Journal Pre-proofs

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Synthesis and biological evaluation of novel antipsychotic *trans*-4-(2-(1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepin-3-yl)ethyl)cyclohexan-1-amine derivatives targeting dopamine/serotonin receptor subtypes

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Abstract

In this study, a series of *trans*-4-(2-(1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepin-3-yl)ethyl)cyclohexan-1-amine derivatives as potential antipsychotics were synthesized and biologically evaluated to discover potential antipsychotics with good drug target selectivity. The preliminary structure-activity relationship was discussed, and optimal compound **12a** showed both nanomolar affinity for D_2/D_3/5-HT_{1A}/5-HT_{2A} receptors and weak α_1 and H_1 receptor binding affinity. In addition, **12a** was metabolically stable *in vitro*, displayed micromolar affinity for the hERG channel, and exhibited antipsychotic efficacy in the animal model of locomotor-stimulating effects of phencyclidine.

Keywords

Antipsychotic; DA receptor; 5-HT receptor; α_1 receptor; H_1 receptor

Schizophrenia is one of the most complex and debilitating mental disorders characterized by positive, negative, and cognitive symptoms.[1] About 0.5-1.0% of the population worldwide is diagnosed with this condition,[2] about 20% of which has chronic symptoms and disability, and more than 50% has intermittent but long-term psychiatric problems.[3] The unemployment rate in individuals with schizophrenia is very high at 80-90%,[4] and life expectancy is reduced by 10-20 years.[5]

Since the 1950s approval of chlorpromazine, several typical antipsychotics (TAs) and atypical antipsychotics (ATs) have been developed. TAs, referred to as dopamine (DA) D_2 receptor (D_2R) antagonists, are effective in treating positive symptoms but are ineffective in alleviating negative symptoms or improving cognitive impairment. TAs can also cause serious side effects such as extrapyramidal symptoms (EPSs) due to their antagonistic effects on DA receptors in the nigrostriatal dopaminergic pathway.[6] ATs, (e.g., lurasidone, risperidone, aripiprazole and cariprazine, **Fig. 1**) are characterized by multi-receptor affinity and offer a number of therapeutic advantages, such as decreasing the incidence of EPSs. However, the treatment can be impaired by metabolic, cardiovascular and anticholinergic side effects, which are likely related to binding to other receptors.[7,8] These include weight gain (histamine H_1 receptor [H_1R] and serotonin $(5\text{-HT})_{2C}$ receptor [$5\text{-HT}_{2C}R$] antagonism), orthostatic hypotension (adrenergic α_1 receptor [α_1R] antagonism[9]), and sedation (H_1R antagonism). Therefore, interdisciplinary collaborations and concerted research efforts are in active progress for the development of multiple-targets antipsychotics with high efficiency and good drug target selectivity.

