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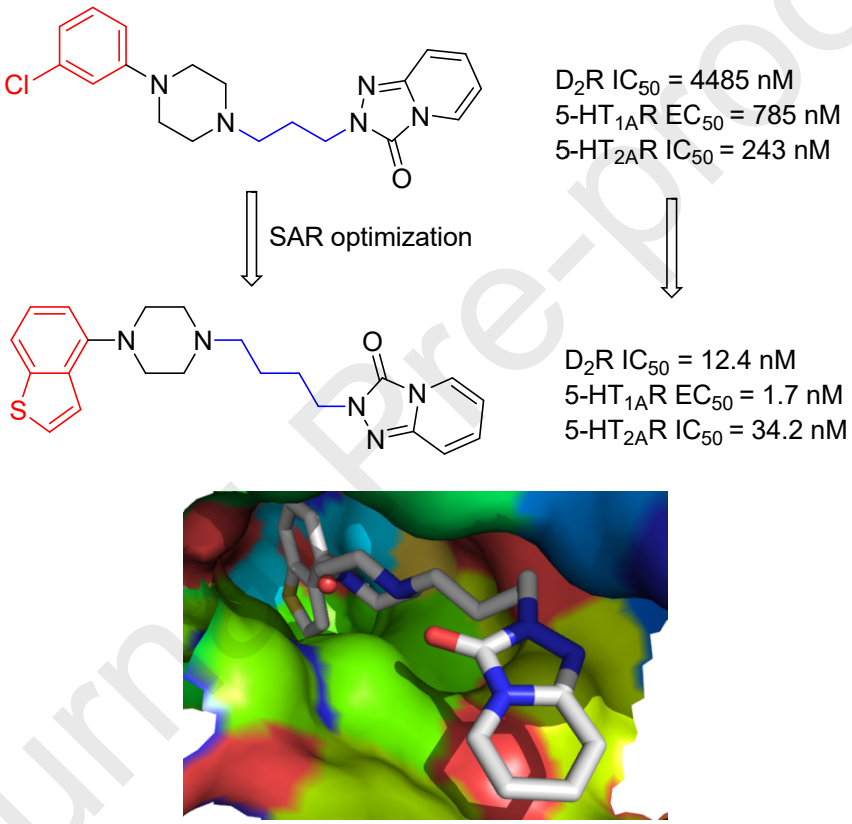

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Synthesis and biological investigation of triazolopyridinone derivatives as potential multireceptor atypical antipsychotics

Wenqiang Shi[a,b], Yu Wang[a], Chunhui Wu[c], Feipu Yang[a], Wei Zheng[a,b], Song Wu[c], Yongjian Liu[c], Zhen Wang [a,*], Yang He[a,b,*], Jingshan Shen[a,b]

[a]*CAS Key Laboratory for Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China*
[b]*University of Chinese Academy of Sciences, No.19A Yuquan Road, Beijing 100049, China*
[c]*Topharman Shanghai Co., Ltd, 388 Jialilue Road, Shanghai 201203, China*

* Corresponding author. E-mail: heyang@simm.ac.cn
* Corresponding author. E-mail: wangzhen@simm.ac.cn

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ABSTRACT

A series of triazolopyridinone derivatives originating from the antidepressant trazodone was designed and pharmacologically evaluated. Most of the compounds with a multireceptor functional profile exhibited high potency at the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors. Compounds **S1**, **S3**, **S9** and **S12** were selected for further evaluation of druggable potential. Among these compounds, **S1**, as a D_2 receptor partial agonist, demonstrated very potent inhibition of quipazine-induced head-twitch response, which validated its 5-HT_{2A} receptor antagonistic efficacy *in vivo*. **S1** also demonstrated a dose-dependent effect on PCP-induced hyperactivity when administered orally. Thus, **S1** endowed with a triazolopyridinone scaffold represents a valuable lead for the development of novel atypical antipsychotics.

Schizophrenia is a common psychiatric disorder that is characterized by three main features, including positive, negative, and cognitive symptoms, which appear to originate from the disruption of brain development because of genetic or environmental factors[1-3]. People with schizophrenia often have additional mental health problems such as anxiety, depression, or substance-use disorders[4]. It has become a major public health conundrum that seriously threatens human health.

