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Synthesis and biological evaluation of fused tricyclic heterocycle piperazine (piperidine) derivatives as potential multi-receptor atypical antipsychotics

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ABSTRACT

Herein, a novel series of multi-receptor ligands was developed as polypharmacological antipsychotic agents using the designed multiple ligand approach between dopamine receptors and serotonin receptors. Among them, compound **47** possessed unique pharmacological features, exhibiting high affinities for D_2, D_3, 5-HT_{1A}, 5-HT_{2A} and 5-HT_6 receptors and low efficacy at the off-target receptors (5-HT_{2C}, histamine H_1, and adrenergic α_1 receptor). Compound **47** showed dose-dependent inhibition of apomorphine- and MK-801-induced motor behavior, and the conditioned avoidance response with low cataleptic effect. Moreover, compound **47** resulted nonsignificantly serum prolactin levels and weight gain change compared with risperidone. Additionally, compound **47** possessed a favorable pharmacokinetic profile with oral bioavailability of 58.8% in rats. Furthermore, compound **47** displayed pro-cognition properties in a novel object recognition task in rats. Taken together, compound **47** may constitute a novel class of atypical antipsychotic drugs for schizophrenia.

INTRODUCTION

Schizophrenia is a chronic neuropsychiatric disorder affecting approximately 1% of the global population[1] and is characterized by a combination of positive symptoms (such as hallucinations and delusions), negative symptoms (such as avolition and psychomotor poverty), disordered thoughts, and cognitive deficits.[2] After nearly a century of research, the etiology and pathophysiology of schizophrenia remain largely unresolved.[3] Adequate treatment for schizophrenia remains a challenge due to the complex pathophysiology.[4] Yet, hyper- and hypo-function of the dopaminergic signal transduction system clearly contribute to some of the symptoms of this disorder. The structures of the dopamine D_2 receptors bound to risperidone have revealed distinct extended binding sites that could shed light on how to design or discover new drugs with fewer side effects than existing therapeutics.[5] Furthermore, all current antipsychotic medications act by blocking dopamine D_2 receptors, which drives their efficacy in treating the positive symptoms of the condition.[6] Despite tremendous progress in the management of schizophrenia since the introduction of current therapies, the so-called "typical" and "atypical" antipsychotics still suffer from several liabilities that limit their overall effectiveness in patients.[7] Chlorpromazine and haloperidol are typical antipsychotics with potential antagonistic activity to D_2 receptor. (**Figure 1**). Although these agents are effective for controlling some of the positive symptoms postulated to arise from hyperdopaminergia in the mesolimbic pathway of the brain, they are relatively ineffective and may exacerbate negative symptoms as well as cognitive dysfunction.[8] Use of these agents also causes

extrapyramidal symptoms (EPSs), including tardive dyskinesia and hyperprolactinemia.[9] This profile, along with unwanted side effects, has led to find the new therapeutic strategies, such as favorable polypharmacology, including the development of multi-receptor agents which targeting specific dopamine receptor subtypes or a range of receptors, and the discovery of new ligands with a selectivity between 5-hydroxytryptamine (5-HT; serotonin) receptors and D_2 receptors, with the aim to improve therapeutic profile.[10] Indeed, second-generation antipsychotics (SGAs) (also known as "atypical drugs"), such as clozapine and olanzapine, show favorable polypharmacology effects (**Figure 1**).[11]

All SGAs antagonize the dopamine D_2 receptor and are effective in alleviating the positive symptoms of schizophrenia.[6] Due to their high affinity for serotonin receptors, particularly the 5-HT_{1A} and 5-HT_{2A} receptors, these agents have also been shown to treat the positive symptoms, such as hallucinations and delusions with fewer EPSs.[12] First, 5-HT_{1A} receptor agonism alleviates the EPS side effects of antipsychotics by activating 5-HT_{1A} receptors located in the primary motor cortex and dorsolateral striatum region.[13] Second, in the frontal cortex, dopamine release is increased by the activation of the postsynaptic 5-HT_{1A} receptor, thus potentiating functions of the mesocortical dopamine pathway, which may inprove negative symptoms and cognitive deficits in schizophrenia patients.[14c,d] Furthermore, multiple preclinical studies supported the hypothesis that 5-HT_{1A} receptor antagonists may reverse cognitive deficits though its ability to both enhance stimulated glutamate efflux and stimulated acetylcholine levels. [14a,b,c] The 5-HT_{2A} receptor is widely