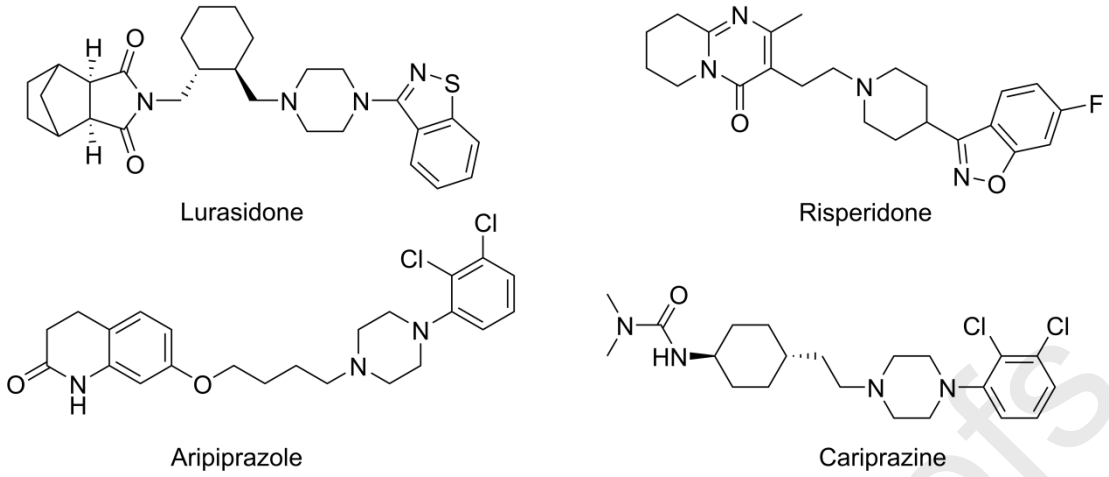


Fig. 1. Structures of reference compounds

D_2R is effective in treating the positive symptoms[1,10] of schizophrenia. D_3R belongs to the subfamily of D_2-like receptors and is localized in the limbic system. D_3R antagonists have cognition-enhancing activity which may be of benefit for the treatment of cognitive dysfunction.[11] Moreover, higher binding affinity for D_3R compared with D_2R offers regionally selective antidopaminergic activity[10,12], resulting in heightened effect on positive symptoms along with a decrease in EPSs. Antagonists of 5-$HT_{2A}R$ increase the release of DA into the prefrontal cortex, which is correlated with effects on cognitive and negative symptoms. Partial agonists of the 5-$HT_{1A}R$ help stabilize the frontal cortex function[1]. The 5-$HT_{1A}R$ has recently garnered increasing attention because of its potential to enhance cognition based on preclinical and clinical evidence.[13] A combination of the therapeutic effects of these receptors, such as via cariprazine, a D_2/D_3/5-HT_{1A} partial agonist and 5-HT_{2A} antagonist with 8-fold selectivity for D_3R/D_2R subtypes, may reduce positive symptoms[14], alleviate negative symptoms, and improve the cognitive impairments[15] associated with schizophrenia.

Blockade of the α_1R can result in orthostatic hypotension[9], which is an adverse effect caused by many antipsychotic drugs. Clinical first-line antipsychotics all have effects on the H_1R, which produces strong to moderate intensity of sedation and are involved in weight gain. **Table 1** displays the affinity of some market antipsychotics for α_1R and H_1R.

Table 1

Affinity for α_1R and H_1R of some market antipsychotics.

Drug	K_i/nmol·L^{-1}	
	α_1	H_1
Risperidone	0.7	20
Olanzapine	19	7
Quetiapine	7	11
Ziprasidone	11	50
Aripiprazole	57	61
Asenapine	1.2	1.0

In our previous study on potential multi-target antipsychotics, a series of novel benzisothiazolylpiperazine cyclohexylamides[16] targeting D_2/D_3/5-HT_{1A}/5-HT_{2A} receptors were discovered. Among these derivatives, compound **I** (**Fig. 2**) showed unique affinities for the D_2/D_3/5-HT_{1A}/5-HT_{2A} receptors. Substituted 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepines[17,18] reportedly have 5-HTR subtype binding affinities without targeting α_1R and H_1R, as represented by the US Food and Drug Administration-approved antiobesity agent lorcaserin (compound **II**, **Fig. 2**). By linking this 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine core with (*trans*)-ethyl cyclohexyl linker, a series of potent DA antagonists, such as D_3 antagonists were identified, as represented by compound **III** (**Fig. 2**)[19]. In our continuous effort to develop selective antipsychotics targeting D_2/D_3/5-HT_{1A}/5-HT_{2A} receptors based upon these findings, we designed and evaluated a series of *trans*-4-(2-(1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepin-3-yl)ethyl)cyclohexan-1-amine derivatives **9**, **11a-e**, **11a-f**, **12a-f** and **13a-b** (**Fig. 2**). The target compounds were evaluated for binding affinity to α_1/H_1/D_2/D_3/5-HT_{1A}/5-HT_{2A} receptors . The preliminary structure-activity relationships (SARs) of target compounds for these receptors were investigated as the function of various substituents in the amide moiety and 1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepin-3-yl fragment. By systematically varying the substituents valuated, we identified the *trans*-tetrahydro-3*H*-benzo[*d*]azepin-3-yl ethyl cyclohexan amine scaffold with weak α_1R and H_1R binding affinity, and

discovered that optimal compound **12a** had expected receptor binding profile and target selectivity. Further pharmacological evaluation was conducted of **12a** including metabolic stability *in vitro*, hERG channel inhibition and antipsychotic efficacy in animal behavior models.

