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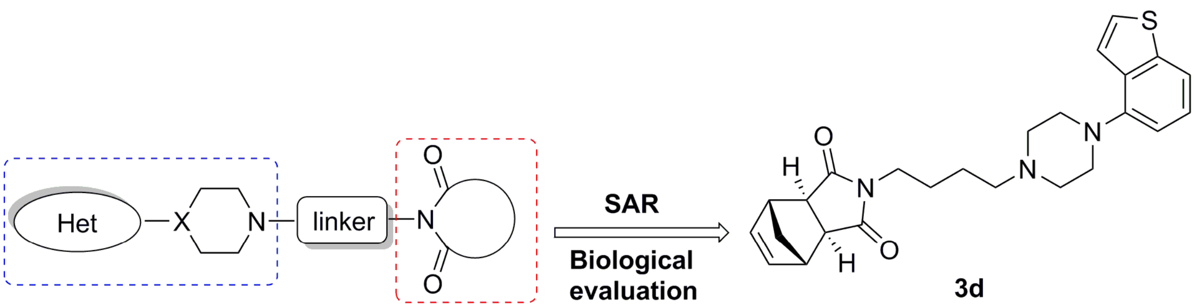

Base moiety **Cyclic imide**

3d

D_2R IC_{50} = 6.4 nM
5-$HT_{1A}R$ EC_{50} = 3.6 nM
5-$HT_{2A}R$ IC_{50} = 24.6 nM
good *in vivo* efficacy and safety profiles
acceptable pharmacokinetics

Synthesis and biological evaluation of a series of multi-target N-substituted cyclic imide derivatives with potential antipsychotic effect

Mingshuo Xu [a, b], Yu Wang [a], Feipu Yang [a], Chunhui Wu [c], Zhen Wang [a], Bin Ye [c], Xiangrui Jiang [a], Qingjie Zhao [a], Jianfeng Li [a], Yongjian Liu [c], Junchi Zhang [a], Guanghui Tian [c], Yang He [a, *], Jingshan Shen [a, *], Hualiang Jiang [a]

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Abstract

In the present study, a series of multi-target N-substituted cyclic imide derivatives which possessed potent dopamine D_2, serotonin 5-HT_{1A} and 5-HT_{2A} receptors properties were synthesized and evaluated as potential antipsychotics. Among these compounds, (3aR,4R,7S,7aS)-2-(4-(4-(benzo[*b*]thiophen-4-yl)piperazin-1-yl)butyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3d**) held a promising pharmacological profile. **3d** not only showed potent and balanced *in vitro* activities on D_2/5-HT_{1A}/5-HT_{2A} receptors, but also endowed with low to moderate activities on 5-HT_{2C}, H_1, α_{1A}, M_3 receptors and hERG channel, suggesting a low liability to induce side effects such as weight gain, orthostatic hypotension and QT prolongation. In animal behavioral studies, **3d** reduced phencyclidine-induced hyperlocomotion with a high threshold for catalepsy induction. Compound **3d** was selected as a potential antipsychotic candidate for further development.

Keywords: antipsychotic, cyclic imide, multi-target, 5-HT_{1A} receptor

1 Introduction

Schizophrenia is a severe neuropsychiatric disorder affecting about 1% of the world's population[1]. It is characterized by three broad categories of core symptoms, e.g. positive symptoms (delusions, hallucinations and thought disorder), negative symptoms (alogia, affective flattening, anhedonia, avolition and apathy) and cognitive impairment[2]. Typical antipsychotics (dopamine D_2 receptor antagonists) were proved to be effective merely in the treatment of positive symptoms[3]. Besides, nonselective inhibition of dopaminergic transmission can cause severe side effects, such as extrapyramidal symptoms (EPS), tardive dyskinesia (TD), hyperprolactinemia[4] and deterioration of the negative and cognitive symptoms[5, 6]. In an effort to improve the efficacy and safety profile, a class of multi-target drugs called atypical antipsychotics was discovered (Fig. 1). Atypical antipsychotics bind not only to D_2 receptor, but also various 5-hydroxytryptamine (5-HT) receptors. These polypharmacological antipsychotic agents have demonstrated some clinical advantage over typical D_2 receptor antagonists in the treatment of negative symptoms and cognitive impairment[7, 8]. Even though atypical antipsychotics cause less EPS and are better tolerated in patients, they tend to result in other unwanted side effects like weight gain, diabetes mellitus, hyperlipidemia and QT interval prolongation after chronic medication[9]. As a result, development of novel antipsychotics with broader therapeutic spectrum as well as minimal side effects is of great significance.

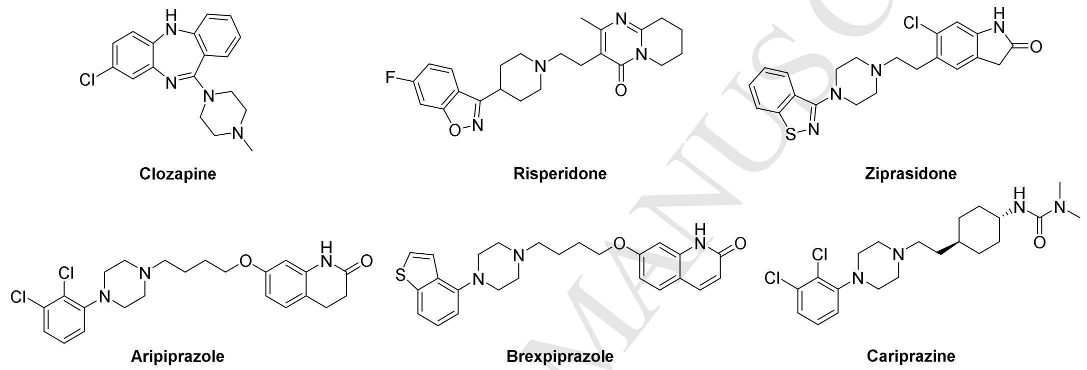


Fig. 1. structure of representative atypical antipsychotic drugs.

5-HT receptors are important therapeutic targets for many central nervous system diseases[10]. $D_2R/5\text{-}HT_{2A}R$ dual antagonism is shared by all atypical antipsychotics[11]. It is asssumed that this characteristic contributes to the substantial reduction in EPS for atypical antipsychotics[3, 12]. In the last few years, considerable attention has been given to 5-HT_{1A} receptor as the new generation of atypical antipsychotics such as aripiprazole, brexpiprazole and cariprazine (Fig. 1) all exhibit affinity for this receptor. 5-HT_{1A} receptor is largely distributed throughout the brain, and it plays an important role in the treatment of various neuropsychiatric disorders, such as schizophrenia[13, 14], anxiety[15, 16] and major depressive disorder[17, 18]. Additional 5-HT_{1A} receptor agonistic activity was proved to improve the safety profile and therapeutic effect of atypical antipsychotics. First, 5-$HT_{1A}R$ agonism could alleviate the EPS side effect of antipsychotics by activating 5-$HT_{1A}R$ located in primary motor cortex and dorsolateral striatum regions[19]. Second, 5-HT_{1A} partial agonist as adjunctive therapy could improve positive symptoms[20], which is the core symptoms of schizophrenzia. Furthermore, 5-$HT_{1A}R$ agonists induced dopamine release in the prefrontal cortex, thus potentiated the function of mesocortical dopamine pathway[14]. As a consequence, negative symptoms and cognitive impairment might be ameliorated[21, 22]. In summary, 5-HT_{1A}R agonism is of great benefit for the improvement of current antipsychotic therapy.

As schizophrenia is a complex psychiatric disease with numerous different symptoms, introducing multi-target drugs with polypharmacological profile has become a widely used therapeutic approach[23]. Thus, developing novel muti-target antipsychotics that act on dopaminergic and serotoninergic receptors with potent and balanced activities as well as with low activities for receptors associated with side effects has been our long-standing research interest. Especiallly, the emphasis was put on effect on 5-HT_{1A} receptor due to its potential therapeutic benefit. 5-HT_{1A} receptor agonists and partial agonists with cyclic imide moieties (e.g. buspirone and tandospirone) have demonstrated clinical efficacy in the treatment of psychiatric disorders. The unique feature of these compounds is a cyclic imide fragment connected to a nitrogen-containing base moiety through a proper linker. On the other side, marketed antipsychotic drugs, such as risperidone and brexpiprazole, are D_2R/5-HT_{2A}R dual ligands. The arylpiperazine or arylpiperdine fragments of these antipsychotics were also shared by many other compounds which targeted to serotonin receptors[24, 25]. By applying molecular hybridization method for multi-target drug design, a series of new N-substituted cyclic imide derivatives (Fig. 2) was synthesized and their activites on D_2R, 5-HT_{1A}R and 5-HT_{2A}R were evaluated. Among these compounds, compound **3d** exhibited best *in vitro* activities, and demonstrated potent antipsychotic effect in *in vivo* behavioral studies. As a result, compound **3d** had the potential to be developed as an antipsychotic drug.

