} [ng × h mL^{-1}]	1485.58	2091.58
AUC_{0-inf} [ng × h mL^{-1}]	1535.55	2115.48
F [%]	35.5	–

hydrochloride (200 mg, 0.75 mmol) and potassium carbonate (258 mg, 1.87 mmol) were added to acetonitrile (3 ml) under a nitrogen atmosphere and the mixture was stirred at reflux for 7 h. The reaction mixture was concentrated, washed three times with brine, dried, subjected to column chromatography using DCM:MeOH (60:1) as eluent to give a crude product. The crude residue was slurried in acetonitrile, filtered, and dried to give **S1** as a white solid (190 mg, 60%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65(s, 1H), 7.85 (d, J=9.5 Hz, 1H), 7.55(d, J=8.0 Hz, 1H), 7.29 (m, 2H), 7.12(m, 2H), 7.03(d, J=8.0 Hz, 1H), 6.42 (d, J=9.5 Hz, 1H), 2.95 (br, 4H), 2.64 (t, J=7.5 Hz, 2H), 2.50 (br, 4H), 2.31(t, J=7.2 Hz, 2H), 1.62 (m, 2H), 1.48 (m, 2H), 1.32(m, 2H). ESI-MS m/z 445.90 $[M+H]^+$.

7-(5-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)pentyl)-3,4-dihydroquinolin-2(1*H*)-one (S2). The title compound was prepared in 53% yield from 5-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)pentyl methanesulfonate and 1-(benzo[*d*]isothiazole-3-yl)piperazine hydrochloride following the procedure described for synthesis of **S1**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.98(s, 1H), 8.03(m, 2H), 7.55(t, J=7.8 Hz, 1H), 7.42(t, J=7.8 Hz, 1H), 7.04(d, J=7.6 Hz, 1H), 6.73(d, J=7.8 Hz, 1H), 6.66(s, 1H), 2.80(t, J=7.5 Hz, 2H), 2.57(br, 4H), 2.42(m, 4H), 2.33(t, J=7.5 Hz, 2H), 1.51(m, 4H), 1.30(m, 2H). ESI-MS m/z 435.48 $[M+H]^+$.

7-(5-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)pentyl)quinolin-2(1*H*)-one (S3). The title compound was prepared in 58% yield from 5-(2-oxo-1,2-dihydroquinolin-7-yl)pentyl methanesulfonate and 1-(benzo[*d*]isothiazole-3-yl)piperazine hydrochloride following the procedure described for synthesis of **S1**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.64(s, 1H), 8.05(d, J=5.1 Hz, 1H), 8.02(d, J=5.1 Hz, 1H), 7.83(d, J=9.5 Hz, 1H), 7.55(m, 2H), 7.42(t, J=7.6 Hz, 1H), 7.10(s, 1H), 7.03(d, J=8.1 Hz, 1H), 6.40(d, J=9.5 Hz, 1H), 3.41(br, 4H), 2.64(t, J=7.6 Hz, 2H), 2.56(br, 4H), 2.33(t, J=7.3 Hz, 2H), 1.61(m, 2H), 1.49(m, 2H), 1.32(m, 2H). ESI-MS m/z 433.31 $[M+H]^+$.

7-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)pentyl)-3,4-dihydroquinolin-2(1*H*)-one (S4). The title compound was prepared in 65% yield from 5-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)pentyl methanesulfonate and 1-(benzo[b]thiophen-4-yl)piperazine hydrochloride following the procedure described for synthesis of **S1**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.68(d, J=5.6 Hz, 1H), 7.60(d, J=8.0 Hz, 1H), 7.38(d, J=5.6 Hz, 1H), 7.26(t, J=7.9 Hz, 1H), 7.04(d, J=7.6 Hz, 1H), 6.88(d, J=7.7 Hz, 1H), 6.74(d, J=7.6 Hz, 1H), 6.67(s, 1H), 3.04(br, 4H), 2.80(t, J=7.5 Hz, 2H), 2.57(br, 4H), 2.49(m, 2H), 2.40(t, J=7.6 Hz, 2H), 2.34(t, J=7.3 Hz, 2H), 1.51(m, 4H), 1.30(m, 2H). ESI-MS m/z 434.30 $[M+H]^+$.