Current drugs to treat this disorder mainly include typical and atypical antipsychotics. Schizophrenia is associated with a dysregulation of dopaminergic circuits (hyperdopaminergic tone in the mesolimbic pathway and hypodopaminergic signaling in the mesocortical pathway), which supports the theory that antagonism toward the D_2 receptor in the mesolimbic pathway reduces psychotic symptoms[5, 6]. Typical antipsychotics (first-generation antipsychotics, FGAs) act primarily via the mechanism of antagonism at the D_2 receptor, whose representative agents are chlorpromazine, haloperidol, chlorprothixene, etc.[7]. However, FGAs have gradually been withdrawn from first-line medication due to high rates of extrapyramidal side effects (EPS), tardive dyskinesia, hyperprolactinemia, and other adverse effects[8]. Atypical antipsychotics (second-generation antipsychotics, SGAs), which show enhanced potency at the 5-HT receptors, especially the 5-HT_{2A} receptor, are preferred by patients and clinicians[9, 10]. On one hand, SGAs were claimed to have a broad efficacy spectrum, which included improved efficacy in negative symptoms or cognitive impairments, and cause a lower incidence of EPS compared to FGAs[11, 12]. On the other hand, chronic treatment with SGAs was usually accompanied by side effects related to off-target effects, such as weight gain, hyperglycemia, hyperlipidemia, and QT interval prolongation[13, 14].

Despite pharmacologic advances, negative symptoms and cognitive deficits are difficulties in the long-term therapy of schizophrenia[15,16]. Atypical antipsychotics with dual antagonistic properties at the D_2 and 5-HT_{2A} receptors have limited efficacy in ameliorating negative symptoms and cognitive deficits[17-19]. Several new antipsychotics, such as aripiprazole and brexpiprazole, could reduce the severity of negative symptoms and produce milder extrapyramidal symptoms, which is partly attributed to their activation at the 5-HT_{1A} receptor. The 5-HT_{1A} receptor is highly expressed in limbic brain areas, such as the hippocampus, lateral septum and the cortex, which is proven to be associated with learning, memory, anxiety, depression, neuropathic pain, and temperature regulation[20-22]. 5-HT_{1A} receptor agonists have been explored for the treatment of various neuropsychiatric disorders (depression, anxiety, ADHD, epilepsy, etc) and non-neuropsychiatric diseases such as levodopa-induced dyskinesia[23, 24]. In recent years, more attention has been brought to the 5-HT_{1A} receptor because of its potential for enhancing cognition based on preclinical and clinical evidence[25, 26]. For example, the anxiolytics tandospirone and buspirone, possessing agonistic potency at the 5-HT_{1A} receptor, were administered orally to patients who were already treated with other

anti[...] improved effect in cognitive function[27]. In a word, an agonistic effect at the 5-HT_{1A} receptor is beneficial for the amelioration of current antipsychotic therapy.

Our previous publications have described the synthesis and biological activity studies of a series of N-substituted cyclic imide derivatives. Some of these derivatives such as **compound 1** demonstrated high activity at the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors (**Figure 1**). Trazodone is mainly used to treat major depressive disorder and anxiety disorders, which might be attributed to serotonin reuptake inhibition, 5-HT_2 receptor antagonism and 5-HT_{1A} receptor partial agonism[28, 29].

Our work aims to continue the search for new compounds with antipsychotic potential. The present study focused on the synthesis and pharmacological evaluation of a new class of antipsychotic agents with a triazolopyridinone system linked to the arylpiperazine (piperidine) group and characterized by high activities for the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors. We designed these triazolopyridinone derivatives using molecular hybridization methods (**Figure 1**). Their structure−activity relationships (SARs) for dopamine and serotonin receptors were associated with variation in the arylpiperazine (piperidine) moieties and the substituents on the triazolopyridinone ring. Among these compounds, we selected **S1** as a potential candidate for further development due to its potent antipsychotic effect in behavioral tests.