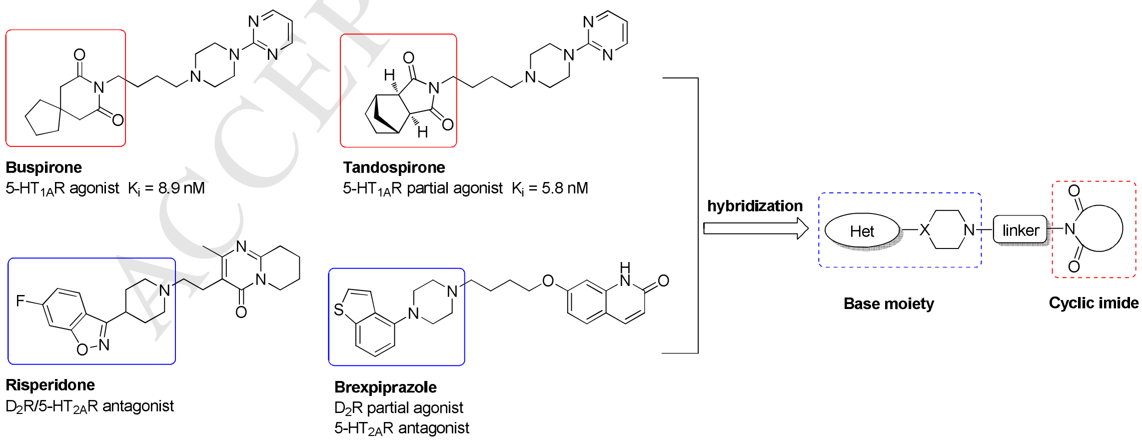


Fig. 2. Design of new N-substituted cyclic imide derivatives.

2. Results and discussion

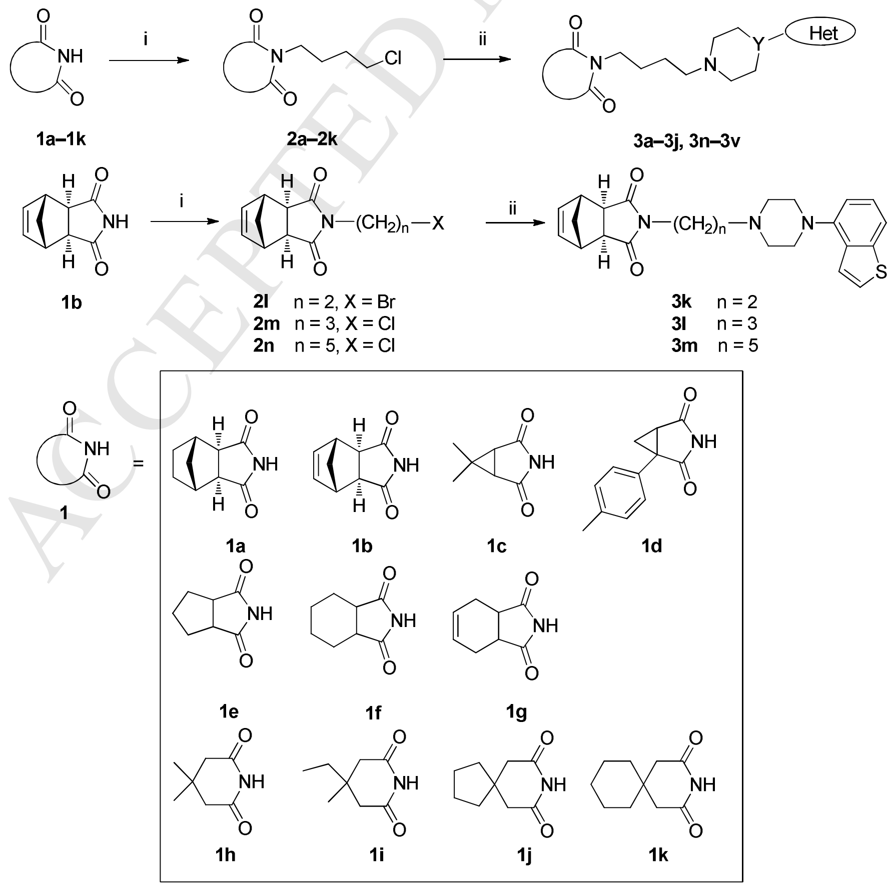
2.1. Chemistry

The synthesis of compounds **3a–3v** was depicted in Scheme 1. As illustrated in Scheme 1, commercially available cyclic imide **1a–1k** was first alkylated with corresponding α,ω-dihaloalkanes under the condition of K_2CO_3 in N,N-dimethyl formamide (DMF) to afford intermediate **2a–2n**. Synthesis of compounds **3a–3v** was accomplished by coupling **2a–2n** with corresponding arylpiperazines or arylpiperidines in the presence of K_2CO_3 and KI in DMF/H_2O system.

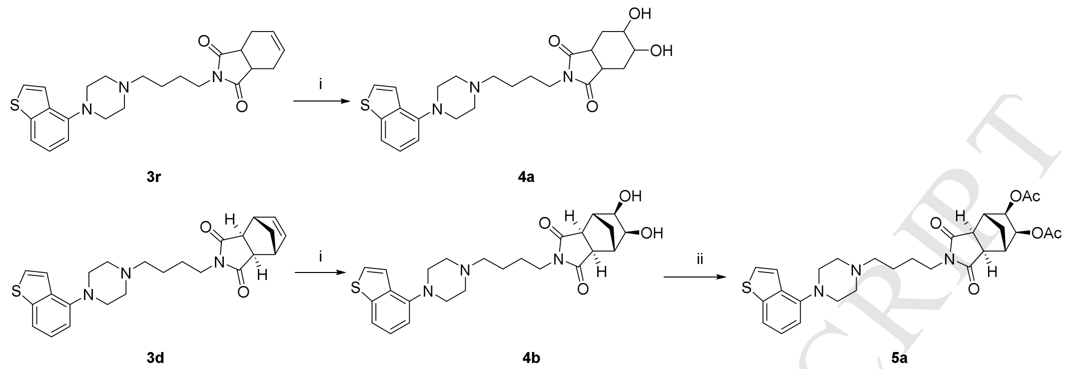
Compounds **4a** and **4b** were obtained by dihydroxylation of olefin compounds **3r** and **3d** respectively in the presence of potassium permanganate (Scheme 2)[26]. Subsequent acetylation of compound **4b** with Ac_2O afforded ester derivative **5a**.

The synthesis of phthalimide derivates **8a–8e** was shown in Scheme 3. Commercially available **6a–6e** were alkylated with 1,4-dibromobutane to provide intermediates **7a–7e**, which were then coupled with 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride under mild base condition to give **8a–8e**.

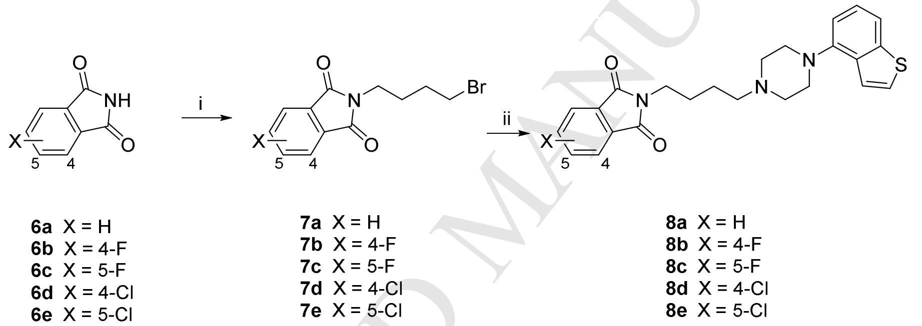
The structure of intermediates 2a–2n, 7a–7e was confirmed by analysis of ^{1}H-NMR as described in supporting information. The structure of final compounds was confirmed by analysis of ^{1}H-NMR and ESI-MS spectra as described in Section 4.



Scheme 1. Reagents and conditions: (i) 1-bromo-4-chlorobutane for **2a–2k**, 1,2-dibromoethane for **2l**, 1-bromo-3-chloropropane for **2m**, 1-bromo-5-chloropentane for **2n**, K_2CO_3, DMF, rt, overnight; (ii) arylpiperazine hydrochloride, K_2CO_3, KI, DMF/H_2O, 95 °C, 12 h.



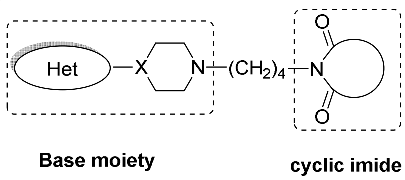
Scheme 2. Reagents and conditions: (i) $KMnO_4$, acetone, 0 °C then rt, 30 min; (ii) Ac_2O, pyridine, rt, 24 h.

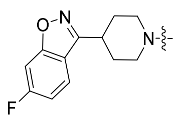
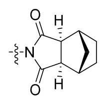
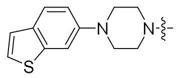
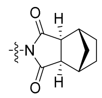


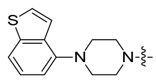
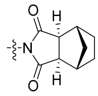
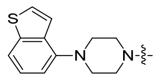
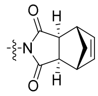
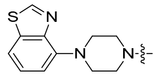
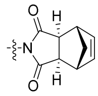
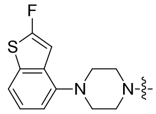
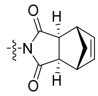
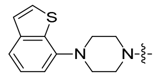
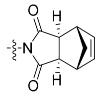
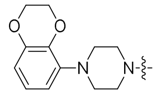
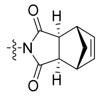
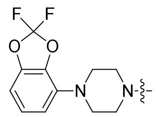
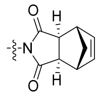
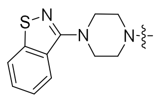
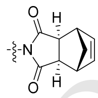
Scheme 3. Reagents and conditions: (i) 1,4-dibromobutane, K_2CO_3, acetone, reflux, 2 h; (ii) 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride, K_2CO_3, KI, MeCN, reflux, 5 h.