7-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)pentyl)quinolin-2(1*H*)-one (S5). The title compound was prepared in 72% yield from 5-(2-oxo-1,2-dihydroquinolin-7-yl)pentyl methanesulfonate and 1-(benzo[b]thiophen-4-yl)piperazine hydrochloride following the procedure described for synthesis of **S1**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65(s, 1H), 7.84(d, J=9.5 Hz, 1H), 7.68(d, J=5.5 Hz, 1H), 7.60(d, J=8.0 Hz, 1H), 7.55(d, J=8.0 Hz, 1H), 7.38(d, J=5.6 Hz, 1H), 7.26(t, J=7.9 Hz, 1H), 7.11(s, 1H), 7.03(dd, J=8.0, 1.4 Hz, 1H), 6.87(d, J=7.7 Hz, 1H), 6.41(d, J=9.5 Hz, 1H), 3.03(br, 4H), 2.65(t, J=7.5 Hz, 2H), 2.57(br, 4H), 2.34(t, J=7.2 Hz, 2H), 1.62(m, 2H), 1.49(m, 2H), 1.33(m, 2H). ESI-MS m/z 432.30 $[M+H]^+$.

7-(5-(4-(benzo[*d*]isothiazol-4-yl)piperazin-1-yl)pentyl)quinolin-2(1*H*)-one (S6). The title compound was prepared in 71% yield from 5-(2-oxo-1,2-dihydroquinolin-7-yl)pentyl methanesulfonate and 1-(benzo[*d*]isothiazole-4-yl)piperazine following the procedure described for synthesis of **S1**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.64 (s, 1H), 9.06 (s, 1H), 7.84 (d, J=9.5 Hz, 1H), 7.74 (d, J=8.2 Hz, 1H), 7.55 (d, J=8.0 Hz, 1H), 7.47 (t, J=7.8 Hz, 1H), 7.10 (s, 1H), 7.03 (dd, J=8.0, 1.4 Hz, 1H), 6.89 (d, J=7.6 Hz, 1H), 6.40 (d, J=9.5 Hz, 1H), 3.16 (br, 4H), 2.66 (t, J=7.6 Hz, 2H), 2.60 (br, 4H), 2.35 (t, J=7.2 Hz, 2H), 1.62 (m, 2H), 1.50 (m, 2H), 1.33 (m, 2H). ^{13}C NMR (100 MHz, $CHCl_3$) δ 162.55, 154.11, 153.63, 148.28, 145.34, 140.48, 139.52, 130.16, 129.47, 128.28, 122.97, 121.38, 117.78, 114.90, 114.81, 113.14, 55.79, 51.46, 49.17, 35.45, 30.58, 26.11, 23.29. ESI-MS m/z 433.2 $[M+H]^+$.

7-(5-(4-(6-chlorobenzo[*d*]isothiazol-3-yl)piperazin-1-yl)pentyl)quinolin-2(1*H*)-one (S7). The title compound was prepared in 55% yield from 5-(2-oxo-1,2-dihydroquinolin-7-yl)pentyl methanesulfonate and 1-(6-chloro-benzo[*d*]isothiazole-3-yl)piperazine hydrochloride following the procedure described for synthesis of **S1**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.23(d, J=1.5 Hz, 1H), 8.03(d, J=8.8 Hz, 1H), 7.83(d, J=9.4 Hz, 1H), 7.54 (d, J=8.0 Hz, 1H), 7.43 (dd, J=8.7, 1.9 Hz, 1H), 7.10 (s, 1H), 7.03 (dd, J=8.0, 1.5 Hz, 1H), 6.40(d, J=9.6 Hz, 1H), 3.40(br, 4H), 2.64(t, J=7.5 Hz, 2H), 2.54(br, 4H), 2.32(t, J=7.2 Hz, 2H), 1.62(m, 2H), 1.48(m, 2H), 1.32(m, 2H). ESI-MS m/z 467.027 $[M+H]^+$.