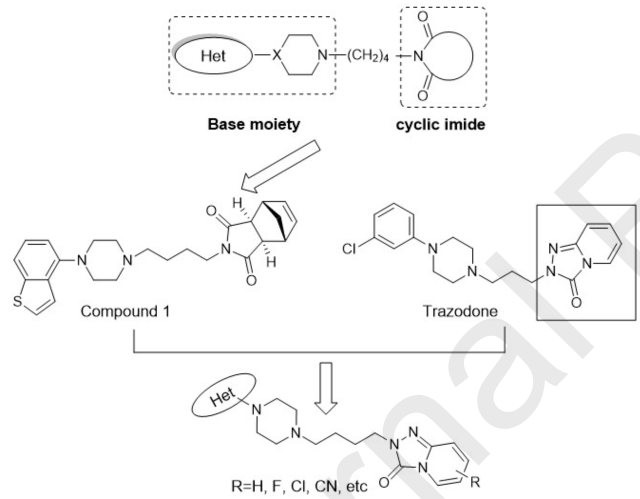
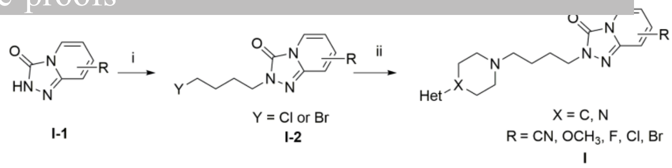


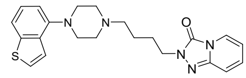
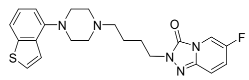
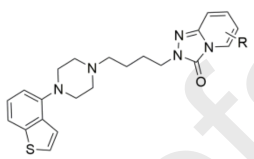
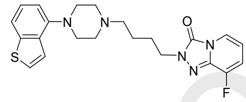
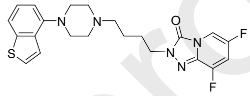
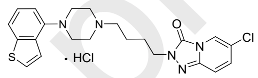
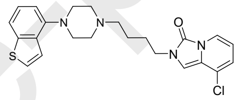
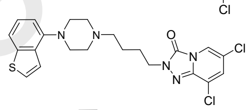
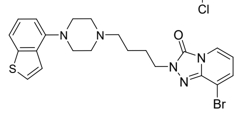
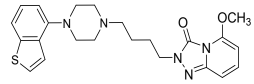
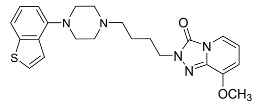
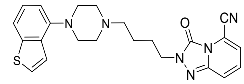
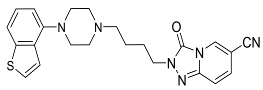
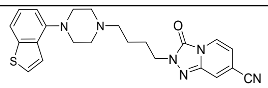
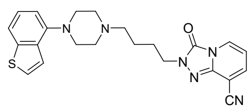
Figure 1. Design of novel triazolopyridinone derivatives

The syntheses of the novel triazolopyridinone derivatives were performed according to the reaction pathways illustrated in Scheme 1. Substituted or unsubstituted triazolopyridinone I-1 was alkylated with 1,4-dibromobutane or 1-bromo-4-chlorobutane to provide intermediates I-2, which was then coupled with various arylpiperazine moieties under mild basic conditions to produce **S1–S18** with the General Formula I.



Scheme 1. Reagents and conditions: (i) 1-bromo-4-chlorobutane or 1,4-dibromobutane, K_2CO_3, DMF, rt, overnight; (ii) K_2CO_3, KI, CH_3CN, reflux, 12 h.

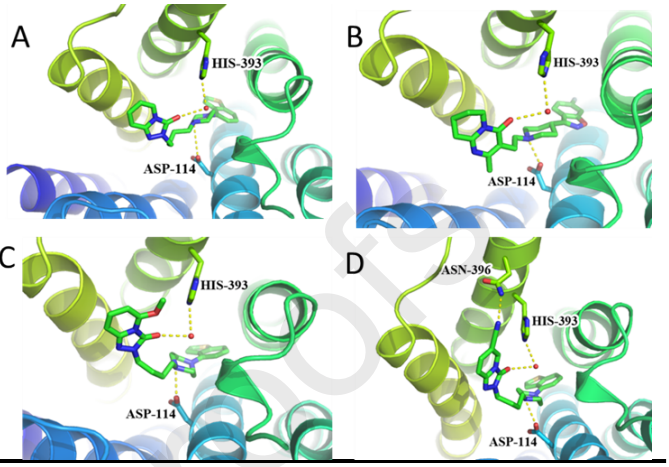
Table 1. Functional activities of compounds **S1–S14** on D_2, 5-HT_{1A}, and 5-HT_{2A} receptors

Cmpd	Structure	D_2R IC_{50} (nM)	5-$HT_{1A}R$ EC_{50} (nM)	5-$HT_{2A}R$ IC_{50} (nM)
S1		12.4	1.7	34.2
S2		26.3	0.1	46.3
				