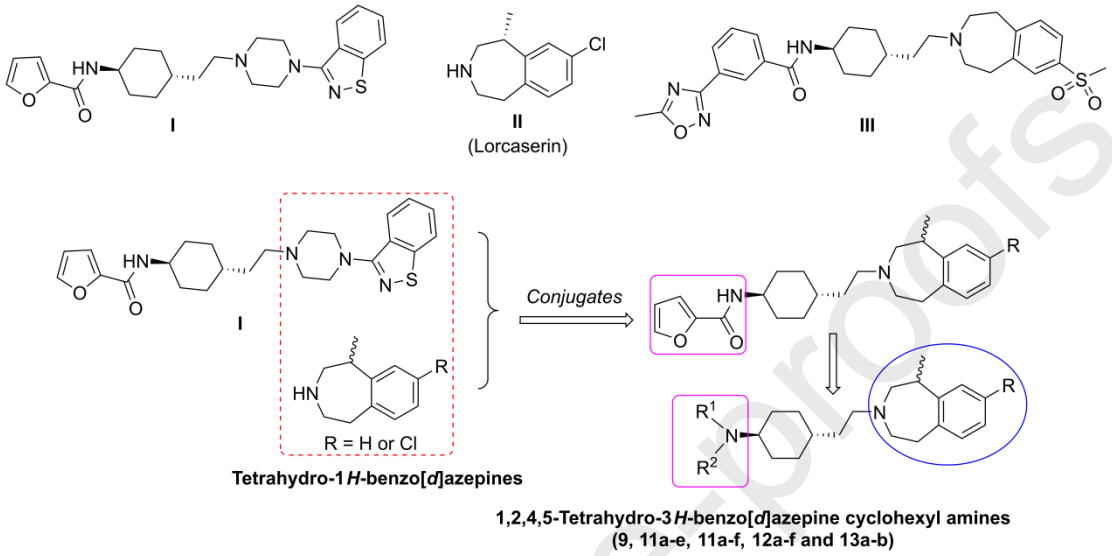
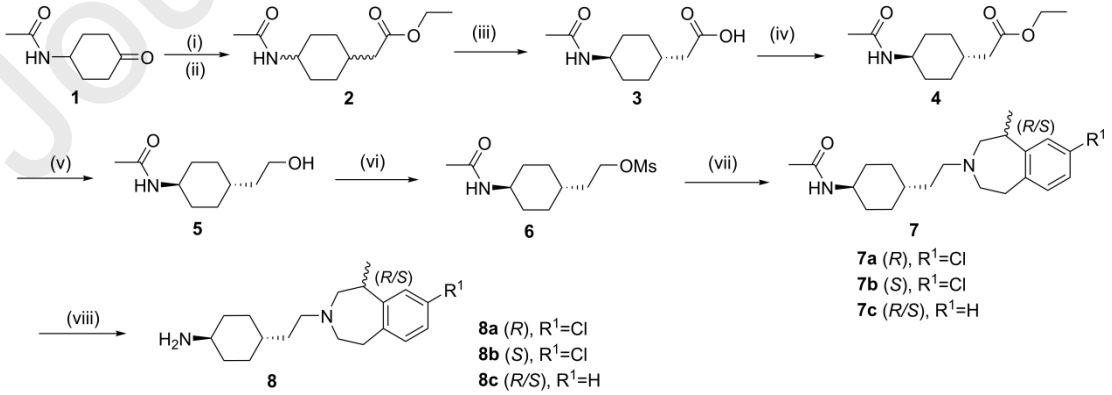


Fig. 2 Representative compounds and design of 1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepine cyclohexyl amines

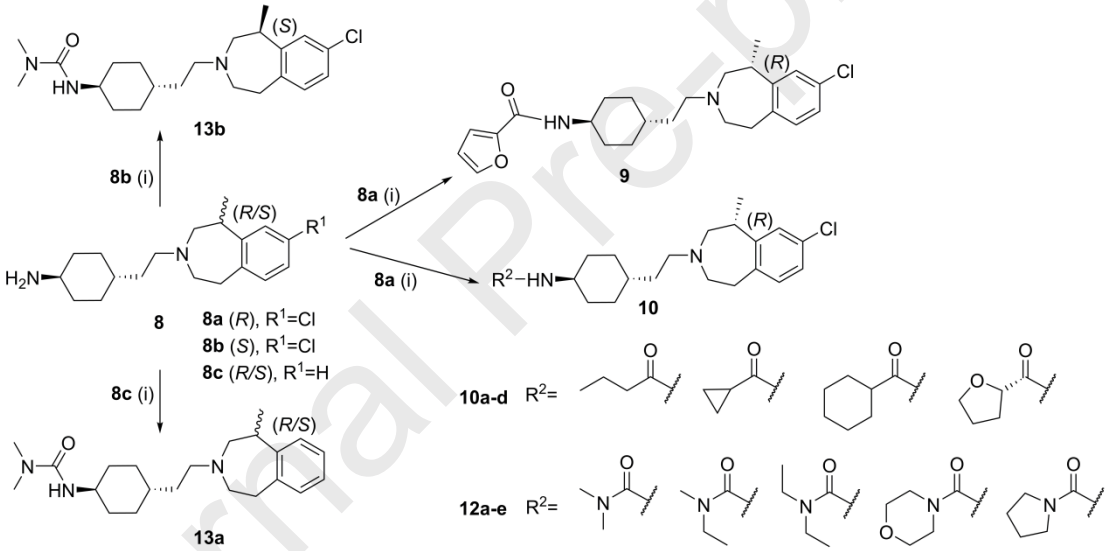
The synthesis of all of the intermediates and target compounds was depicted in Schemes **1-5**. Scheme **1** outlines the synthesis of key intermediates **8a-c**. Intermediate **6** was prepared according to our previous method[16], which was coupled with 1-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine fragments to yield intermediates **7a-c**. Then, **7a-c** were refluxed under 3% aqueous hydrochloric acid conditions to yield the key intermediates **8a-c**.