7-(5-(4-(2-fluorobenzo[b]thiophen-4-yl)piperazin-1-yl)pentyl)quinolin-2(1*H*)-one hydrochloride (S8). The title compound was prepared in 63% yield from 5-(2-oxo-1,2-dihydroquinolin-7-yl) pentyl methanesulfonate and 1-(2-fluorobenzo[b]thiophen-4-yl)piperazine following the procedure described for synthesis of **S1**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.70(s, 1H), 10.67(br s, 1H), 7.85(d, J=9.4 Hz, 1H), 7.61(d, J=8.0 Hz, 1H), 7.57(d, J=8.0 Hz, 1H), 7.31(t, J=7.9 Hz, 1H), 7.13(m, 2H), 7.05(d, J=8.2 Hz, 1H), 7.01(d, J=7.7 Hz, 1H), 6.42(d, J=9.4 Hz, 1H), 3.55(d, J=10.4 Hz, 2H), 3.44(d, J=11.6 Hz, 2H), 3.05–3.29(m, 6H), 2.67(t, J=7.5 Hz, 2H), 1.77(m, 2H), 1.64(m, 2H), 1.35(m, 2H). ESI-MS m/z 450.2 $[M+H]^+$.

7-(5-(4-(2-chlorobenzo[b]thiophen-4-yl)piperazin-1-yl)pentyl)quinolin-2(1*H*)-one (S9). The title compound was prepared in 65% yield from 5-(2-oxo-1,2-dihydroquinolin-7-yl)pentyl methanesulfonate and 1-(2-chlorobenzo[b]thiophen-4-yl)piperazine following the procedure described for synthesis of **S1**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.66(br s, 1H), 7.84(d, J=9.5 Hz, 1H), 7.55(m, 2H), 7.36(s, 1H), 7.29(t, J=7.9 Hz, 1H), 7.10(s, 1H), 7.03(d, J=8.0 Hz, 1H), 6.91(d, J=7.7 Hz, 1H), 6.41(d, J=9.4 Hz, 1H), 3.00(br, 4H), 2.64(t, J=7.4 Hz, 2H), 2.56(br, 4H), 2.33(t, J=7.0 Hz, 2H), 1.61(m, 2H), 1.49(m, 2H), 1.32(m, 2H). ESI-MS m/z 466.26 $[M+H]^+$.

7-(5-(4-(6-fluorobenzo[b]thiophen-4-yl)piperazin-1-yl)pentyl)quinolin-2(1*H*)-one (S10). The title compound was prepared in 74% yield as off-white solid from 5-(2-oxo-1,2-dihydroquinolin-7-yl) pentyl methanesulfonate and 1-(6-fluorobenzo[b]thiophen-4-yl)piperazine following the procedure described for synthesis of **S1**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65(s, 1H), 7.84(d, J=9.5 Hz, 1H), 7.65(d, J=5.5 Hz, 1H), 7.55(d, J=7.9 Hz, 1H), 7.49(dd, J=8.4, 1.2 Hz, 1H), 7.35(d, J=5.6 Hz, 1H), 7.10(s, 1H), 7.03(d, J=8.1 Hz, 1H), 6.73(dd, J=11.7, 1.9 Hz, 1H), 6.41(d, J=9.6 Hz, 1H), 3.06(br, 4H), 2.64(t, J=7.6 Hz, 2H), 2.57(br, 4H), 2.35(t, J=7.1 Hz, 2H), 1.62(m, 2H), 1.49(m, 2H), 1.33(m, 2H). ESI-MS m/z 449.90 $[M+H]^+$.

6-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)pentyl)quinazolin-4(3H)-one (S11). The title compound was prepared in 57% yield as off-white solid from 5-(4-oxo-3,4-dihydroquinazolin-6-yl)pentyl methanesulfonate and 1-(benzo[b]thiophen-4-yl)piperazine hydrochloride following the procedure described for synthesis of **S1**. ^{1}H-NMR(500 Hz, DMSO-d_6) δ 12.15(br s, 1H), 8.03(s, 1H), 7.93(d, J=1.7 Hz, 1H), 7.68(d, J=5.6 Hz, 1H), 7.66(d, J=1.9 Hz, 1H), 7.61(d, J=4.1 Hz, 1H), 7.58(d, J=4.3 Hz, 1H), 7.38(d, J=5.6 Hz, 1H), 7.27(t, J=7.8 Hz, 1H), 6.87(d, J=7.6 Hz, 1H), 3.03(br, 4H), 2.74(t, J=7.5 Hz, 2H), 2.58(br, 4H), 2.35(t, J=7.2 Hz, 2H), 1.65(m, 2H), 1.51(m, 2H), 1.33(m, 2H). ESI-MS m/z 433.42 $[M+H]^+$.