S3		30.2	1.8	35.5
S4		62.8	1.2	27.0
S5		135	9.5	144
S6		94.7	12.1	368
S7		406	0.1	652
S8		105	7.0	131
S9		12.4	2.0	13.0
S10		102	2.2	85.2
S11		42.6	20.2	104
S12		1.03	9.7	11.0
S13		146	5.9	726
S14		1.5	1.4	155
Trazodone	/	4485	785	243

activity against the D_2 and 5-HT_{2A} receptors as well as their agonistic activity at the 5-HT_{1A} receptor using HTRF cAMP and FLIPR calcium assays. The results were summarized in **Table 1**. Generally, most of the compounds manifested obviously improved potency compared to trazodone at the D_2 and 5-HT_{1A} receptors. Compound **S1** possessing a triazolopyridinone scaffold was a substantially active molecule. Then, various substituent groups were introduced to the [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one ring at positions 5–8 to explore the influence on functional activities of the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors. We first investigated the effect of introducing halogen atoms to the [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one moiety (compounds **S2–S8**). The 6-fluoro substituted derivative **S2**, 8-fluoro substituted derivative **S3,** and 6,8-difluoro substituted derivative **S4** all showed decreased activity at the D_2 receptor, whereas they remained active at the 5-HT_{2A} receptor. Compared to **S1**, **S2** was 16-fold more potent at the 5-HT_{1A} receptor. However, 6-chloro substituted derivative **S5**, 8-chloro substituted derivative **S6** and 6,8-dichloro substituted derivative **S7** all showed a substantially reduced potency at the D_2 and 5-HT_{2A} receptors. Notably, compound **S7** exhibited the same potency as **S2** at the 5-HT_{1A} receptor. Additionally, when a bromo atom was introduced to the [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one moiety at the C8 position, reduced activities of compound **S8** were observed for all three receptors. In short, the introduction of F, Cl or Br at the C6 or C8 position of the [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one moiety appeared to be detrimental to the functional activities of these derivatives at the D_2 and 5-HT_{2A} receptors.

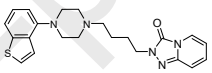
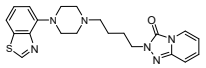
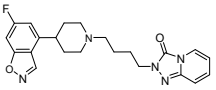
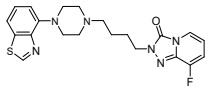
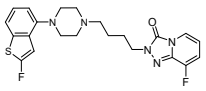
Compounds **S9–S14** with methoxy and cyano substituted at different positions of the [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one moiety were designed to investigate the effect of substituent positions and electrical factors. The 5-methoxy substituted derivative **S9** demonstrated comparable D_2 and 5-HT_{1A} receptor potencies to **S1** and its potency at the 5-HT_{2A} receptor increased to some extent. The 8-methoxy substituted derivative **S10** exhibited weaker activities at the D_2 and 5-HT_{2A} receptors than **S1** while retaining similar agonistic activity at the 5-HT_{1A} receptor. 5-cyano substitution (**S11**) or 7-cyano substitution (**S13**) led to a decrease in the activity, especially in the case of **S13** at the 5-HT_{2A} receptor. To our surprise, the 6-cyano substituted compound (**S12**) and the 8-cyano substituted compound (**S14**) showed very potent antagonistic activity at the D_2 receptor with 12-fold and 8-fold more potency than **S1**, respectively.

To explore the molecular basis of the antagonistic potency of these new compounds at the D_2 receptor, we selected compounds **S1**, **S10**, and **S14** to perform molecular docking studies. Compared to risperidone, compound **S1** shared a similar interaction with the D_2 receptor. The carbonyl oxygen of the [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one moiety had an interaction with residue (His393) via a water molecule. In addition, the nitrogen atom of piperazine or piperidine could form a hydrogen bond with the OH group of Asp114. The benzothiophene moiety of compounds **S1**, **S10** and **S14** could also form hydrophobic interactions with the binding pocket. The docking results of compounds **S10** and **S14** with the D_2 receptor indicated that the H-bond established between the OH group of Asn396 and the cyano nitrogen of **S14**, but not the methoxy oxygen of **S10**, may explain why **S14** showed more potent activity than **S10** at the D_2 receptor (**Figure 2**).