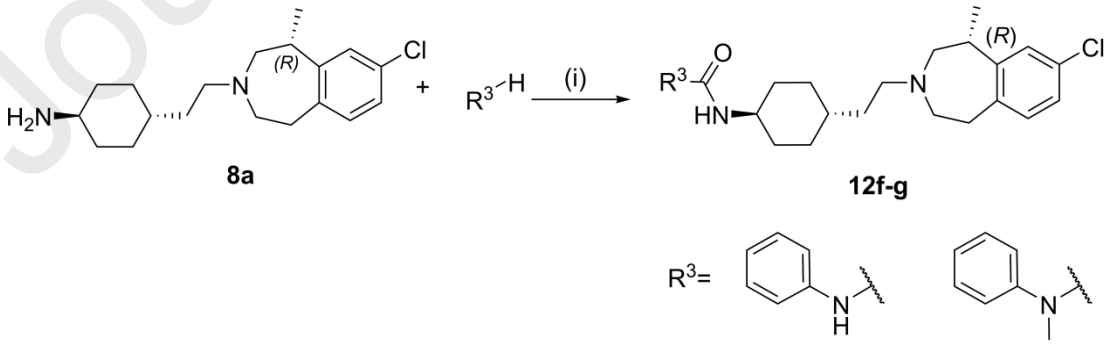
Scheme 1. Reagents and conditions: (i) Triethyl phosphonoacetate, *t*-BuOK, THF, 0-5°C; (ii) H_2, 5%Pd/C, EA, rt; (iii) LiOH·H_2O, THF, 10%HCl; EtOH, recrystallization; (iv) EtOH, EDCI,

DMAP, rt; (v) $NaBH_4$, MeOH, THF, reflux; (vi) Et_3N, MsCl, DMF; (vii) Na_2CO_3, KI, ACN, reflux; (viii) 3%HCl, reflux.

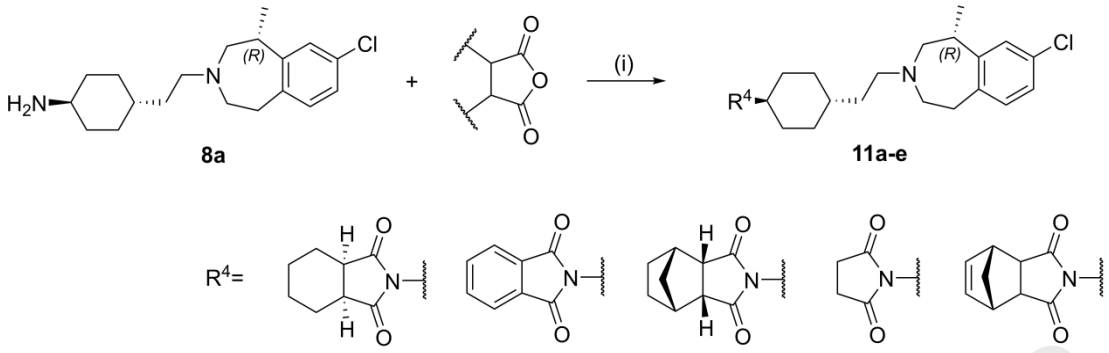
Scheme **2** shows the preparation of compounds **9**, **10a-d**, **12a-e** and **13a-b** through acylation. In scheme **3**, intermediate **8a** along with triethylamine in CH_2Cl_2 was added to a solution of triphosgene at 0-5°C. Then the substituted amines were added to the solution yielding **12f-g**. Scheme **4** shows the preparation of **11a-e** through the reaction of intermediate **8a** with different dicarboxylic anhydrides under acetic acid conditions. Scheme **5** shows the preparation of compounds **10e** and **11f**. Compound **10e** was obtained via acylation. Intermediate **8a** refluxed with 8-oxaspiro[4.5]decane-7,9-dione (**15**), generating compound **11f** in the presence of *p*-toluenesulfonic anhydride.



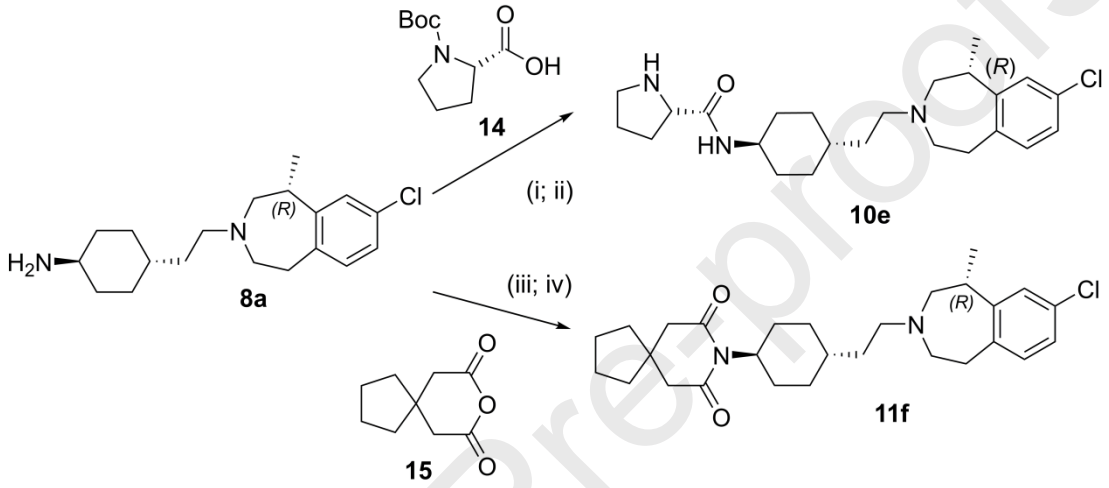
Scheme 2. Reagents and conditions: (i) R^2Cl, TEA, DMAP, CH_2Cl_2, rt.