6-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)pentyl)-2-methylquinazolin-4(3H)-one (S12). The title compound was prepared in 37% yield as off-white solid from 6-(5-chloropentyl)-2-methylquinazolin-4(3H)-one and 1-(benzo[b]thiophen-4-yl)piperazine

hydrochloride following the procedure described for synthesis of **S1**. ^{1}H-NMR (300 Hz, $CDCl_3$) δ 10.84(br s, 1H), 8.05(s, 1H), 7.51–7.63(m, 3H), 7.38(m, 2H), 7.27(t, J=8.7 Hz, 1H), 6.91(d, J=7.5 Hz, 1H), 3.27(br, 4H), 2.83(br, 4H), 2.77(t, J=7.5 Hz, 2H), 2.57(m, 2H), 2.54(s, 3H), 1.72(m, 4H), 1.41(m, 2H). ESI-MS m/z 447.32 $[M+H]^+$.

6-(5-(4-(benzo[*d*]isothiazol-4-yl)piperazin-1-yl)pentyl)-2-methylquinazoli-n-4(3H)-one (S13). The title compound was prepared in 51% yield as off-white solid from 6-(5-chloropentyl)-2-methylquinazolin-4(3H)-one and 1-(benzo[*d*]isothiazole-4-yl)piperazine following the procedure described for synthesis of **S1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.75 (br, 1H), 8.94 (s, 1H), 8.05 (s, 1H), 7.56 (m, 3H), 7.40 (t, J=7.8 Hz, 1H), 6.84 (d, J=7.5 Hz, 1H), 3.34 (br, 4H), 2.84 (br, 4H), 2.77 (t, J=7.6 Hz, 2H), 2.58 (m, 5H), 1.71 (m, 4H), 1.41 (m, 2H). ESI-MS m/z 448.30 $[M+H]^+$. ^{13}C NMR (100 MHz, $CHCl_3$) δ 163.99, 153.72, 153.05, 152.53, 147.72, 141.07, 135.65, 130.49, 128.74, 127.00, 125.00, 120.16, 113.44, 112.28, 58.40, 53.24, 51.90, 45.87, 35.55, 31.07, 26.98, 20.02.

7-(5-(4-(2,3-dichlorophenyl)piperazin-1-yl)pent-1-yn-1-yl)quinolin-2(1*H*)-one (S14). 7-(5-chloropent-1-yn-1-yl)quinolin-2(1*H*)-one (150 mg, 0.61 mmol), 1-(2,3-dichlorophenyl)piperazine hydrochloride (171 mg, 0.64 mmol), potassium carbonate (126 mg, 0.92 mmol) and sodium iodide (3 mg, 0.02 mmol) were added to acetonitrile (3 ml) under a nitrogen atmosphere and the mixture was stirred at reflux for 24 h. The reaction mixture was poured into ice water to precipitate a pale yellow solid. The resulting solid was filtered, washed three times with ice water, then slurried in acetonitrile, filtered, and dried to give **S14** as a pale yellow solid (170 mg, yield: 63%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.74 (s, 1H), 7.89 (d, J=9.5 Hz, 1H), 7.62 (d, J=8.1 Hz,1H), 7.30 (m, 3H), 7.15 (m, 2H), 6.49 (d, J=9.5 Hz, 1H), 3.00 (br, 4H), 2.57 (br, 4H), 2.49 (m, 4H), 1.75 (m, 2H). ESI-MS m/z 440.3 $[M+H]^+$.

7-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)pent-1-yn-1-yl)-3,4-dihydro-quinolin-2(1*H*)-one (S15). The title compound was prepared in 82% yield as off-white solid from 7-(5-chloropent-1-yn-1-yl)-3,4-dihydroquinolin-2(1*H*)-one and 1-(benzo[b]thiophen-4-yl)piperazine hydrochloride following the procedure described for synthesis of **S14**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 7.69 (d, J=5.5 Hz, 1H), 7.62 (d, J=8.0 Hz, 1H), 7.40 (d, J=5.5 Hz, 1H), 7.28 (t, J=7.8 Hz, 1H), 7.13 (d, J=7.7 Hz, 1H), 6.93 (d, J=7.7, 1.3 Hz, 1H), 6.90 (d, J=7.6 Hz, 1H), 6.86 (d, J=1.3 Hz, 1H), 3.08 (br, 4H), 2.86 (t, 2H), 2.63 (br, 4H), 2.40–2.53 (m, 6H), 1.74 (m, 2H). ESI-MS m/z 430.41 $[M+H]^+$.