expressed in the brain, interacts with neurotransmitter systems, especially acts on dopaminergic neurotransmission. Blocking the serotonin 5-HT_{2A} receptor counteracted the effect of D_2 receptor blockade in striatum, thus alleviates the EPS side effects.[12] Moreover, 5-HT_{2A} receptor antagonism has been implicated in the enhanced efficacy against negative schizophrenic symptoms.[12a,b] It is now apparent that these SGAs, including clozapine and olanzapine, are antagonists at both 5-HT_{2A} and dopamine D_2 receptors and that activity at both of these receptors is necessary for the antipsychotic efficacy of this class of drugs.[15] However, the favorable polypharmacology observed with many atypical antipsychotics was achieved through a serendipitous discovery rather than a rational drug design process.[11] Treatment with these atypical antipsychotics is accompanied by various other risks, such as excessive weight gain, hyperglycemia and abnormal blood lipid,[16] which are primarily caused by high affinity binding to other off-target receptors, such as the histamine H_1 receptor, the 5-HT_{2C} receptor, and the α_1-adrenoceptor.[17–19] Moreover, no current antipsychotic drug addresses the cognitive deficits associated with schizophrenia, which is an equally important component in the etiology of schizophrenia.[10]

Current hypotheses suggest that cognition-enhancing actions may be due to interactions with the 5-HT_6 or D_3 receptor.[11] The 5-HT_6 receptor modulates multiple neurotransmitter systems possibly linked with the cognitive dysfunction of schizophrenia.[12a, 20] Blocking the 5-HT_6 receptor not only enhances prefrontal cortical dopamine release, but may also modulate glutamatergic systems by disinhibiting GABAergic neurons in the frontal cortex.[21] Given this ability of the 5-HT_6 receptor, a

large amount of scientific data have indicated that 5-HT_6 receptor ligands are effective procognitive agents in preclinical studies.[22] Although the role of this receptor in the regulation of psychotic symptoms is currently unclear, it may result in cognitive improvements though the way: blockade of D_3 recepor in the frontal cortex may enhance acetylcholine release.[23] Preclinical studies suggest that the D_3 receptor may be proposed as a high pharmacotherapeutic target and D_3 receptor ligands may constitute a promising approach to treat the negative and cognitive symptoms in schizophrenia and drug abuse disorders.[24]

These observations encouraged us to design multi-target ligands that can precisely modulate the activity of several monoaminergic receptors (D_2, D_3, 5-HT_{1A}, 5-HT_{2A} and 5-HT_6 receptors), expecting that this multifunctional profile will contribute to the therapeutic potential for patients with schizophrenia.[22] This three receptors (D_2, 5-HT_{1A} and 5-HT_{2A}) have been identified as crucial molecular targets in the development of new potential anti-psychotic agents because drugs acting via these targets effectively treat the positive and negative symptoms. The pharmacological profile of the newly designed molecules with high affinities for the D_3 and 5-HT_6 receptors is presumed to be improved and enhanced with procognitive activities. Herein, we present the design, synthesis and bio-evaluation of a series of heterocyclic piperazine (piperidine) analogues as multimodal agents. The most promising molecule in the whole series was further characterized in extended pharmacological studies.

Tricyclic scaffolds containing an indole and indoline moiety have been barely explored in medicinal chemistry. Compounds based on the pyrano[2,3,4-cd]indole

scaffold show high affinity for the 5-HT_6 receptor.[25] A series of potent and selective CYP11B1 inhibitors based on the heteroaryl substituted 1,2,5,6-tetrahydro pyrrolo[3,2,1-ij]quinolin-4-ones have been reported to treat Cushing's syndrome.[26] Ligands based on the fused tricyclics with substituted 3-(piperidin-4-yl)-1H-indole that show high binding to D_2, 5-HT_{2A} and the human serotonin transporter (hSERT) have been reported by Pfizer.[27] The structure of compound **1** displays key pharmacophoric features of many D_2 receptor ligands shown in an earlier publication (**Figure 2**).[28]