Scheme 3. Reagents and conditions: (i) triphosgene, TEA, CH_2Cl_2, 0-5°C.



Scheme 4. Reagents and conditions: (i) DMAP, AcOH, reflux.



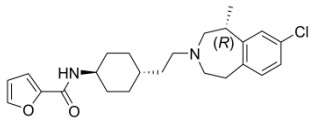
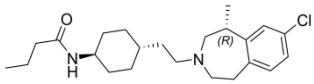
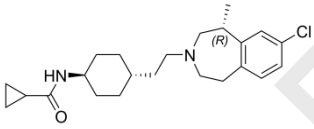
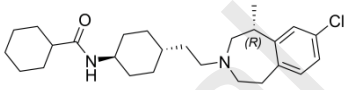
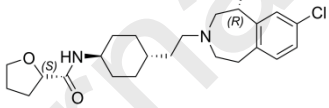
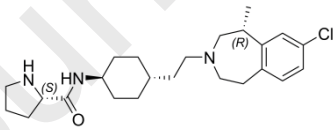
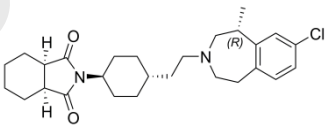
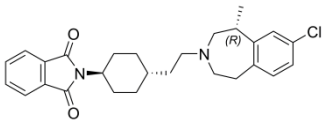
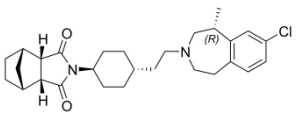
Scheme 5. Reagents and conditions: (i) EDCI, DMAP, CH_2Cl_2; HCl in EA; (ii) $TsOH \cdot H_2O$, reflux; (iii) Ac_2O, NaOAc, reflux.

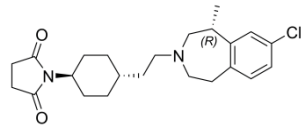
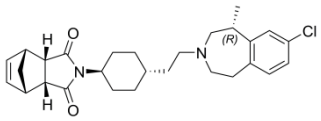
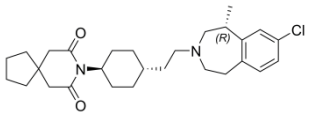
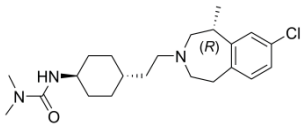
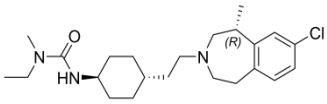
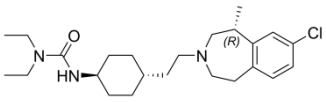
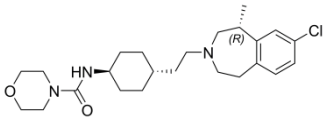
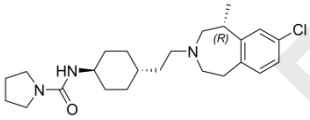
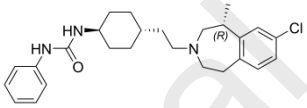
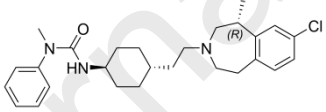
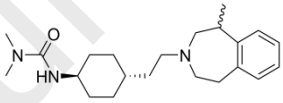
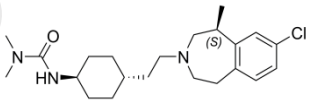
The target compounds were tested for binding affinities of $\alpha_1/H_1/D_{2L}/D_3/5\text{-}HT_{1A}/5\text{-}HT_{2A}$ receptors. The detailed results are summarized in **Table 2**. The K_i values were determined when the inhibition ratios were over 90% measured at a concentration of 10 μM. The following specific radioligands and tissue sources were used: (a) α_1Rs, [^{3}H]prazosin, rat cerebral cortex; (b) H_1Rs, [^{3}H]pyrilamine, human recombinant (HEK-293 cells); (c) D_{2L}Rs, [^{3}H]spiperone, human recombinant (CHO cells); (d) D_3Rs, [^{3}H]methyl-spiperone, human recombinant (CHO cells); (e) 5-HT_{1A}Rs, [^{3}H]8-OH-DPAT, human recombinant (HEK-293 cells); (f) 5-HT_{2A}Rs, [^{3}H]ketanserin, human recombinant (HEK-293 cells). The biological studies were conducted by Eurofins Cerep SA, Celle l'Evescault, France. The recently launched atypical antipsychotic agent cariprazine was used as a reference.