7-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)pent-1-yn-1-yl)quinolin-2(1*H*)-one (S16). The title compound was prepared in 86% yield as off-white solid from 7-(5-chloropent-1-yn-1-yl)quinolin-2(1*H*)-one and 1-(benzo[b]thiophen-4-yl)piperazine hydrochloride following the procedure described for synthesis of **S14**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.74 (s, 1H), 7.88 (d, J=9.5 Hz, 1H), 7.69 (d, J=5.5 Hz, 1H), 7.61 (m, 2H), 7.40 (dd, J=5.5, 0.8 Hz, 1H), 7.27 (m, 2H), 7.15 (dd, J=8.1, 1.4 Hz, 1H), 6.89 (d, J=7.6 Hz, 1H), 6.48 (d, J=9.5 Hz, 1H), 3.08 (br, 4H), 2.64 (br, 4H), 2.51 (m, 4H), 1.77 (m, 2H). ESI-MS m/z 428.34 $[M+H]^+$.

7-(5-(4-(2,3-dichlorophenyl)piperazin-1-yl)pentanoyl)quinolin-2(1*H*)-one (S17). Compound **S14** (200 mg, 0.45 mmol) was suspended in methanol, 4% sulfuric acid solution (2 mL) and mercury sulfate (40 mg, 0.3 eq) were added and the mixture was stirred at 50 °C for 40 h. The reaction mixture was adjusted to pH = 7 ~ 8 with sodium bicarbonate aqueous solution, extracted with DCM, washed three times with brine, dried, subjected to column chromatography using DCM : MeOH (30:1) as eluent to give a crude product. The crude residue was slurried in acetonitrile, filtered, and dried to give **S17** as a white solid (155 mg, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 7.98 (d, J=9.5 Hz, 1H), 7.87 (s, 1H), 7.78 (m, 2H), 7.29 (m, 2H), 7.10 (m, 1H), 6.62 (d, J=9.5 Hz, 1H), 3.08 (t, J=7.1 Hz, 2H), 2.95 (br, 4H), 2.51 (br, 4H), 2.37 (t, J=6.9 Hz, 2H), 1.68 (m, 2H), 1.53 (m, 2H). ESI-MS m/z 458.31 $[M+H]^+$.

7-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)pentanoyl)-3,4-dihydroquinolin-2(1*H*)-one (S18). The title compound was prepared in 70% yield as off-white solid from 7-(5-(4-(benzo[b]thiophen-4-yl) piperazin-1-yl)pent-1-yn-1-yl)-3,4-dihydroquinolin-2(1*H*)-one **S15** following the procedure described for synthesis of **S17**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.68 (d, J=5.5 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.57 (dd, J=8.1, 1.5 Hz, 1H), 7.43 (d, J=1.4 Hz, 1H), 7.38 (d, J=5.5 Hz, 1H), 7.31 (d, J=7.9 Hz, 1H), 7.26 (t, J=7.8 Hz, 1H), 6.87 (d, J=7.6 Hz, 1H), 3.04 (br, 4H), 2.96 (m, 4H), 2.59 (br, 4H), 2.42 (m, 4H), 1.65 (m, 2H), 1.52 (m, 2H). ESI-MS m/z 448.30 $[M+H]^+$.

7-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)pentanoyl)quinolin-2(1*H*)-one (S19). The title compound was prepared in 62% yield as off-white solid from 7-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl) pent-1-yn-1-yl)quinolin-2(1*H*)-one **S16** following the procedure described for synthesis of **S17**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.89 (s, 1H), 7.97 (d, J=9.6 Hz, 1H), 7.88 (s, 1H), 7.77 (m, 2H), 7.68 (d, J=5.5 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.38 (d, J=5.5 Hz, 1H), 7.25 (t, J=7.9 Hz, 1H), 6.85 (d, J=7.7 Hz, 1H), 6.62 (d, J=9.5 Hz, 1H), 3.08 (t, J=7.0 Hz, 2H), 3.03 (br, 4H), 2.59 (br, 4H), 2.41 (t, J=7.0 Hz, 2H), 1.68 (m, 2H), 1.54 (m, 2H). ESI-MS m/z 446.26 $[M+H]^+$.