Table 1

Functional acivities on D_2, 5-HT_{1A} and 5-HT_{2A} receptors of compound **3a–3j**.



Cmpd	Base	Cyclic imide	D_2R IC_{50} (nM)	5-$HT_{1A}R$ EC_{50} (nM)	5-$HT_{2A}R$ IC_{50} (nM)
3a			4.8	> 100000	5.2
3b			80.2	91.3	130

3c			6.1	6.9	27.5
3d			6.4	3.6	24.6
3e			9.6	3.3	956
3f			2.5	10.6	82.3
3g			5.3	2.4	32.0
3h			9.8	3.6	854
3i			2.0	6.1	2840
3j			4.2	14	35.8

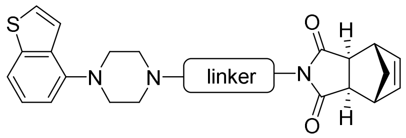
2.2. In vitro receptor functional activities and structure-activity relationship (SAR)

The influence of base moiety on functional activities of three target receptors was first evaluated at the beginning of our study. The results were summarized in Table 1. As anticipated on the basis of our previous study, compound **3a** bearing (6-fluorobenzo-[*d*]isoxazol-3-yl)piperidine as base moiety was devoid of 5-HT$_{1A}$R agonistic activity. Compound **3b** with 1-(benzo[*b*]thiophen-6-yl)piperazine as base moiety possessed moderate but balanced activity on three receptors (IC$_{50}$ or EC$_{50}$ value ≈ 100 nM). When changing piperazine substituent on benzothiophene ring from 6–position to 4–position, the activities on three receptors showed a remarkable elevation for D$_2$R and 5-HT$_{1A}$R (**3c** vs **3b**). Compound **3d**, the olefin analogue of **3c**, displayed slightly enhanced agonistic activity on 5-HT$_{1A}$R, while retained high D$_2$R and 5-HT$_{2A}$R potency. Replacement of benzothiophene with its bioisostere, benzo[*d*]thiazole, led to a sharp decline in 5-HT$_{2A}$R antagonistic activity with little change on D$_2$R and 5-HT$_{1A}$R activities.(**3e** vs **3d**). Introduction of a fluorine atom at 2-position of benzothiophene ring resulted in a decrease in 5-HT$_{1A}$R and 5-HT$_{2A}$R potency by 2-fold, while D$_2$R potency increased slightly (**3f** vs **3d**). Interestingly, shifting the relative position of piperazine ring on benzothiophene ring from 4-position to 7-position made nearly no change on receptor profile (**3g** vs **3d**). Transforming benzothiophene moiety to oxygen-containing benzoheterocycles like 2,3-dihydrobenzo[*b*][1,4]dioxine and 2,2-difluorobenzo[*d*][1,3]dioxole was proved to be detrimental for 5-HT_{2A}R antagonistic activities as IC_{50} values of compounds **3h** and **3i** dropped to micromolar level. Finally, Compound **3j** bearing 4-(1,2-benzisothiazol-3-yl)piperazine moiety showed excellent activities for all the three receptors.

Encouraged by the above results, we proceeded with our investigation by introducing different linkers or cyclic imide moieties. 1-(benzo[*b*]thiophen-4-yl)piperazine was chosen as potential pharmacophoric moiety as previous studies demonstrated that compounds bearing this pharmacophoric core exhibited high activities for D_2, 5-HT_{1A}R and 5-HT_{2A}R (**3c** and **3d** in Table 1). Previous SAR studies on psychotropic drugs have suggested that the linker length and flexibility play an important role in determining receptor function and the tetramethylene space was generally considered as the optimal length of spacer[27-29]. Therefore, investigation of linker moiety was focused on chain length around four carbons. As shown in Table 2, the functional activities for D_2R gradually increased as chain length increasing from two to four carbons. Further elongation of the spacer from four carbons to five carbons caused decrease in the D_2R antagonistic activity (**3m** vs **3d**). However, this was not the case for 5-HT_{1A}R and 5-HT_{2A}R, as the potency trend following the order: $(CH_2)_4$ > $(CH_2)_2$ > $(CH_2)_3$ > $(CH_2)_5$. Notably, compound **3m** was completely devoid of 5-HT_{1A}R agonism activity. Taken together, four carbon chain was proved to be optimal as expected and maintained unchanged in the next modification.

Table 2

Functional acivities on D_2, 5-HT_{1A} and 5-HT_{2A} receptors of compounds **3d** and **3k–3m**.



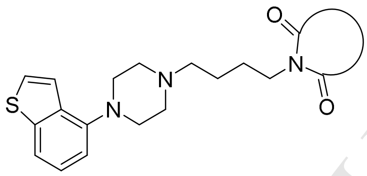
Cmpd	linker	D_2R	5-HT_{1A}R	5-HT_{2A}R
		IC_{50} (nM)	EC_{50} (nM)	IC_{50} (nM)
3k	$(CH_2)_2$	119	13.8	82.4
3l	$(CH_2)_3$	32.4	107	113
3d	$(CH_2)_4$	6.4	3.6	24.6

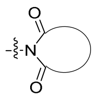
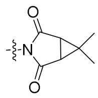
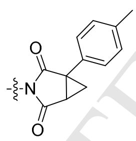
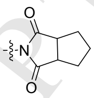
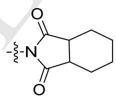
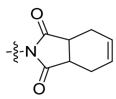
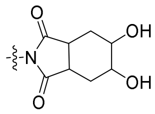
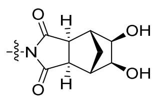
3m	$(CH_2)_5$	28	> 100000	314

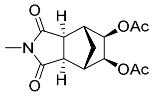
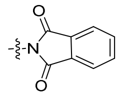
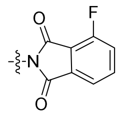
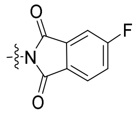
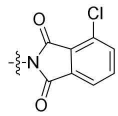
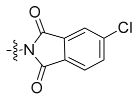
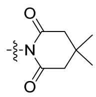
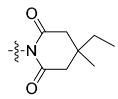
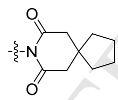
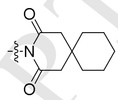
Imide moiety is the common fragment of the azapirone psychotropic drugs, which is thought to modulate the activity and selectivity for 5-HT_{1A} receptor[30]. We therefore decided to explore structural transformation of this part extensively. These compounds could be roughly divided into two types: succinimide derivatives (compounds **3n–3r**, **4a–4b**, **5a**, **8a–8e**) and glutarimide derivatives (compound **3s–3v**). The data on functional activities were summarized in Table 3.

Table 3

Functional acivities on D_2, 5-HT_{1A} and 5-HT_{2A} receptors of compound **3n–3v**, **4a–4b**, **5a** and **8a–8e**.



Cmpd		D_2R	5-$HT_{1A}R$	5-$HT_{2A}R$
		IC_{50} (nM)	EC_{50} (nM)	IC_{50} (nM)
3n		8.4	> 100000	10.4
3o		80.6	11.6	1660
3p		13	8.8	1.1
3q		4.3	1.7	34
3r		8.5	0.9	0.6
4a		9.4	10.5	84.9
4b		14.1	17.4	81.5

5a		44.6	3.1	546
8a		131	21.3	683
8b		38.1	1.1	318
8c		213	13.3	254
8d		30.1	5.8	282
8e		543	47.9	7250
3s		7.2	1.6	134
3t		10.9	1.24	25.9
3u		24.4	7.7	29.1
3v		11	1.2	103

The SAR study of succinimide derivatives was emphasized on the influence of substituent size and electric properities of the fused rings. As shown in Table 3, compound **3n** with gem-dimethyl substitution displayed good potency for D_2R and 5-$HT_{2A}R$, but it was completely devoid of 5-$HT_{1A}R$ agonistic effect with EC_{50} > 100 μM. In contrast, compound **3o** with a p-tolyl substituent exhibited outstanding 5-$HT_{1A}R$ potency, but bulky substituent appeared to be detrimental for D_2R and 5-$HT_{2A}R$ activities. Replacement of the gem-dimethyl substituted cyclopropyl ring with cyclopentyl ring resulted in higher potency for all the three receptors (**3p**). Further enlargement of the cyclopentyl ring to a six-membered cyclohexyl ring had an obviously negative impact on 5-$HT_{2A}R$ activity (compound **3q** vs **3p**). Compared with compound **3q**, its olefin analogue **3r** exhibited stronger activities on 5-$HT_{1A}R$ and 5-$HT_{2A}R$ while retaining antagonistic activity on D_2R, which was consistent with the result of compounds **3c** and **3d** (Table 1). This indicated that introduce of C-C double bond had some advantage, and we presumed that the decrease in molecular flexibility of olefine compound might account for higher potency for 5-HT_{1A}R. However, replacement of the cyclohexyl ring with more rigid phenyl ring led to reduced activities on all three receptors (compound **8a** vs compound **3r**). We speculated that the potency decline after aromatization might be due to electronic factors as well as steric factors.