) (C), and **S14** (D) with D_2 receptor. Key residues of the receptor were shown as sticks. Hydrogen bonding interactions were marked as yellow dashed lines. The figure depicting the binding modes was generated with PyMOL.

Table 2. Functional activities of **S15–S18** at the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors

Cmpd	Structure	D_2R IC_{50} (nM)	5-$HT_{1A}R$ EC_{50} (nM)	5-$HT_{2A}R$ IC_{50} (nM)
S1		12.4	1.8	34.2
S15		117	2.8	2730
S16		40.5	>10000	15.2
S17		7.0	0.1	77.8
S18		11.1	1.53	1070

The next SAR focus was on the base moiety after summarizing the previous study. As depicted in **Table 2**, compounds **S15–S18** exhibited moderate to good antagonistic activity at the D_2 receptor, but their efficacy at the 5-HT_{1A} and 5-HT_{2A} receptors varied considerably. Although thiazole is one of the common pharmacophores and has been widely used as a bioisostere of the thiophene moiety, such replacement led to a sharp decline at the D_2 and 5-HT_{2A} receptor antagonistic activities with little change on 5-HT_{1A} receptor activity (**S15** vs **S1**). Compared with **S15**, its 8-fluoro substituted derivative **S17** displayed ameliorated activities for all three receptors, which may be due to the formation of the potential H-F hydrogen bond. Compound **S16**, bearing (6-fluorobenzo-[d]isoxazol-3-yl)piperidine as base moiety, was devoid of 5-HT_{1A} receptor agonistic activity, although it showed strong antagonistic activities for the D_2 and 5-HT_{2A} receptors. Maybe the arylpiperazine moiety is vital for these derivatives to keep agonistic activity at the 5-HT_{1A} receptor instead of arylpiperidine. The introduction of a fluorine atom at the 2-position of the benzothiophene ring resulted in an appreciably decreased potency at the 5-HT_{2A} receptor while D_2 receptor potency increased slightly (**S18** vs **S3**). Furthermore,

high
compared to **S1**.

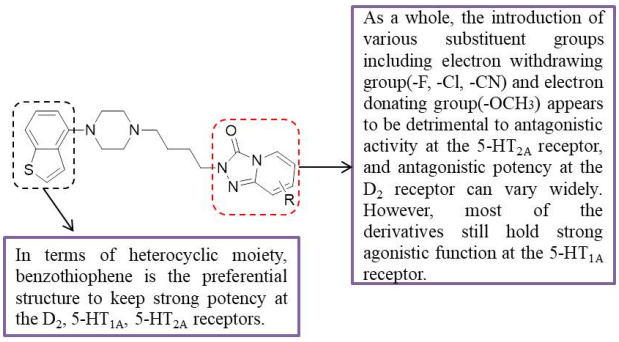


Figure 3. Summary of the SAR studies on various regions of the triazolopyridinone derivatives.

We selected compounds **S1**, **S3**, **S9**, and **S12** for further *in vitro* and *in vivo* bioassays for two main reasons. One is that these four compounds had higher potency at the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors (IC_{50} or EC_{50} value < 40 nM). An additional factor is that the potency ratio between any two of the three receptors should be no greater than 20 to achieve a relatively balanced receptor activity profile. We also evaluated if these selected compounds could act as partial agonists at the D_2 receptor, which is claimed to result in a unique clinical profile related to efficacy against schizophrenia and improved tolerability (low EPS liability, low propensity to induce weight gain and a low risk to elevate prolactin). As shown in **Table 3**, Compound **S3** was devoid of D_2 receptor agonistic activity, indicating that it was a full antagonist at the D_2 receptor. Both compounds **S1** and **S12** showed slightly lower agonistic potency than brexpiprazole at the D_2 receptor in terms of EC_{50} values.

Table 3. Agonistic activities of selected compounds at the D_2 receptor

Compound	D_2 receptor	
	EC_{50}(nM)	Emax(%)
S1	13.6	19
S3	—	<20
S9	/	/
S12	27.3	41
risperidone	—	<20
trazodone	—	<20
brexpiprazole	6.3	29

/: not tested; —: not active. Emax, expressed as percentage of the effect of 10μM dopamine.