7-(5-(4-(2,3-dichlorophenyl)piperazin-1-yl)-1-hydroxypentyl)quinolin-2(1*H*)-one (S20). Compound **S17** (100 mg, 0.22 mmol) was dissolved in DCM/MeOH (1 mL/1 mL) system, $NaBH_4$ (33 mg, 0.87 mmol) was added and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was extracted with dichloromethane, washed with brine, dried, subjected to column chromatography to give **S20** as a white solid (65 mg, 65%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.70 (s, 1H), 7.85 (d, J=9.5 Hz, 1H), 7.57 (d, J=8.2 Hz, 1H), 7.28 (m, 3H), 7.10 (m, 2H), 6.42 (d, J=9.5 Hz, 1H), 5.31 (d, J=4.1 Hz, 1H), 4.57 (m, 1H), 2.93 (br, 4H), 2.48 (br, 4H), 2.28 (t, J=6.4 Hz, 2H), 1.60 (m, 2H), 1.20–1.49 (m, 4H). ESI-MS m/z 461.40 $[M+H]^+$.

7-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)-1-hydroxypentyl)-3,4-dihydroquinolin-2(1*H*)-one (S21). The title compound was prepared in 70% yield as off-white solid from **S18** following the procedure described for synthesis of **S20**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.02 (s, 1H), 7.67 (d, J=5.5 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.37 (dd, J=5.6, 0.7 Hz, 1H), 7.26 (t, J=7.8 Hz, 1H), 7.07 (d, J=8.3 Hz, 1H), 6.85 (m, 3H), 5.09 (d, J=4.1 Hz, 1H), 4.42 (m, 1H), 3.04 (br, 4H), 2.82 (t, J=7.5 Hz, 2H), 2.56 (br, 4H), 2.41 (t, J=7.5 Hz, 2H), 2.32 (t, J=7.1 Hz, 2H), 1.44 (m, 6H). ESI-MS m/z 450.61 $[M+H]^+$.

(*E*)-7-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)pent-1-en-1-yl)-3,4-dihydroquinolin-2(1*H*)-one hydrochloride (S22). Compound **S21** (100 mg, 0.23 mmol) was dissolved in hydrochloric acid (6 N, 1 mL) and methanol (5 mL) and refluxed overnight. Methanol was concentrated and the mixture was adjusted to pH = 7 with aqueous sodium hydroxide solution. The mixture was extracted twice with dichloromethane. The combined organic phase was dried, concentrated and the residue was purified by column chromatography to obtain **S22** as a white solid (75 mg, 83%).^{1}H NMR (300 MHz, DMSO-d_6) δ 10.93 (s, 1H), 10.06 (s, 1H), 7.74 (d, J=5.1 Hz, 1H), 7.68 (d, J=7.9 Hz, 1H), 7.46 (d, J=5.4 Hz, 1H), 7.29 (t, J=7.7 Hz, 1H), 7.09 (d, J=8.4 Hz, 1H), 6.95 (m, 2H), 6.85 (s, 1H), 6.38 (d, J=16.1 Hz, 1H), 6.15 (m, 1H), 3.53 (m, 4H), 3.21 (m, 6H), 2.81 (t, J=7.3 Hz, 2H), 2.40 (t, J=7.3 Hz, 2H), 2.25 (m, 2H), 1.93 (m, 2H). ESI-MS m/z 432.26 $[M+H]^+$.

7-((3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propoxy)methyl)-3,4-dihydroquinolin-2(1*H*)-one (S23). 3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl methanesulfonate (300 mg, 0.82 mmol), 7-(hydroxymethyl)-3,4-dihydroquinolin-2(1*H*)-one (122 mg,

0.69 mmol), NaH (15 mg, 0.62 mmol) was added into dry THF (5 mL). The reaction mixture was refluxed for 8 h, cooled to room temperature, and then purified by column chromatography using DCM : MeOH (60:1) as eluent to give **S23** (80 mg, 26%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.37 (m, 2H), 7.20 (m, 2H), 7.14 (s, 1H), 6.98 (d, J=7.5 Hz, 1H), 4.52 (s, 2H), 3.97 (t, J=6.9 Hz, 2H), 3.58 (m, 2H), 3.43 (m, 2H), 3.19 (m, 6H), 2.87 (t, J=7.1 Hz, 2H), 2.55 (t, J=7.6 Hz, 2H), 2.04(m, 2H). ESI-MS m/z 448.00 $[M+H]^+$.