We further investigated the effect of introducing halogen atoms to the phthalimide moiety (compounds **8b–8e**, Table 3). According to the results, the 4-flouro substituted derivative **8b** and 4-chloro substituted derivative **8d** displayed improved activities for all the three receptors. By contrast, 5-flouro substituted derivative **8c** showed increased activities for 5-HT_{1A}R and 5-HT_{2A}R receptors while decreased activity for D_2R, and 5-chloro substituted derivative **8e** exhibited a dramatic decline in activities for all three receptors. On the whole, the potency trend for three receptors followed the order: ortho-substitution (**8b**, **8d**) > no substitution (**8a**) > meta-substitution (**8c**, **8e**); F-substitution > Cl-substitution (**8b** vs **8d**, **8c** vs **8e**). Disappointingly, none of these phthalimide derivatives showed comparable activity as compounds **3q** and **3r**, which suggested that aromatic rings were inferior to aliphatic rings for succinimide derivatives. Further oxidation of C-C double bond of compounds **3d** and **3r** gave corresponding dihydroxyl compounds **4b** and **4a** with activities on three receptors decreasing to some extent. Biacetylation of hydroxyl groups had a positive effect on 5-HT_{1A}R potency, albeit activities on D_2R and 5-HT_{2A}R reduced (**5** vs **4a**).

Glutarimide derivatives **3s–3v** modified in the spiro moiety gave interesting results as well. As shown in Table 3, compound **3t** with ethyl methyl disubstitution showed higher potency for 5-HT_{2A}R than compound **3s** with gem-dimethyl substitution, although their activities on D_2R and 5-HT_{1A}R were comparable. After formal ring closure, compound **3u** showed weaker activities than **3t** for D_2R and 5-HT_{1A}R while potency for 5-HT_{2A}R retained. Enlargement of the cyclopentyl spiro moiety of **3u** gave compound **3v**, which was less active on 5-HT_{2A}R while slightly more active on D_2R and 5-HT_{1A}R.

In order to juggle the potency and selectivity of synthesized compounds for further biological evaluation, two primary selection creteria were set: (a) high potency for D_2R, 5-HT_{1A}R and 5-HT_{2A}R (IC_{50} or EC_{50} value < 30 nM); (b) to obtain a balanced receptor activity profiles, the potency ratio between any two of the three receptors should be no greater than 10. As a result, compounds **3c**, **3d**, **3t** and **3u** were selected to assess their liability to cause antipsychotic-induced side effects.

2.3. In vitro receptor functional activities on safety profile and hERG affnities

Although atypical antipsychotics have low liability to cause serious adverse effects (EPS and TD), they are associated with a wide range of other adverse effects, such as weight gain, hyperglycaemia, dyslipidaemia and cardiovascular disease[9]. These side effects were associated with unintentional engagement of multiple pharmacological targets, which led to undesired consequences and poor medication adherence. Therefore, further characterization of pharmacological profiles of candidate compounds is essential.

Various receptors were involved in the emergence of these side effects, including 5-HT_{2C} receptor, M_3 cholinoceptor, α_{1A} adrenergic receptor and H_1 histaminergic receptor[31-33]. 5-HT_{2C} and H_1 receptors were closely related to the contol of feeding and body weight, and might be responsible for weight gain side effect of antipsychotic drugs. According to Table 4, all selected compounds showed moderate activities for H_1 receptor, and they displayed much weaker potency for 5-HT_{2C} receptor than risperidone. On the basis of the above results, compounds **3c**, **3d**, **3t** and **3u** had low potential to elicit antipsychotic-induced weight gain. Inhibition of peripheral α_{1A} adrenergic receptor was presumed to be associated with antipsychotic-induced orthostatic hypotension. Compounds **3c**, **3d**, **3t** and **3u** showed moderate α_{1A} receptor antagonistic activities, comparable to that of aripiprazole and weaker than that of risperidone, suggesting that they had low liability to cause orthostatic hypotension. Pancreatic M_3 cholinoceptor appeared to control cholinergic-dependent insulin release, blocking which might lead to hyperglycaemia and type II diabetes mellitus. For example, olanzapine and clozapine exhibited the highest clinical incidence of diabetes side effect, both of which are potent M_3 receptor antagonists[34]. All selected compounds as well as risperidone and aripiprazole were devoid of M_3 receptor antagonistic activity, indicating a low propensity to elicit hyperglycaemia.

Morever, blocking human ether-a-go-go-related gene (hERG) potassium channel causes QT interval prolongation, which is associated with potentially fatal arrhythmia called Torsades de Pointes[35]. As a result, inhibitory potency for hERG has become a major safety concern for drug discovery. As shown in Table 4, all tested compounds exhibited quite weak hERG blocking potency, indicating that they held low propensity to elicit treatment-induced QT interval prolongation.

On the basis of what was discussed above, we drew the conclusion that compounds **3c**, **3d**, **3t** and **3u** had low potential to cause serious adverse effects associated with antipsychotic drugs.

Table 4

Activities on 5-HT_{2C}, H_1, α_{1A}, M_3 receptors and hERG of seleceted compounds and reference antipsychotics.

Cmpd	5-HT$_{2C}$	H_1	α_{1A}	M_3	hERG
	IC_{50} (nM)	IC_{50} (nM)	IC_{50} (nM)	IC_{50} (nM)	IC_{50} (nM)
3c	188	174	124	> 100000	7520
3d	341	195	178	> 100000	7850
3t	606	253	376	> 100000	6210
3u	400	305	375	> 100000	2630
RIS[a]	1.81	454	10.9	> 100000	1330
ARI[b]	1380	420	170	> 100000	3860

[a] **RIS** = Risperidone.

[b] **ARI** = Aripiprazole.

2.4. Behavioral studies

Based on the *in vitro* pharmacological profile, compounds **3c**, **3d**, **3t** and **3u** were then subjected to *in vivo* behavioral study to verify their effects on schizophrenia.

2.4.1. PCP-induced hyperlocomotion

Phencyclidine (PCP), a N-methyl-D-aspartic acid receptor (NMDAR) antagonist, has been found to simulate schizophrenia[36], and this effect can be reversed by antipsychotics[37]. Currently, PCP-induced hyperlocomotion is a widely used model to assess antipsychotic-like efficacy of potential antipsychotic agents. In this assay, compounds **3c**, **3d**, **3t** and **3u** all attenuated PCP-induced hyperlocomotion significantly in ICR mice at the dose of 3 mg/kg, among which **3d** exhibited most potent inhibitory effect. Moreover, compound **3d** produced significant dose-dependent responses with an ED_{50} value of 1.80 mg/kg (Fig. 3), which was consistent with its potent *in vitro* D_2R antagonistic activity. On the basis of the data presented, compound **3d** clearly differentiated itself from **3c**, **3t** and **3u**, justifying further *in vivo* evaluation.

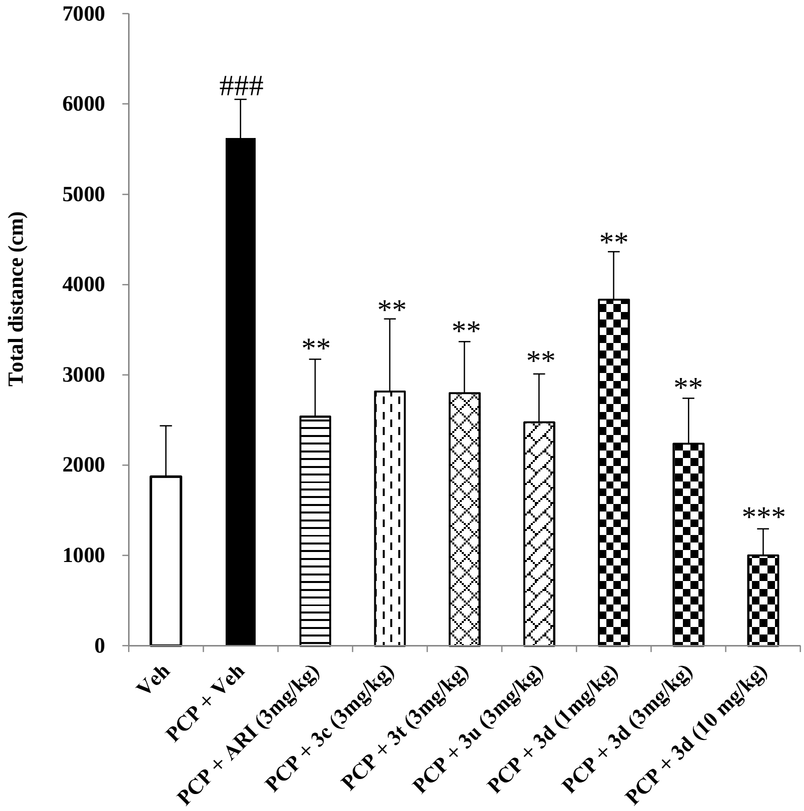


Fig. 3. Effects of compounds **3c**, **3d**, **3t**, **3u** and aripiprazole on PCP-induced hyperlocomotion in mice (7 mg/kg, ip, 6/group). Animals were habituated for 10 min before the 75 min measurement period. Results were expressed as the means ± SEM of distance traveled. Statistical evaluation was performed by two-way ANOVA followed by student's t test for multiple comparisons. *p < 0.05 versus PCP treatment; **p < 0.01 versus PCP treatment; ***p < 0.001 versus PCP treatment; ###p < 0.001 versus vehicle treatment.

2.4.2. Catalepsy

Catalepsy is a frequently used model to predict liability of antipsychotics to induce EPS side effect in humans[38]. As shown in Table 5, compound **3d** exhibited low potential for catalepsy with an ED_{50} value of 14.10 mg/kg. The therapeutic index of compound **3d** based on its efficacy and side effect (catalepsy) was 7.83, while the therapeutic index of aripiprazole was 2.43. Compound **3d** had a higher threshold for catalepsy compared with aripiprazole, which might translate into lower clinical EPS liability.