The serotonin transporter (SERT) is the target of many antidepressant medications of the SSRI and tricyclic antidepressant classes, and its dysfunction is associated with many psychiatric disorders. We used a fluorescence-based high-throughput assay to measure the SERT inhibitory activity of selected compounds, and citalopram was used as the control. Modification on the [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one ring had no appreciable influence on 5-HT reuptake activities. As shown in **Table 4**, all the tested compounds showed similar, moderate antagonistic activities at the SERT and displayed stronger potency compared to aripiprazole. This pharmacological characteristic may contribute to the amelioration of the comorbid depressive symptoms in schizophrenia.

Table 4. Effects of selected compounds on inhibitory activity of SERT

Compound	SERT(IC_{50}, nM)
S1	536.9
S9	203.0
S12	341.6
Aripiprazole	21% inhibition @ 400nM
Citalopram	13.41

Many adverse effects of atypical antipsychotics are associated with off-target effects. In particular, the inhibition of the α_{1A}, H_1, and 5-HT_{2C} receptors and hERG is closely related to side effects such as weight gain, hyperglycemia, dyslipidemia, and cardiovascular diseases. Therefore, further characterization of the pharmacological profiles of candidate compounds is essential.

Blockade of the α_1-adrenoceptor (especially the peripheral α_{1A}-adrenoceptor) can result in orthostatic hypotension, which is an undesirable side effect accompanied by many antipsychotic drugs. Compounds **S1**, **S3,** and **S12** showed weaker antagonistic activity than risperidone at the α_{1A}-adrenoceptor, suggesting that they may run a lower risk of causing orthostatic hypotension. The H_1 and 5-HT_{2C} receptors are involved in the regulation of diet and weight, so the inhibition of these two kinds of receptors might be responsible for atypical antipsychotics-induced weight gain. Although all the tested compounds showed stronger and moderate inhibitory potency at the H_1 receptor compared to risperidone, they all exhibited a substantially reduced activity at the 5-HT_{2C} receptor, which indicates low liability to lead to weight gain. The pancreatic M_3 cholinergic receptor is related to acetylcholine-dependent insulin release, inhibition of the M_3 receptor may cause hyperglycemia and diabetes. Clozapine and olanzapine, which have a strong inhibitory effect on the M_3 receptor, have a high risk of inducing diabetes in clinical practice. All tested compounds hardly have antagonistic activity at the M_3 receptor, indicating that they have little possibility to cause hyperglycemia.

Additionally, as hERG potassium channel blockade is a crucial indicator of potential pro-arrhythmic tendency, investigation of the hERG channel blockade has become an important step in the process of drug discovery. It is less likely for all the tested compounds to elicit treatment-induced QT interval prolongation because of their weak potency at the hERG channel.

Table 5. Functional activities at the α_{1A}, H_1, and 5-HT_{2C} receptors and hERG of compounds **S1**, **S3**, **S9** and **S12**.

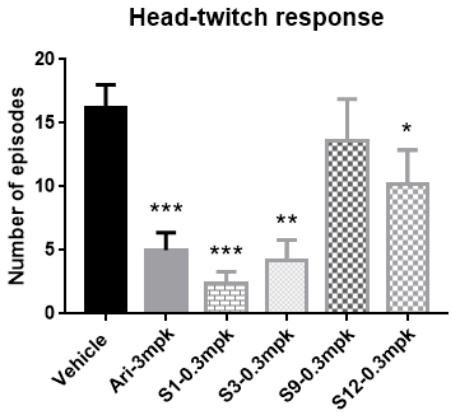
Compound	IC_{50}/nM				
	α_{1A}	H_1	5-HT_{2C}	M_3	hERG
S1	15.1	88.5	>10000	>10000	3010
S3	17.4	30.9	2100	>10000	2200
S9	/	/	/	/	/
S12	87.8	76.6	3290	>10000	1050
Risperidone	10.9	454	1.81	>10000	1330

/: not tested

The quipazine-induced head-twitch response (HTR) is a rapid side-to-side head movement that occurs in mice and rats after the 5-HT_{2A} receptor is activated. The HTR is used as a behavioral model to assess the *in vivo* efficacy of 5-HT_{2A} receptor antagonists. Preliminary results indicated that **S1** exhibited dose-dependent high potency at inhibiting head twitches, which is nicely in accordance with their *in vitro* high potency at the 5-HT_{2A} receptor (**See Supplemental Figure S1**). Then, we compared the inhibitory action of the four promising compounds on the HTR at the same dose. As depicted in **Figure 2,** compound **S9** shows a slight inhibition of HTR in mice, whereas compounds **S1** and **S3** greatly inhibit HTR, which is superior to aripiprazole at a low dose (0.3 mg/kg). Next, we selected

com and hyperlocomotion *in vivo* after analyzing and summarizing previous results.