The metabolic stability of the optimal compound was measured using rat and human liver microsomes *in vitro*. The ability to block hERG potassium channels was determined by electrophysiology using cloned hERG potassium channels expressed in CHO-K1 cells. The animal behavior model of locomotor-stimulating effects of phencyclidine was used to evaluate antipsychotic efficacy *in vivo*.

Table 2

The binding affinities of target compounds for $\alpha_1/H_1/D_{2L}/D_3/5\text{-}HT_{1A}/5\text{-}HT_{2A}$ receptors.

Compound	Structure	Receptor affinity K_i (nM)					
		α_1[a]	H_1[a]	D_{2L}[b]	D_3[b]	5-HT_{1A}[b]	5-HT_{2A}[a]
9		51.3	82.1	93.9	101.4	96.9	77.3
10a		18.7%	27.0%	84.0	8.1	81.3%[a]	52.7%
10b		57.6%	33.2%	9.8	8.2	191.4	56.6%
10c		35.3%	36.8%	99.3	17.5	69.9%[a]	38.2%
10d		36.4%	32.2%	20.6	19.1	98.3	69.6%
10e		75.8%	60.1%	25.3	9.5	74.7	89.0%
11a		63.2%	86.1%	14.1	9.3	6.6	76.9%
11b		37.2%	40.8%	5.8	82.0%[a]	82.6%[a]	36.3%
11c		79.2%	194.6[b]	31.6	3.3	24.9	80.8%

11d		62.1%	62.4%	79.8%[a]	190.7	93.4	47.4%
11e		74.4%	312.3[b]	43.7	6.9	22.8	82.8%
11f		60.9%	293.2[b]	12.1	1.2	4.3	16.2
12a		44.1%	59.6%	5.9	0.5	14.5	25.6
12b		43.5%	49.7%	23.9	7.2	36.0	85.9%
12c		29.1%	69.2%	91.1	15.0	75.2%[a]	73.6%
12d		48.0%	33.3%	2.9	1.8	86.1%[a]	50.6%
12e		60.3%	56.8%	6.3	1.1	5.3	87.4%
12f		53.8%	88.2%	2.8	1.5	87.4%[a]	67.0%
12g		38.6%	75.0%	188.7	17.2	82.3%[a]	58.8%
13a		38.0%	25.8%	54.5%[a]	68.0%[a]	26.9%[a]	19.6%
13b		48.3%	46.5%	290.5	194.8	83.9%[a]	72.2%
Cariprazine	/	155.0[c]	23.2[c]	0.49[c]	0.085[c]	2.6[c]	18.8[c]

[a] Mean inhibitory rates from two independent experiments done in duplicate with 10 μmol/L concentration.

[b] Mean K_i values from two independent experiments with eight concentrations in duplicate.

[c] Data for cariprazine reported by Citrome.[20]

Initially, we investigated the effects of aryl and alkyl amide moieties. The affinity profile of compound **9** bearing furan-2-carboxamide moiety at the cyclohexyl

side of the molecule was investigated (**Table 2**). Nanomolar affinities for D_2, D_3, and 5-HT_{1A}Rs (K_i = 19.3 nM, 1.8 nM, and 10.6 nM, respectively), and yet low potential affinity for 5-HT_{2A}R (87.3%, inhibition ratio) were observed. Moreover, compound **9** had low potential affinity for H_1R (82.1%, inhibition ratio) and very weak affinity for α_1R (51.3%, inhibition ratio). Other alkyl amide substituted derivatives (**10a-e**) also displayed nanomolar affinities for D_2, D_3, and 5-HT_{1A}Rs, except for **10c** (69.9% inhibition ratio for 5-HT_{1A}R), but still exhibited moderate to low 5-HT_{2A}R inhibition ratio (< 90%). The affinities for both α_1R and H_1R were kept at a low level (inhibition ratio < 80%). Among these derivatives, compound **9** had both high affinities for D_2, D_3, and 5-HT_{1A}Rs with low α_1R and H_1R affinity.