Table 5

In vivo pharmacological profile of compound **3d**.

Cmpd	PCP[a]	CAT[b]	CAT/PCP
3d	1.80	14.10	7.83
ARI	2.93	7.13	2.43

[a] PCP: PCP-induced hyperlocomotion (ED_{50}, mg/kg, ig).

[b] CAT: Catalepsy (ED_{50}, mg/kg, ig).

[c] **ARI** = Aripiprazole.

2.4.3. Quipazine-induced head twitch response in mice

Quipazine-induced head twitch response (HTR) in mice was 5-HT_{2A}R-dependent, so it was an important model to verify the *in vivo* efficacy of 5-HT_{2A}R antagonists. As shown in Table 6, compound **3d** exhibited dose-dependent inhibitory effect on HTR (Table 6). Particularly, HTR in mice was completely inhibited by compound **3d** at the dose of 3 mg/kg, which was superior to aripiprazole (reduction ratio = 70.8%).

Table 6

Effect of compound **3d** on Quipazine-induced head twitches response in mice.

Treatment	Dose (mg/kg)	Head twitches[a] (number of episodes)	% of HTR reduction
Vehicle	0	13.0 ± 2.1	
3d	1	8.4 ± 2.2*	35.4%
3d	3	0***	100%
ARI[b]	3	3.8 ± 1.2	70.8%

[a] Values represent the number of head twitches (mean ± SEM) during the 15 min test.

[b] **ARI** = Aripiprazole

* $p < 0.05$ versus Quipazine-treated group.

** $p < 0.01$ versus Quipazine-treated group.

*** $p < 0.001$ versus (±)-Quipazine-treated group.

2.5. Evaluation of pharmacokinetics

The pharmacokinetic properties of **3d** were measured in rats (Table 7). The area under the curve (AUC) value of compound **3d** was 3144.58 ng × h/mL after intravenous administration vs 1002.26 ng × h/mL after oral administration. Then, the oral bioavailability of compound **3d** was caclulated as ratio of

AUC (po) to AUC (iv). Oral bioavailability of **3d** was 32%. The elimination half-lifves of 3d were 2.66 h and 3.26 h after intravenous and oral administration, respectively. The C_{max} value after oral dosing of **3d** was 85.95 ng/mL, and T_{max} value was 5.33 h. These encouraging preclinical data suggested that **3d** possessed acceptable drug-like human pharmacokinetic properties.

Further metabolite profiling studies of compound **3d** in rats and subsequent structural analysis of metabolites revealed an important metabolite **4b** which formed in significant amounts (~21% based on AUCs) relative to the parent compound **3d**. As compound **4b** was found to be slightly less potent for D_2, 5-HT_{1A} and 5-HT_{2A} receptors than parent compound **3d** in the previous discussion, it might contribute significantly to the *in vivo* pharmacology of **3d**.

Table 7

plasma pharmacokinetic data following the administration of Compound **3d** in rats (n = 3/group).

dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-24h} (ng × h/mL)	*F* (%)
10 (iv)	2658.99	0.083	2.66	3144.58	-
10 (po)	85.95	5.33	3.26	1002.26	32
10 (po)	16.63[a]	3.67[a]	11.15[a]	210.47[a]	-

[a] plasma pharmacokinetic data of metabolite **4b** following the administration of compound **3d** in rats.

In summary, a series of new N-substituted cyclic imide compounds were synthesized and evaluated for their antipsychotic activities. The efforts to explore SAR provided some beneficial clues to the development of multi-target antipsychotic drugs. Among the synthesized compounds, **3d** exhibited not only potent and balanced *in vitro* activities on D_2R/5-$HT_{1A}R$/5-$HT_{2A}R$, but also favorable *in vivo* profiles on behavioral assays. Besides, with low to moderate potency for M_3, 5-HT_{2C}, H_1 and α_{1A} receptor and hERG channel, compound **3d** had low risk of inducing side effects associated with these targets. Moreover, compound **3d** exhibited acceptable pharmacokinetic properties. As a result, compound **3d** had the potential to be developed into novel multi-target antipsychotic drug.

4. Experimental

4.1. Chemistry experimental

All chemicals and solvents were purchased from commercial suppliers (e.g. Sinopharm Chemical Reagent Co., Ltd.) and were 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 (126 MHz for ^{13}C NMR)spectrometer with TMS in DMSO-d_6 or $CDCl_3$ solution as an internal standard. Chemical shifts were given in δ 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). High resolution mass spectra (HRMS) were obtained using Agilent G6520 Q-TOF mass spectrometer; Low resolution mass spectra (LRMS) were obtained using Finnigan MAT95 mass spectrometer. TLC on silica gel GF254 was used to monitor the progress of all reactions. Column chromatographic purification was carried out using silica gel (200–300 mesh). The HPLC conditions were as follows: column, Agilent ZORBAX SB-C18 (4.6×150mm, 5μm); mobile phase, 0.02 mol/L sodium 1-octanesulfonate (PH = 2.0 adjusted by 85% H_3PO_4)/acetonitrile 65/35–30/70; UV detection, 220 nm; injection volume, 10 μL; flow rate, 1.0 mL/min; column temperature, 30 °C.

*4.1.1 General procedure for the preparation of compounds of **2a–2n**.*

To a suspension of corresponding cyclic imide **1a–1k** (4 mmol), potassium carbonate (4.4 mmol) in DMF (5 mL), 1-bromo-4-chlorobutane (1,2-dibromoethane (5 eq) for **2l**, 1-bromo-3-chloropropane for **2m**, 1-bromo-5-chloropentane for **2n**) (4.4 mmol) was added dropewise at 0 °C. The mixture was stirred at room temperature overnight and then partitioned between ethyl acetate (EA, 20 mL) and water (30 mL). The organic layer was washed successively with water (3 × 30 mL), saturated brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography using petroleum ether(PE) : EA (8:1) as eluent to give **2a–2n** as colorless oil.

*4.1.2 General procedure for the preparation of compounds of **3a–3v**.*

Arylpiperazine or arylpiperidine (0.2 mmol), **2a–2n** (0.3 mmol), potassium iodide (0.2 mmol), potassium carbonate (0.7 mmol) were added to DMF (2 mL)/H_2O (0.5 mL), and then the reaction mixture was heated at 95 °C for 12 h. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate (EA, 2 mL) and water (30 mL). The organic layer was washed successively with water (3 × 20 mL), saturated brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography using DCM : MeOH (80:1) as eluent to afford colorless oil. The oil was dissolved in ethyl acetate and acidified with 1 M hydrochloride in ethyl acetate solution, keeping stirring for 30 min. Then the resulting solid was collected by filtration to give (**3a–3v**) as a white solid in the hydrochloride salt form.

4.1.2.1.

*(3aR,4S,7R,7aS)-2-(4-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)butyl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3a**).* The title compound was prepared from 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole hydrochloride and **2a** as a white solid (free base). Yield 69%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.67 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.26 (td, *J* = 9.1, 2.2 Hz, 1H), 2.96 – 2.86 (m, 2H), 2.64 (s, 2H), 2.53 – 2.44 (m, 5H), 2.30 (t, *J* = 6.8 Hz, 2H), 2.13 – 1.92 (m, 4H), 1.89 – 1.72 (m, 2H), 1.62 – 1.24 (m, 8H), 1.15 (d, *J* = 10.7 Hz, 1H), 0.97 (d, *J* = 10.7 Hz, 1H). MS (ESI) *m/z* = 440.4 ([M+H]$^+$).

4.1.2.2.

*(3aR,4S,7R,7aS)-2-(4-(4-(benzo[b]thiophen-6-yl)piperazin-1-yl)butyl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3b**).* The title compound was prepared from 1-(benzo[*b*]thiophen-6-yl)piperazine and **2a** as a white solid. Yield 62%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.50 (d, *J* = 5.4 Hz, 1H), 7.31 (d, *J* = 5.4 Hz, 1H), 7.17 (dd, *J* = 8.8, 2.2 Hz, 1H), 3.85 (d, *J* = 12.8 Hz, 2H), 3.52 (d, *J* = 11.6 Hz, 2H), 3.37 (t, *J* = 7.2 Hz, 2H), 3.29 – 3.04 (m, 5H), 2.67 (s, 2H), 1.78 – 1.64 (m, 2H), 1.62 – 1.41 (m, 5H), 1.38 – 1.25 (m, 2H), 1.16 (d, *J* = 10.7 Hz, 2H), 0.99 (d, *J* = 10.7 Hz, 2H). MS (ESI) *m/z* = 438.5 ([M+H]$^+$).

4.1.2.3.

*(3aR,4S,7R,7aS)-2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)hexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3c**).* The title compound was prepared from 1-(benzo[b]thiophen-4-yl)piperazine hydrochloride and **2a** as a white solid. Yield 75%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.20 (s, 1H), 7.76 (d, *J* = 5.0 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 5.0 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 3.64 – 3.45 (m, 4H), 3.38 (t, *J* = 7.0 Hz, 2H), 3.33 – 3.21 (m, 4H), 3.20 – 3.08 (m, 2H), 2.67 (s, 2H), 1.83 – 1.66 (m, 2H), 1.65 – 1.43 (m, 4H), 1.37 – 1.21 (m, 4H), 1.16 (d, *J* = 10.3 Hz, 1H), 0.99 (d, *J* = 10.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 178.57, 146.49, 140.59, 133.30, 126.52, 125.04, 121.72, 117.69, 112.54, 54.82, 51.05, 48.28, 47.97, 39.06, 37.27, 32.85, 27.38, 24.58, 20.50. MS (ESI) *m/z* = 438.4 ([M+H]$^+$). HRMS (ESI) *m/z* calcd for $C_{25}H_{32}N_3O_2S$ ([M+H]$^+$), 438.2210; found 438.2214.