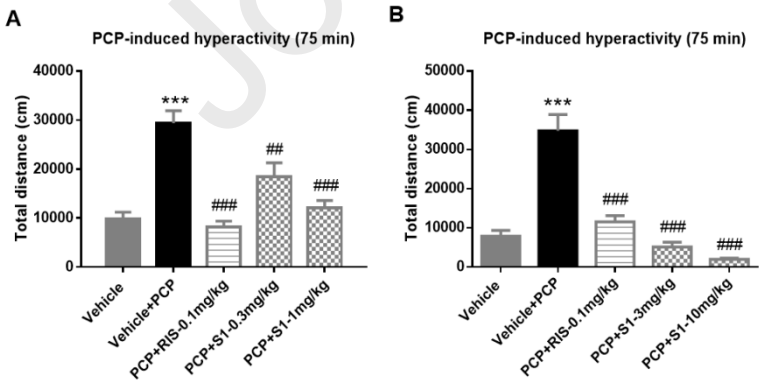
Figure 4. Effect of selected compounds on ICR mice model of Quipazine-induced head-twitch response. Mice were orally provided selected compounds or vehicle after intraperitoneal administration of quipazine in a single dose. Data represent the number of head twitches(mean ± SEM)



during the 15min test with n=5 in each group. **P*<0.05, ***P*<0.01, ****P*<0.001 compared with the quipazine-treated group.

Phencyclidine (PCP) with a noncompetitive antagonism property at the N-methyl-D-aspartate (NMDA) receptor has been widely used in experimental animal models to study the underlying neurobiology of schizophrenia. Acute administration of PCP could lead to an increase in locomotion, which is used as a model to evaluate the antipsychotic-like efficacy of agents by attenuating locomotion. In this test, compound **S1** produced substantial dose-dependent responses, which was consistent with the potent D_2 receptor antagonistic activity *in vitro* (**Figure 3**). Moreover, the spontaneous locomotor activity of mice could be influenced after administration of **S1** at 3 or 10 mg/kg, but not at 0.3 mg/kg (**See Supplemental Figure S2–S3**), suggesting that **S1** was devoid of the unpleasant side effect of sedation at the effective dose of 0.3 mg/kg.

Figure 5. Mice were orally administrated compounds **S1** and risperidone (0.1mg/kg) after intraperitoneal administration of PCP in a single dose (7mg/kg). Data are reported as the mean ± SEM (n=8). Statistical evaluation was performed by one-way ANOVA followed by Dunnett's post-hoc test for multiple comparisons. ****p* < 0.001 versus vehicle treatment; #p<0.05,



##p<0.01, ###*p* < 0.001 versus PCP treatment.

nephrotoxicity of compound **S1** were also investigated. Compound **S1** displayed a weaker inhibitory activity at the HEK293 cells and Chang liver cells compared to brexpiprazole, but it showed a stronger inhibitory potency compared to that of risperidone. In a word, compound **S1** has a good safety profile.

Table 6. Cell viability of compound **S1** and reference antipsychotics

Compound	Hepatotoxicity IC_{50}(μg/ml)	Nephrotoxicity IC_{50}(μg/ml)
S1	62.2	108.1
Risperidone	238.8	>600
Brexpiprazole	44.2	19.1

In summary, a series of novel triazolopyridinone derivatives with a multireceptor functional profile was designed and pharmacologically evaluated. Compound **S1** showed remarkable potency at the D_2, 5-HT_{1A} and 5-HT_{2A} receptors, which is in accordance with its *in vivo* profile in behavioral models. Additionally, compound **S1** had a good safety profile due to its weak inhibitory effect at the α_{1A}, H_1, and 5-HT_{2C} receptors and hERG. Specifically, **S1** may preferentially activate the 5-HT_{1A} receptor and barely occupy other receptors *in vivo* at a low dosage and could have advantages in treating several neuropsychiatric disorders in which the 5-HT_{1A} receptor was deeply involved. Accordingly, compound **S1** represents a potential candidate for further preclinical investigation.

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