Therefore, using the tricyclic heterocycle structure of compound **1** as the primary scaffold, the privileged structures from known antipsychotic drugs were introduced into new compounds that simultaneously modulate several receptors using the designed multiple ligand approach described by Morphy. This approach takes two separate pharmacophores with distinct pharmacology and integrates them into one molecule with the attributes of both parent molecules.[10a, 29] The privileged structures from known antipsychotic drugs were covered (**Figure 3**): (1) phenylpiperazines, which are known to be important motifs for the functional activity of antipsychotics; the preclinical and clinical tests demonstrated that compounds incorporating the 2,3-dichlorophenylpiperazine and 2-methoxyphenylpiperazine scaffolds are useful in the design of atypical antipsychotics;[28a] and (2) benzisoxazoles and benzoisothiazoles, which are important fragments, and some medications containing these moieties have been approved for human clinical use, including atypical antipsychotics (risperidone, paliperidone, ziprasidone, and lurasidone). The activities of the piperazine or

piperidine moiety at D_2 and 5-HT_{2A} receptors followed by similar structural heterocycles have proven useful for antipsychotic efficacy.[30] Moreover, the appropriate linker between the tricyclic heterocycles and the privileged structures is important for new compounds binding to the desired multi-receptors (D_2, D_3, 5-HT_{1A}, 5-HT_{2A} and 5-HT_6 receptors).

A series of new compounds in **Tables 1–5** was prepared by this strategy, which were used to identify their pharmacological affinities and determine binding specificity for the multiple receptors in structure–activity relationship studies. Among the derivatives prepared, compound **47** not only exhibited high affinity for the desired multi-target, but was also endowed with low to moderate activities on off-target receptors (5-HT_{2C}, H_1 and α_1 receptors) and low hERG channel inhibitiomn. Furthermore, compound **47** reversed significantly apomorphine-induced and MK-801-induced motor behavior with a low propensity to induce catalepsy. In addition, compound **47** led to negligible weight gain and resulted nonsignificantly serum prolactin levels change compared with risperidone. Moreover, compound **47** displayed procognitive properties in a novel object recognition task in rats and showed favorable pharmacokinetic properties. Thus, compound **47** was developed as atypical antipsychotics to validate the novel approach to treat schizophrenia based on its unique polypharmacological antipsychotic profile.

CHEMISTRY

The syntheses of **3–54** are shown in Schemes **1** and **2**. The new compounds

8–22, 24, 29–33, and **37–54** were prepared by synthetic route shown in Scheme **1**. Tricyclic heterocycle core **3** was synthesized as the initial building block from commercially available 1,2,3,4-tetrahydroquinoline or 2,3-dihydro-1*H*-indole via N-acylation with 3-chloropropionyl chloride and subsequent Friedel–Crafts cyclization with $AlCl_3$ under molten conditions. The central building blocks **4** and **6** were produced with the Friedel–Crafts acylation reaction and an appropriate amount of chloroalkyl chloride. As shown in Scheme **1**, compounds **8–22, 24,** and **37–48** were prepared by coupling **4** or **6** with corresponding arylpiperazines or arylpiperidines in CH_3CN. Compounds **29–33** and **49–51** were prepared though two method routes. The final compounds were obtained by catalytic reduction of their corresponding ketone precursors in the presence of triethylsilicon hydride (Et_3SiH) and trifluoroacetic acid (TFA) from method A. According to method B, the intermediates **5** and **7** were obtained from the reduction reaction of the corresponding intermediates **4** and **6**, followed by a reaction with the corresponding arylpiperazines or arylpiperidines to afford the target compounds. Compounds **35, 36,** and **52–54** were yielded after further reduction of their ketone precursors in the presence of $NaBH_4$.

The methyl group-substituted tricyclic heterocycle compounds **23** and **34** was prepared though the route depicted in Scheme **2**. Intermediate **25** was prepared starting from 1,2,3,4-tetrahydroquinoline and treatment with ethyl acetoacetate and subsequent sulfuric acid-mediated cyclization to afford the methyl group substituted tricyclic heterocycle **26**. The key building block **27** was obtained by reduction with Pd/C, which was subsequently coupled with 4-chlorobutanoyl to give the

corresponding ketone **28**. Final compound **23** was prepared by coupling **28** with 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole in CH_3CN, and compound **34** was yielded after further reduction of compound **23**.