4.1.2.4.

*(3aR,4R,7S,7aS)-2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3d**)*. The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2b** as a white solid. Yield 52%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 7.78 (d, *J* = 5.5 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 5.5 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.33 – 6.32 (m, 2H), 3.57 – 3.52 (m, 4H), 3.41 (t, *J* = 7.2 Hz, 2H), 3.33 – 3.22 (m, 4H), 3.20 – 3.09 (m, 4H), 2.73 (s, 2H), 1.82 – 1.70 (m, 2H), 1.58 – 1.51 (m, 2H), 1.40 (d, *J* = 9.7 Hz, 1H), 1.16 (d, *J* = 9.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 177.85, 146.68, 140.77, 137.81, 133.48, 126.69, 125.22, 121.90, 117.86, 112.72, 55.02, 51.25, 48.47, 47.48, 44.64, 42.68, 37.44, 24.72, 20.70. MS (ESI) *m/z* = 436.4 ([M+H]$^+$). HRMS (ESI) *m/z* calcd for $C_{25}H_{30}N_3O_2S$ ([M+H]$^+$), 436.2053; found 436.2053.

4.1.2.5.

*(3aR,4R,7S,7aS)-2-(4-(4-(benzo[d]thiazol-4-yl)piperazin-1-yl)butyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3e**)*. The title compound was prepared from 4-(piperazin-1-yl)benzo[*d*]thiazole hydrochloride and **2b** as a white solid. Yield 45%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.72 (s, 1H), 9.32 (s, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.33 – 6.28 (m, 2H), 4.19 (d, *J* = 10.4 Hz, 2H), 3.57 (d, *J* = 9.6 Hz, 2H), 3.39 (t, *J* = 7.1 Hz, 2H), 3.33 – 3.07 (m, 8H), 2.70 (s, 2H), 1.80 – 1.64 (m, 2H), 1.59 – 1.45 (m, 2H), 1.37 (d, *J* = 9.8 Hz, 1H), 1.13 (d, *J* = 9.8 Hz, 1H). MS (ESI) *m/z* = 437.3 ([M+H]$^+$).

4.1.2.6.

*(3aR,4R,7S,7aS)-2-(4-(4-(2-fluorobenzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3f**)*. The title compound was prepared from 1-(2-fluorobenzo[*b*]thiophen-4-yl)piperazine 2,2,2-trifluoroacetate and **2b** as a white solid. Yield 61%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 3.0 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.36 – 6.31 (m, 2H), 3.54 (d, *J* = 11.8 Hz, 2H), 3.50 – 3.38 (m, 4H), 3.31 – 3.22 (m, 2H), 3.21 – 3.09 (m, 6H), 2.73 (s, 2H), 1.79 – 1.66 (m, 2H), 1.55 (p, *J* = 7.5 Hz, 2H), 1.40 (d, *J* = 9.7 Hz, 1H), 1.16 (d, *J* = 9.7 Hz, 1H). MS (ESI) *m/z* = 454.4 ([M+H]$^+$).

4.1.2.7.

*(3aR,4R,7S,7aS)-2-(4-(4-(benzo[b]thiophen-7-yl)piperazin-1-yl)butyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3g**)*. The title compound was prepared from 1-(benzo[*b*]thiophen-7-yl)piperazine hydrochloride and **2b** as a white solid. Yield 75%; ^{1}H NMR (400

MHz, DMSO-d_6) δ 10.37 (s, 1H), 7.77 (d, *J* = 5.4 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 5.4 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 6.35 – 6.30 (m, 2H), 3.72 – 3.53 (m, 4H), 3.41 (t, *J* = 7.2 Hz, 2H), 3.34 – 3.15 (m, 6H), 3.12 (s, 2H), 2.72 (s, 2H), 1.73 (s, 2H), 1.55 (q, *J* = 7.6 Hz, 2H), 1.40 (d, *J* = 9.6 Hz, 1H), 1.15 (d, *J* = 9.6 Hz, 1H). MS (ESI) *m/z* = 436.4 ($[M+H]^+$).

4.1.2.8.

*(3aR,4R,7S,7aS)-2-(4-(4-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperazin-1-yl)butyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3h**).* The title compound was prepared from 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-5-yl)piperazine hydrochloride and **2b** as a white solid. Yield 63%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 – 10.69 (m, 1H), 6.75 (t, *J* = 8.1 Hz, 1H), 6.57 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.51 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.35 – 6.29 (m, 2H), 4.29 – 4.19 (m, 4H), 3.47 (d, *J* = 8.7 Hz, 4H), 3.39 (t, *J* = 7.2 Hz, 2H), 3.17 – 2.99 (m, 8H), 2.71 (s, 2H), 1.70 (d, *J* = 10.3 Hz, 2H), 1.57 – 1.45 (m, 2H), 1.38 (d, *J* = 9.7 Hz, 1H), 1.14 (d, *J* = 9.7 Hz, 1H). MS (ESI) *m/z* = 438.4 ($[M+H]^+$).

4.1.2.9.

*(3aR,4R,7S,7aS)-2-(4-(4-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)piperazin-1-yl)butyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3i**).* The title compound was prepared from 1-(2,2-difluorobenzo[*d*][1,3]dioxol-4-yl)piperazine hydrochloride and **2b** as a white solid. Yield 65%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 – 10.58 (m, 1H), 7.14 (t, *J* = 8.3 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.32 (s, 2H), 3.72 (d, *J* = 13.0 Hz, 2H), 3.53 (d, *J* = 12.0 Hz, 2H), 3.45 – 3.22 (m, 4H), 3.21 – 3.04 (m, 6H), 2.71 (s, 2H), 1.79 – 1.63 (m, 2H), 1.51 (p, *J* = 7.5 Hz, 2H), 1.39 (d, *J* = 9.7 Hz, 1H), 1.14 (d, *J* = 9.7 Hz, 1H). MS (ESI) *m/z* = 460.4 ($[M+H]^+$).

4.1.2.10.

*(3aR,4R,7S,7aS)-2-(4-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)butyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3j**).* The title compound was prepared from 3-(piperazin-1-yl)benzo[*d*]isothiazole hydrochloride and **2b** as a white solid. Yield 37%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 8.17 – 8.07 (m, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 6.32 (s, 2H), 4.06 (d, *J* = 13.4 Hz, 2H), 3.62 – 3.36 (m, 6H), 3.31 – 3.07 (m, 6H), 2.71 (s, 2H), 1.80 – 1.65 (m, 2H), 1.53 (p, *J* = 7.5 Hz, 2H), 1.39 (d, *J* = 9.6 Hz, 1H), 1.14 (d, *J* = 9.6 Hz, 1H). MS (ESI) *m/z* = 437.3 ($[M+H]^+$).

4.1.2.11

(3aR,4R,7S,7aS)-2-(2-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)ethyl)-3a,4,7,7a-tetrahydro-1H-4,7-me

*thanoisoindole-1,3(2H)-dione hydrochloride (**3k**).* The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2l** as a white solid. Yield 64%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.42 (s, 1H), 7.76 (d, *J* = 5.5 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 5.5 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.32 (s, 2H), 3.84 (t, *J* = 6.3 Hz, 2H), 3.68 (d, *J* = 10.3 Hz, 2H), 3.53 (d, *J* = 10.9 Hz, 2H), 3.44 – 3.20 (m, 6H), 3.10 (s, 2H), 2.78 (s, 2H), 1.38 (d, *J* = 9.6 Hz, 1H), 1.22 (d, *J* = 9.6 Hz, 1H). MS (ESI) *m/z* = 408.0 ([M+H]$^+$).

4.1.2.12.

*(3aR,4R,7S,7aS)-2-(3-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)propyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3l**).* The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2m** as a white solid. Yield 85%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.36 (s, 1H), 7.76 (d, *J* = 5.5 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 5.5 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.32 (s, 2H), 3.64 – 3.40 (m, 6H), 3.37 – 3.07 (m, 8H), 2.72 (s, 2H), 2.07 – 1.92 (m, 2H), 1.39 (d, *J* = 9.8 Hz, 1H), 1.18 (d, *J* = 9.8 Hz, 1H). MS (ESI) *m/z* = 421.9 ([M+H]$^+$).

4.1.2.13.

*(3aR,4R,7S,7aS)-2-(5-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)pentyl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione hydrochloride (**3m**).* The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2n** as a white solid. Yield 56%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 7.76 (d, *J* = 5.5 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 5.5 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.35 – 6.28 (m, 2H), 3.62 – 3.48 (m, 4H), 3.38 (t, *J* = 7.2 Hz, 2H), 3.35 – 3.17 (m, 4H), 3.17 – 3.06 (m, 4H), 2.71 (s, 2H), 1.84 – 1.71 (m, 2H), 1.52 (p, *J* = 7.4 Hz, 2H), 1.39 (d, *J* = 9.7 Hz, 1H), 1.35 – 1.25 (m, 2H), 1.13 (d, *J* = 9.6 Hz, 1H). MS (ESI) *m/z* = 450.4 ([M+H]$^+$).