The effect of replacing the amide moiety at the cyclohexyl side of the molecule with imide moiety was investigated (compounds **11a-f**; **Table 2**). Compounds **11a**, **11c** and **11e-f** with 1,2-cyclohexanedicarboximide, methanoisoindole-1,3(2*H*)-dione and tetramethyleneglutarimide substituents showed nanomolar affinities for D_2, D_3 and 5-HT_{1A} receptors and low potential affinity for α_1R (inhibition ratio < 80%). Nanomolar affinity for the 5-HT_{2A}R was observed for **11f** (16.2 nM, K_i). However, **11f** showed moderate affinity for the H_1R (293.2 nM, K_i), as well as **11c** and **11e** (194.6 nM and 312.3 nM, K_i), which was not expected.

The effect of urea moiety at the cyclohexyl side of the molecule was explored (**Table 2**, compounds **12a-g**). The dimethyl urea **12a** showed high affinities for D_2, D_3, 5-HT_{1A} and 5-HT_{2A} receptors (K_i < 30 nM, respectively) along with very low affinities for both α_1R and H_1R (inhibition ratio < 60%, respectively). Unexpectedly, other alkyl urea, such as ethyl substituted urea (**12b-c**) and cyclic urea (**12d-e**) exhibited low potential 5-HT_{2A}R affinity (inhabitation ratio < 89%) albeit with nanomolar receptor affinity for D_2 and D_3, and low α_1R and H_1R inhibition (< 70%). Analogues with aryl substituents (**12f-g**) also showed nanomolar receptor affinity for D_2 and D_3, but the potential affinities for 5-HT_{1A}R and 5-HT_{2A}R were low (inhibition ratio < 90%). Based on these results, structural modification with methyl urea moiety (**12a**) yielded ideal ligand that possessed both high affinity for D_2R, D_3R, 5-HT_{1A}R, 5-HT_{2A}R and very low affinities for α_1R and H_1R.

Compounds **13a-b** (**Table 2**) were prepared to investigate the effect of substitution on the phenyl moiety and chirality of the methyl on the azepine ring. Compound **13a** bearing unsubstituted phenyl ring and racemic methyl on the azepine ring lost binding affinities for both D_2, D_3, 5-HT_{1A}, 5-HT_{2A} receptors and α_1R and H_1R (inhabitation ratio < 70%). **13b**, enantiomer of compound **12a** with expected binding character, had no affinity for α_1R and H_1R. The D_2R and D_3R affinities of **13b** were decreased to moderate degrees (290.5 nM and 194.8 nM, K_i) as well as low potential affinity for 5-HT_{1A}/5-HT_{2A} receptors (inhibition ratio < 85%).

Through investigation of substituents in amide moiety, modifications in substituted 1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepine core and preliminary SAR analysis, the optimal receptor affinity balance was obtained for compound **12a** displaying nanomolar range affinities for the D_2, D_3, 5-HT_{1A} and 5-HT_{2A} receptors, and low affinities for α_1 and H_1 receptors. **12a** was selected for further metabolic stability evaluation *in vitro* (**Table 3**) and hERG channel binding assay. The data indicated that **12a** displayed a suitable half-life ($t_{1/2}$ values were 32.7 min in human liver microsomes and 23.2 min in rat liver microsomes). **12a** was tested in the hERG functional patch clamp inhibition assay (Qpatch) and micromolar affinity with IC_{50} = 1.23 μM was observed.

Table 3

Rat and human liver microsomal metabolic stability assay.

Compound	Species	$T_{1/2}$ (min)	CL (μL/min/mg)
12a	Human	32.7	42.4
	Rat	23.2	59.7
Dextromethorphan	Human	7.2	36.0
Omeprazole	Rat	38.5	193.3

Based on *in vitro* studies, **12a** was further characterized in animal models for behavioral studies. Acute phencyclidine (PCP) can imitate positive symptoms[21] and has been used to simulate schizophrenia symptoms in animals. **12a** (1.0, 2.0, and 10.0 mg/kg, p.o.), and classic antipsychotic agent clozapine (10.0 mg/kg, p.o.) and recently launched cariprazine (0.8 mg/kg, p.o.) produced significant dose-dependent responses

in this model compared with PCP-treated group (**Fig. 3**).