7-((3-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)propoxy)methyl)-3,4-dihydroquinolin-2(1*H*)-one (S24). The title compound was prepared as an off-white solid in 37% yield from 7-(hydroxymethyl)-3,4-dihydroquinolin-2(1*H*)-one and 3-(4-(benzo[b]thiophen-4-yl) piperazin-1-yl)propyl methanesulfonate following the procedure described for synthesis of **S23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21(s, 1H), 7.80(d, J=5.5 Hz, 1H), 7.73(d, J=8.1 Hz, 1H), 7.52(d, J=5.5 Hz, 1H), 7.34(t, J=7.9 Hz, 1H), 7.22(m, 2H), 7.01(d, J=8.0 Hz, 1H), 6.99(d, J=7.7 Hz, 1H), 4.55(s, 2H), 4.02(t, J=7.1 Hz, 2H), 3.62(m, 2H), 3.56(m, 2H), 3.31(m, 6H), 2.90(t, J=6.8 Hz, 2H), 2.58(t, J=6.8 Hz, 2H), 2.13(m, 2H). ESI-MS m/z 435.70 $[M+H]^+$.

Experimental Protocol for in vitro Biological Evaluation

Functional Activity Assays

All the compounds were screened on 5-HT_{1A} agonist, D_2 agonist & D_2 antagonist mode assays using Ultra Lance. Several compounds were screened on H_1, $Alpha_{1A}$, M_3, 5-HT_{2A}, 5-HT_{2C} antagonist mode assays using FLIPR. Ultra Lance cAMP assay and FLIPR assay were conducted according to our previous literature.[1] Selected compounds were tested for effect on hERG potassium channels by automated patch clamp method (QPatch^{HTX}, Sophion, Stockholm, Sweden) at Shanghai ChemPartner Co. Ltd.

Assay Protocol for SERT

1) On the first day, HEK-hSERT cells were seeded into 384 wells plate at 20000 cells per well in 20 μL. Then incubate cells in the incubator at 37 °C overnight.
2) On the second day, the reference compound was made 10 doses, 4-fold serial dilution in assay buffer containing 0.1% BSA at the top concentration of 2 μM. The testing compounds were made 10 doses, 4-fold serial dilution in assay buffer containing 0.1% BSA at the top concentration of 20 μM.
3) Remove the cell plate from the incubator. Aspirate the medium from the wells, and transfer 25 μL per well of the compound into the plate. Note: For High control wells, a 25 μL assay buffer containing BSA is added. For Low control wells, 25 μL of 2 μM reference solution is added.
4) Incubate at 37 °C for 30 minutes.
5) After incubation of the cells with compounds, add 25 μL of dye solution per well. Incubate at 37 °C for 30 minutes.
6) Read plate on Flexstation 3 and analyze data using Prism.

Cell Viability Assay

Cell viability of all the tested compounds against Chang liver cells and HEK-293 cells was determined using the CCK-8 assay. The cells were plated in 96-well culture plates at a density of 10000 cells per well and incubated for 24 h at 37 °C in a 5% CO_2 incubator. The tested compounds were dissolved in DMSO and diluted with culture medium (DMSO final concentration $<$0.4%). The vehicle control was prepared by mixing the culture medium with a corresponding concentration of DMSO. Then the diluted solution of tested compounds and the vehicle control were treated with the cells for 24 h at 37 °C in a 5% CO_2 incubator. After that, removal of the supernatant liquor, 100 μL of new media diluted CCK-8 solution (10% CCK-8) was added to each well and the plates were incubated for 1 h. The cell survival was evaluated by measuring the absorbance at 450 nm and calculated by the formula (cell viability = $(OD_{positive}-OD_{control})/(OD_{negtive}-OD_{control})$). All experiments were carried out in triplicate. Calculate the IC_{50} value of the test sample according to the inhibition rate using the Logit method.

Experimental Protocol for in vivo Biological Evaluation

PCP-Induced Hyperlocomotion

Male ICR mice (18~22 g, n=8) were individually placed into a Plexiglas open field arena (40×40×45 cm) for 10 min. After intragastric administration of vehicle, **S6** (1, 3 and 10 mg kg^{-1}) or aripiprazole (3 mg kg^{-1}) for 45 min, animals were treated with PCP (7 mg kg^{-1}, i.p.), and placed back into the experimental apparatus. The locomotor activity of each animal was recorded for 75 min. Results are expressed as the means ± SEM of distance traveled. Statistical evaluation was performed by one-way ANOVA followed by Dunnett's post-hoc test. $^{***}p<0.001$ versus vehicle treatment; $^{\#}p<0.05$ versus PCP treatment; $^{\#\#}p<0.01$ versus PCP treatment; $^{\#\#\#}p<0.001$ versus PCP treatment.