4.1.2.14.

*3-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione hydrochloride (**3n**).* The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2c** as a white solid. Yield 66%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.71 (s, 1H), 7.77 (d, *J* = 5.5 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 5.5 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 3.64 – 3.46 (m, 4H), 3.38 – 3.10 (m, 8H), 2.54 (s, 2H), 1.80 – 1.65 (m, 2H), 1.50 (p, *J* = 7.5 Hz, 2H), 1.20 (s, 3H), 1.12 (s, 3H). MS (ESI) *m/z* = 412.4 ([M+H]$^+$).

4.1.2.15.

*3-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-1-(p-tolyl)-3-azabicyclo[3.1.0]hexane-2,4-dione hydrochloride (**3o**)*. The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2d** as a white solid. Yield 53%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 7.76 (d, *J* = 5.4 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 5.4 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 2H), 6.96 (d, *J* = 7.7 Hz, 1H), 3.62 – 3.46 (m, 4H), 3.40 – 3.19 (m, 6H), 3.20 – 3.08 (m, 2H), 2.93 (dd, *J* = 8.3, 3.5 Hz, 1H), 2.29 (s, 3H), 2.04 (t, *J* = 4.1 Hz, 1H), 1.92 (dd, *J* = 8.3, 4.5 Hz, 1H), 1.79 – 1.67 (m, 2H), 1.59 – 1.47 (m, 2H). MS (ESI) *m/z* = 474.3 ([M+H]$^+$).

4.1.2.16.

*2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)tetrahydrocyclopenta[c]pyrrole-1,3(2H,3aH)-dione hydrochloride (**3p**)*. The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2e** as a white solid. Yield 70%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 7.77 (d, *J* = 5.5 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 5.5 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 3.62 – 3.48 (m, 4H), 3.40 (t, *J* = 7.0 Hz, 2H), 3.34 – 3.08 (m, 8H), 1.97 – 1.61 (m, 7H), 1.53 (p, *J* = 7.3 Hz, 2H), 1.29 – 1.12 (m, 1H). MS (ESI) *m/z* = 412.3 ([M+H]$^+$).

*4.1.2.17. 2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)hexahydro-1H-isoindole-1,3(2H)-dione hydrochloride (**3q**)*. The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2f** as a white solid. Yield 55%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 7.77 (d, *J* = 5.5 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 5.5 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 3.67 – 3.48 (m, 4H), 3.42 (t, *J* = 6.9 Hz, 2H), 3.24 – 3.08 (m, 4H), 3.01 – 2.90 (m, 2H), 1.83 – 1.48 (m, 8H), 1.48 – 1.19 (m, 4H). MS (ESI) *m/z* = 426.4 ([M+H]$^+$).

4.1.2.17.

*2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione hydrochloride (**3r**)*. The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2g** as a white solid. Yield 45%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.32 (s, 1H), 7.76 (d, *J* = 5.5 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 5.5 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 5.96 – 5.84 (m, 2H), 3.58 – 3.47 (m, 4H), 3.39 (t, *J* = 6.8 Hz, 2H), 3.35 – 3.06 (m, 8H), 2.47 – 2.35 (m, 2H), 2.18 (dt, *J* = 14.6, 4.4 Hz, 2H), 1.78 – 1.59 (m, 2H), 1.51 (q, *J* = 7.0 Hz, 2H). MS (ESI) *m/z* = 424.4 ([M+H]$^+$).

*4.1.2.18. 1-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-4,4-dimethylpiperidine-2,6-dione hydrochloride (**3s**).* The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2h** as a white solid. Yield 62%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 7.77 (d, J = 5.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 5.5 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H), 3.69 (t, J = 7.3 Hz, 2H), 3.62 – 3.47 (m, 4H), 3.36 – 3.10 (m, 6H), 2.55 (s, 4H), 1.80 – 1.66 (m, 2H), 1.49 (p, J = 7.6 Hz, 2H), 0.99 (s, 6H). MS (ESI) *m/z* = 414.3 ([M+H]$^+$).

*4.1.2.19. 1-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-4-ethyl-4-methylpiperidine-2,6-dione hydrochloride (**3t**).* The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2i** as a white solid. Yield 47%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.20 (s, 1H), 7.77 (d, J = 5.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 5.6 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 3.68 (t, J = 7.3 Hz, 2H), 3.59 – 3.45 (m, 4H), 3.26 (d, J = 9.0 Hz, 4H), 3.20 – 3.06 (m, 2H), 2.66 – 2.42 (m, 4H), 1.83 – 1.65 (m, 2H), 1.48 (p, J = 7.4 Hz, 2H), 1.31 (q, J = 7.4 Hz, 2H), 0.92 (s, 3H), 0.81 (t, J = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 172.05, 146.50, 140.59, 133.30, 126.51, 125.04, 121.71, 117.68, 112.53, 54.99, 51.03, 48.31, 43.51, 37.91, 32.44, 31.40, 24.76, 23.46, 20.58, 7.80. MS (ESI) *m/z* = 428.4 ([M+H]$^+$). HRMS (ESI) *m/z* calcd for $C_{24}H_{34}N_3O_2S$ ([M+H]$^+$), 428.2366; found 428.2372.

*4.1.2.20. 8-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-8-azaspiro[4.5]decane-7,9-dione hydrochloride (**3u**).* The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2j** as a white solid. Yield 59%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.27 (s, 1H), 7.76 (d, J = 5.5 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 5.5 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 3.67 (t, J = 7.2 Hz, 2H), 3.61 – 3.42 (m, 4H), 3.38 – 3.20 (m, 4H), 3.19 – 3.08 (m, 2H), 2.63 (s, 4H), 1.83 – 1.67 (m, 2H), 1.67 – 1.57 (m, 4H), 1.54 – 1.36 (m, 6H). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 172.22, 146.51, 140.60, 133.31, 126.52, 125.05, 121.72, 117.69, 112.54, 55.03, 51.08, 48.34, 43.83, 37.92, 36.85, 24.82, 23.68, 20.58. MS (ESI) *m/z* = 440.4 ([M+H]$^+$). HRMS (ESI) *m/z* calcd for $C_{25}H_{34}N_3O_2S$ ([M+H]$^+$), 440.2366; found 440.2366.

*4.1.2.21. 3-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-3-azaspiro[5.5]undecane-2,4-dione hydrochloride (**3v**).* The title compound was prepared from 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride and **2k** as a white solid. Yield 61%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 7.77 (d, J = 5.5 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 5.5 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 3.67 (t, J = 7.4 Hz, 2H), 3.61 – 3.47 (m, 4H), 3.32 – 3.12 (m, 6H), 2.61 (s, 4H), 1.79 – 1.64 (m, 2H), 1.56 – 1.24 (m, 12H). MS (ESI) *m/z* = 454.4 ($[M+H]^+$).

*4.1.3. preparation of compounds **4a**, **4b** and **5a**.*

*4.1.3.1. 2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-5,6-dihydroxyhexahydro-1H-isoindole-1,3(2H)-dione (**4a**)*

Free base of **3r** (424 mg, 1 mmol) was dissolved in acetone (10 mL), cooling to 0 °C, and potassium permanganate aqueous solution (25 mL, contain potassium permanganate 158 mg) was added dropwise. Then the reaction mixture was stirred at room temperature for 30 min, extracted with ethyl acetate (40 mL). The aqueous layer was filtered, saturated with NaCl, exacted with ethyl acetate (2 × 30 mL). The organic phase was combined, dried over anhydrous Na_2SO_4, purified by column chromatography using DCM : MeOH (100:1 – 10:1) as eluent to give **4a** (200 mg, 44%) as a white foamed solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.69 (d, *J* = 5.4 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 5.4 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 4.70 – 4.64 (m, 2H), 3.51 – 3.41 (m, 2H), 3.37 (d, *J* = 6.3 Hz, 2H), 3.13 – 2.94 (m, 6H), 2.58 (s, 4H), 2.36 (t, *J* = 6.7 Hz, 2H), 2.00 – 1.83 (m, 2H), 1.71 – 1.32 (m, 6H). MS (ESI) *m/z* = 458.4 ($[M+H]^+$).

*4.1.3.2. (3aR,4S,5S,6R,7R,7aS)-2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-5,6-dihydroxyhexahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**4b**)*

Following the same procedure as **4a**, compound **4b** was prepared from the free base of **3d** as a white solid. Yield 35%; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 5.5 Hz, 1H), 7.36 (d, *J* = 5.5 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 3.87 – 3.82 (m, 2H), 3.58 – 3.49 (m, 2H), 3.29 (s, 4H), 2.88 (s, 4H), 2.68 – 2.53 (m, 6H), 1.84 (d, *J* = 11.8 Hz, 1H), 1.73 – 1.58 (m, 4H), 0.99 (d, *J* = 11.8 Hz, 1H). MS (ESI) *m/z* = 470.4 ($[M+H]^+$).

*4.1.3.3. (3aR,4S,5S,6R,7R,7aS)-2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-1,3-dioxooctahydro-1H-4,7-methanoisoindole-5,6-diyl diacetate (**5a**)*

4b (127 mg, 0.27 mmol) was dissolved in pyridine (3 mL), and then Ac_2O (127 μL, 1.35 mmol) was added dropwise, stirred at room temperature for 24 h. The solvent was evaporated under vacuum, and the residue was partitioned between ethyl acetate (30 mL) and water (20 mL). The organic layer was washed successively with water and saturated brine, dried over anhydrous Na_2SO_4, purified by column chromatography using DCM : MeOH (100:1 – 20:1) as eluent to give **5a** (100 mg, 67%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, *J* = 5.5 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 5.5 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 4.87 (s, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 3.08 (s, 4H), 2.89 (s, 2H), 2.75 – 2.28 (m, 6H), 2.01 (s, 6H), 1.73 (d, *J* = 11.7 Hz, 1H), 1.59 – 1.33 (m, 4H), 1.06 (d, *J* = 11.7 Hz, 1H). MS (ESI) *m/z* = 554.3 ($[M+H]^+$).