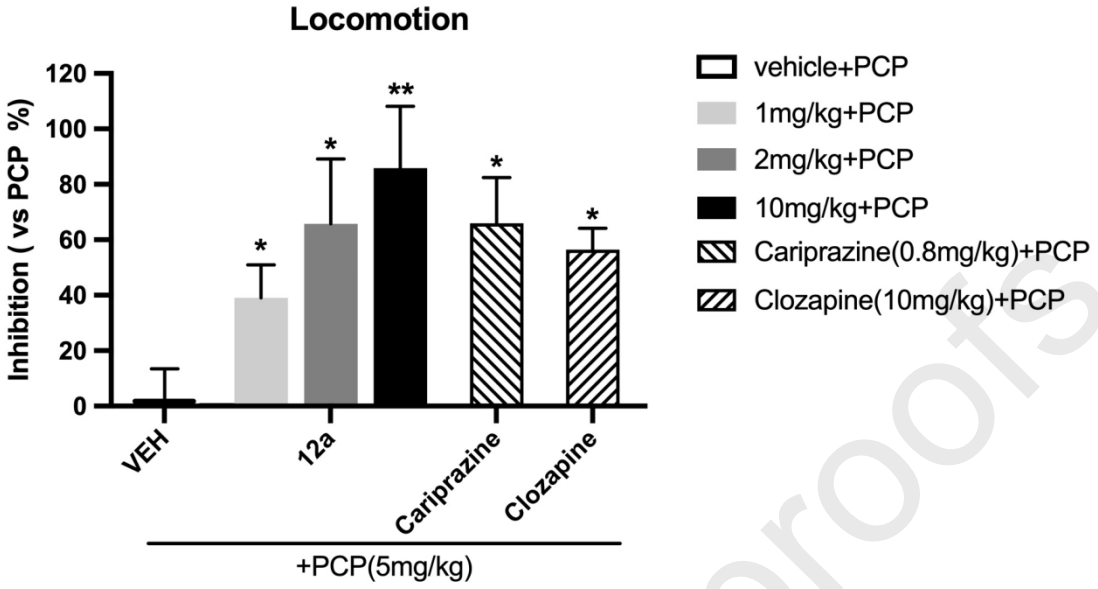


Fig. 3. Inhibition of PCP induced hyperactivity by tested compound and reference antipsychotic agents clozapine and cariprazine in male Sprague-Dawley rats. Compounds were administered 20 min before PCP (5 mg/kg) injection. Locomotor activities were measured for a 1 h duration after PCP administration and the total travel distance was expressed as Mean ± standard error of the mean (n = 8-10). * and **, $P<0.05$ and $P<0.01$ versus PCP treated group.

In this work, a series of *trans*-4-(2-(1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepin-3-yl)ethyl)cyclohexan-1-amine derivatives were designed and synthesized to identify potential antipsychotics that target D_2/D_3/5-HT_{1A}/5-HT_{2A} receptors and have low affinities for α_1R and H_1R. Preliminary SAR between the designed compounds and four drug targets, as well as α_1 and H_1 receptors was also discussed. The SAR results revealed that the *trans*-tetrahydro-3*H*-benzo[*d*]azepin-3-yl cyclohexyl amine scaffold was a kind of privileged structure having low α_1 and H_1 receptor affinity. The substitutions on the amine, substitutions at the phenyl and the chirality of the methyl on the azepine ring had influence on the affinity for the D_2, D_3, 5-HT_{1A} and 5-HT_{2A} receptors both individually and collectively. Among these derivatives, compound **12a** was confirmed as an optimal compound. **12a** also exhibited suitable metabolic stability and

micromolar affinity for hERG channel. Further *in vivo* animal model tests showed that **12a** was a potential multi-receptor antipsychotic. This study provides insights into the development of novel multi-target antipsychotic molecule with potential therapeutic effects and good drug target selectivity.

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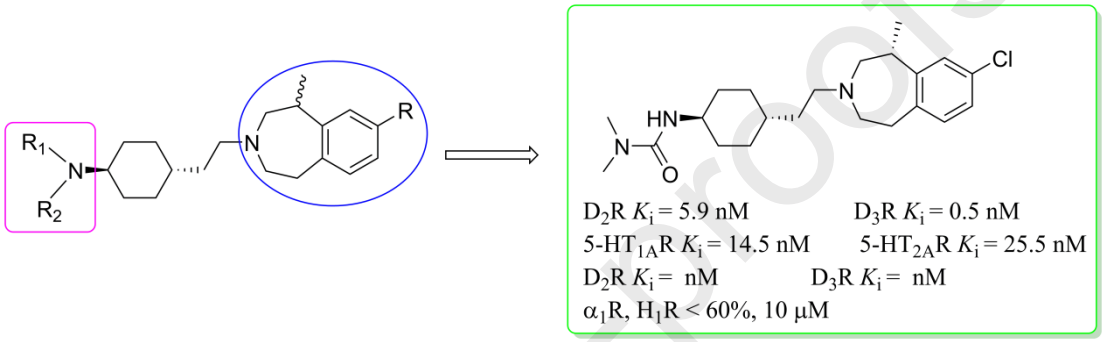

22.

Highlights

- A series of novel 1,2,4,5-tetrahydro-3*H*-benzo[*d*]azepine derivatives have been synthesized.

- All compounds were evaluated for D_2/D_3/5-HT_{1A}/5-HT_{2A}/α_1/H_1 binding affinities *in vitro*.

The optimal compound was screened using the animal model of locomotor-stimulating effects of phencyclidine.

Compound **12a** was a potential multireceptor antipsychotic in animal behavioral models with good metabolic stability and target selectivity.

23.