Induction of Head Twitches in ICR Mice

Quipazine (s.c., 5 mg kg^{-1}) was used to induce head twitches in ICR mice. Antagonism of head twitches induced by Quipazine in mice indicates anti-serotonergic activity. Vehicle, **S6** or brexpiprazole was given ig 30 min before Quipazine treatment. The mice were returned to the test cages and then head twitches were assessed for 15 min, starting 30 min after the Quipazine treatment. An observer made all observations unaware of the specific drug treatments. The results were shown as means ± SEM and compared with one-way analysis of variance, the inter-group significance or post hoc comparison was analyzed using Dunnet's *t*-test.

Forced Swimming Test

We use transparent Plexiglas cylindrical tanks (30 cm height × 10 cm diameters) for the forced swimming test in mice. The water level of every test is 12 cm from the bottom of the tanks consistently and water temperature is maintained at 24 ± 1 °C. The swimming time of mice is six minutes, from start to finish. The immobility time of mice is recorded during the last 4 min of 6 min test. Movements that are necessary to balance the body and keep the head above the water belong to immobility behavior.

Catalepsy Test

ICR mice were orally dosed with vehicle or compounds. Assessment of catalepsy was done by placing the forepaws of mice on a horizontal bar 0.3 cm in diameter kept positioned 4.5 cm above the platform with hind paws resting on the platform. The evaluation of catalepsy was done by recording how long the mice retained their forepaws on the horizontal bar during the observation periods of 3 min. A mean immobility score of 20 s was used as the criterion for the presence of catalepsy.

Muscle Relaxation Test

Muscle relaxation test was conducted according to our previous literature.[46]

Experimental Protocol for in vivo Pharmacokinetic Study

In Vivo Pharmacokinetics in Rats. Pharmacokinetic studies were performed in male SD rats weighing 165 ~ 195 g (n = 3). Pharmacokinetic parameters were obtained by single intravenous (5 mg kg^{-1}) or oral administration of **S6** (10 mg kg^{-1}), which was dissolved in a mixed solution (DMSO/PEG400/NaCl (5 : 40 : 55, *v/v/v*)). Heparinized samples of blood were collected at 0.083 h, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 8 h, and 24 h after dosing. Plasma was separated by centrifugation and stored frozen at −20 °C until subsequent analysis. Bioanalysis of samples was analyzed by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS).

Abbreviations

5-HT	serotonin
NE	norepinephrine
DA	dopamine
SERT	serotonin transporter
hERG	human ether-a go-go-related gene
PK	pharmacokinetics

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: D_2 · 5-HT_{1A} · 5-HT_{2A} · serotonin · SERT · PCP-induced hyperactivity

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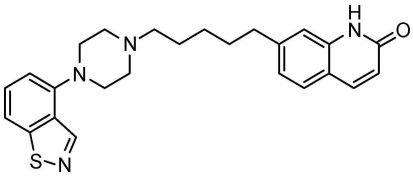
FULL PAPERS

Toward new antipsychotics! We report the design, synthesis, and biological evaluation of a series of five-atom-linker-based arylpiperazine derivatives with an atypical antipsychotic profile. One of the derivatives, **S6**, with high potency for all the desired targets (D_2, 5-HT_{1A}, 5-HT_{2A}, and SERT) displayed a promising preclinical profile, opening up new directions for the development of next-generation antipsychotic drugs.



S6

D_2R IC_{50} = 8.5 nM (partial agonist)
5-$HT_{1A}R$ EC_{50} = 9.9 nM
5-$HT_{2A}R$ IC_{50} = 358 nM
SERT IC_{50} = 39.7 nM
good *in vivo* efficacy and safety profiles
acceptable pharmacokinetics

Dr. C. Wu, Dr. Y. Wang, Dr. F. Yang, Dr. W. Shi, Prof. Z. Wang, Prof. L. He, Dr. Y. He*, Prof. J. Shen*

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Synthesis and Biological Evaluation of Five-Atom-Linker-Based Arylpiperazine Derivatives with an Atypical Antipsychotic Profile