*4.1.4. Preparation of compounds **8a–e**.*

*4.1.4.1. 2-(4-bromobutyl)isoindoline-1,3-dione (**7a**)*

Phthalimide **6a** (148 mg, 1 mmol), 1,4-dibromobutane (1.080 g, 5 mmol), potassium carbonate (276 mg, 2 mmol) was added to acetone (3 mL), and the reaction mixture was refluxed for 2 h. After cooling to room temperature, the reaction mixture was purified by column chromatography using PE : acetone (40:1) as eluent to give **7a** (185 mg, 66%) as a white solid.

*4.1.4.2. 2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)isoindoline-1,3-dione (**8a**)*

7a (89 mg, 0.32 mmol), 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride (107 mg, 0.42 mmol), potassium carbonate (88 mg, 0.64 mmol) and potassium iodide (27 mg, 0.16 mmol) was added into MeCN (5 mL). The reaction mixture was refluxed for 5 h, cooled to room temperature, and then purified by column chromatography using DCM : MeOH (70:1) as eluent to give **8a** (117 mg, 87%) as light yellow oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.90 – 7.79 (m, 2H), 7.76 – 7.66 (m, 2H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.30 – 7.22 (m, 1H), 6.88 (dd, *J* = 7.7, 0.9 Hz, 1H), 3.74 (t, *J* = 7.0 Hz, 2H), 3.23 – 3.11 (m, 4H), 2.77 – 2.61 (m, 4H), 2.55 – 2.43 (m, 2H), 1.85 – 1.52 (m, 4H). MS (ESI) *m/z* = 420.4 ($[M+H]^+$).

*4.1.4.3. 2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-4-fluoroisoindoline-1,3-dione hydrochloride (**8b**)*

The title compound was prepared from **6b** following the procedure described for the synthesis of compound **8a** as a white solid in hydrochloride salt form. Yield 97%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.95 – 7.84 (m, 1H), 7.80 – 7.63 (m, 4H), 7.48 (d, *J* = 5.5 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 3.72 – 3.47 (m, 6H), 3.40 – 3.10 (m, 6H), 1.89 – 1.60 (m, 4H). MS (ESI) *m/z* = 438.3 ($[M+H]^+$).

*4.1.4.4. 2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-5-fluoroisoindoline-1,3-dione hydrochloride (**8c**)*

The title compound was prepared from **6c** following the procedure described for the synthesis of compound **8a** as a white solid in hydrochloride salt form. Yield 60%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.95 – 7.84 (m, 1H), 7.80 – 7.63 (m, 4H), 7.48 (d, *J* = 5.5 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 3.72 – 3.47 (m, 6H), 3.40 – 3.10 (m, 6H), 1.89 – 1.60 (m, 4H). MS (ESI) *m/z* = 438.3 ($[M+H]^+$).

*4.1.4.5. 2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-4-chloroisoindoline-1,3-dione (**8d**)*

The title compound was prepared from **6d** following the procedure described for the synthesis of compound **8a** as a light yellow solid in hydrochloride salt form. Yield 55%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 – 7.78 (m, 3H), 7.68 (d, *J* = 5.5 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 5.5 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 3.60 (t, *J* = 6.9 Hz, 2H), 3.04 (s, 4H), 2.58 (s, 4H), 2.38 (t, *J* = 7.1 Hz, 2H), 1.65 (p, *J* = 7.1 Hz, 2H), 1.49 (p, *J* = 7.1 Hz, 2H). MS (ESI) *m/z* = 454.3 ($[M+H]^+$).

*4.1.4.6. 2-(4-(4-(benzo[b]thiophen-4-yl)piperazin-1-yl)butyl)-5-chloroisoindoline-1,3-dione hydrochloride (**8e**)*

The title compound was prepared from **6e** following the procedure described for the synthesis of compound **8a** as a white solid in hydrochloride salt form. Yield 40%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28 (s, 1H), 7.98 (s, 1H), 7.91 (s, 2H), 7.77 (d, *J* = 5.5 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 5.6 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 3.73 – 3.44 (m, 6H), 3.14 (d, *J* = 20.1 Hz, 6H), 1.87 – 1.59 (m, 4H). MS (ESI) *m/z* = 454.2 ($[M+H]^+$).

4.2. Biological evaluation

4.2.1. Functional activity Assays

All the compounds were screened on 5-HT_{1A} agonist & D_2 antagonist mode assays using LANCE® Ultra. Some compounds were screened on H_1, M_3, α_{1A}, 5-HT_{2A}, 5-HT_{2C} antagonist mode assays using FLIPR. Refenrence compounds for D_2, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, H_1, M_3, α_{1A} receptor functional assays were risperidone, 8-OH-DPAT, risperidone, methysergide, pyrilamine, atropine and WB4101 respectively.

Lance Ultra cAMP assay:

1) Transfer compound to assay plate by Echo;

2) Collect cells with stimulation buffer;

3) Reaction: a) Transfer 10 µl of cell solution to assay plate, b) Centrifuge at 600 rpm for 3 minutes and incubate 60 minutes at room temperature, c) Add 5 µl 4X Eu-cAMP trace solution and 5 µL 4X

ULight^{TM}-anti-cAMP solution to assay plate, d) Centrifuge at 600 rpm for 3 minutes and incubate 60 minutes at room temperature.

4) Reading plate on EnVision.

FLIPR assay:

1) Seed cells at the density of 10K cell/well, 37°C, 5% CO_2 incubates for 16-24 hours;

2) Loading cells with 30 uL of Calcium 5 and 37°C, 5% CO_2 incubates for 1 hours;

3) Tranfer compound to compound plate with 30 μL Assay Buffer by Echo;

4) Add 15 μL/well of compound and incubate for 10min at room temperature;

5) Add 22.5 μL/well of inducer and measure calcium flux signal with FLIPR.

4.2.2. hERG assay

Selected compounds was tested for effect on hERG potassium channels by automated patch clamp method (QPatch^{HTX}, Sophion, Stockholm, Sweden) at WuXi AppTec (Shanghai, China).

4.2.3. Behavioral studies

4.2.3.1. PCP-induced hyperlocomotion.

Male ICR mice (18~22 g, 6 mice in each group) were used. Animals were individually placed into a Plexiglas open field arena (40 × 40 × 45 cm) for 45 min after intragastric administration of the test compounds (1, 3 and 10 mg/kg) or aripiprazole (3 mg/kg), animals were treated with PCP (7 mg/kg, i.p.), and placed back into the experimental apparatus. Animals were habituated for 10 min before the 75 min measurement period. Results are expressed as the means ± SEM of distance traveled. Statistical evaluation was performed by two-way ANOVA followed by student's t test for multiple comparisons. *$p < 0.05$ versus PCP treatment; **$p < 0.01$ versus PCP treatment; ***$p < 0.001$ versus PCP treatment; ###$p < 0.001$ versus vehicle treatment.

4.2.3.2. Catalepsy test

Mice were orally dosed with vehicle or test compounds. Catalepsy was evaluated on a metal bar 0.3 cm in diameter positioned 4.5 cm above the tabletop. The test consisted in positioning the animal with its forepaws on the bar and recording how long it remained hanging onto the bar. A mean immobility score of 20 s was used as the criterion for the presence of catalepsy.

4.2.3.3. Quipazine-induced head twitches

ICR mice (18~30 g, 7 mice/dose/test compound) were fasted for 12 h and then placed in individual cells of a clear Lucite box. Varing dose of test compounds or normal saline were given i.g.

30 min before s.c. administration of quipazine (5 mg/kg). The behavioral observation was initiated 30 min after quipazine treatment, The number of stereotyped head twitch movements was counted for each mouse by a trained observer over a 15 min period. The results were shown as means ± SEM and compared with one-way analysis of variance, with intergroup comparisons for individual compounds being calculated with Dunnett’s test.

4.2.3.4. Pharmacokinetic study

Pharmacokinetic studies were performed in male SD rats (3 in each group) weighing 200g ~ 250 g. Pharmacokinetic parameters were obtained by single intravenous (i.v.) and p.o. administration of the test compound 10 mg/kg. The test compound was dissolved in mixed solution of DMSO (5%), PEG400 (40%) and normal saline (55%). Heparinized samples of blood were collected at 5 min, 15min, 30 min, 1 h, 2 h, 4 h, 8 h and 24 h after oral or intravenous administration. Plasma was obtained after centrifugation (8000 rpm, 6min, 2~8 °C) and stored frozen at −80°C for analysis. Plasma samples were analyzed by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS).

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Research highlights

- A series of N-substituted cyclic imide derivatives was synthesized.
- Four compounds were evaluated for activities on 5-HT_{2C}, H_1, α_{1A}, M_3 receptors and hERG channel.
- Compound **3d** showed excellent efficacy in animal behavioral studies of schizophrenia.
- Compound **3d** possessed acceptable pharmacokinetic properties.
- Compound **3d** was a promising antipsychotic candidate.