RESULTS AND DISCUSSION

Structure–activity relationships

As previously noted, most of the presently approved atypical antipsychotic drugs exhibit polypharmacology, with appreciable affinities for a variety of biogenic amine receptors (such as D_2, 5-HT_{1A} and 5-HT_{2A} receptors). Due to their multi-receptors affinities, ligands contained different chemical groups are of high pharmacotherapeutic interest in schizophrenia, which has been extensively developed as a potential strategy to find a novel antipsychotics. In this study, a class of new compounds by introducing different privileged structures were characterized the binding to the D_2, 5-HT_{1A} and 5-HT_{2A} receptors.

Effect of the tricyclic heterocycle (containing 1,2,3,4-tetrahydroquinoline) on different privileged structures

In this study, our starting point focused on the impact of various privileged structures (**Table 1**, compounds **9**–**18**). Compound **9** bearing a phenylpiperazine exhibited weak binding to D_2 and 5-HT_{1A} receptors at micromolar concentrations (D_2, K_i = 1764.8 ± 212.4 nM; 5-HT_{1A}, K_i = 1856.2 ± 208.1 nM), with low activity to 5-HT_{2A} receptor (K_i = 752.3 ± 121.2 nM). Replacing the phenyl ring with its bioisostere, pyridine (**10**) and pyrimidine (**11**), resulted in similar affinities as shown

for compound **9**, while a low 5-HT_{2A} affinity for the two compounds was observed (**10**, K_i = 675.2 ± 102.4 nM; **11**, K_i = 557.4 ± 84.6 nM). Compound **12** showed decreased D_2 receptor binding affinity when the methoxy groups was introduced in the ortho position of phenylpiperazine, while 5-HT_{1A} receptor binding affinity increased slightly (K_i = 964.8 ± 125.3 nM), and a good 5-HT_{2A} receptor affinity with with K_i values of 178.2 ± 28.5 nM was obtained, compared to compound **9**. Compound **13** exhibited good 5-HT_{1A} and 5-HT_{2A} receptors affinities with K_i of 196.1 ± 21.3 nM and 207.3 ± 23.4 nM after replacing 2,3-dimethylphenylpiperazine, compared with risperidone, but weak binding to the D_2 receptor. Introducing a chlorine atom to the 4-position (**14**) of the phenyl ring did not change the receptor profile compared with that of compound **9**. Derivative **15** of the 2,3-di-Cl-substituted counterpart maintained potent activities on the 5-HT_{1A} and 5-HT_{2A} receptors with K_i of 268.6 ± 30.1 nM and 207.4 ± 28.3 nM, respectively. When the privileged structure phenylpiperazine was replaced with heterocyclic piperazine, compound **16** with 3-(piperazin-1-yl)benzo[d]isothiazole, a remarkable increase in activity for the D_2 receptor (K_i = 182.1 ± 14.2 nM), and good binding activitie to the 5-HT_{1A} (K_i = 128.7 ± 13.0 nM) and 5-HT_{2A} (K_i = 72.0 ± 8.2 nM) were observed, compared with compound **9**. Compounds **17** and **18** showed different affinities for the main targets when piperazine was replaced by piperidine. Compound **17** with piperidine resulted in a decrease in D_2 (K_i = 861.2 ± 54.6 nM), 5-HT_{1A} (K_i = 392.0 ± 43.2 nM) and 5-HT_{2A} (K_i = 173.0 ± 28.1 nM) receptor potency by four-, three-, and two-fold, respectively, compared with compound **16**. Interestingly, transforming the benzo[d]thiazole moiety

to an oxygen-containing benzoheterocycle, such as 6-fluorobenzo[d]isoxazole, in compound **18** resulted in an increase in D_2 (K_i = 58.2 ± 6.4 nM) and 5-HT_{1A} (K_i = 62.9 ± 7.3 nM) receptor potency by three- and two-fold, while 5-HT_{2A} (K_i = 52.3 ± 5.8 nM) receptor potency increased only slightly, compared to compound **16**.

Effect of the different linkers between the tricyclic heterocycle (containing 1,2,3,4-tetrahydroquinoline) and privileged structures

The optimal linker between the tricyclic heterocycle containing 1,2,3,4-tetrahydroquinoline and the privileged structures was determined in compound **18**. As shown in **Table 2**, when 4-chlorobutyryl chloride was introduced and the linker was changed to a longer (4-unit) alkyl chain, compound **19**, bearing 2,3-dimethylphenylpiperazine, and compound **20**, containing 2,3-dichlorophenyl piperazine, showed similar affinity for 5-HT_{1A}, while D_2 and 5-HT_{1A} receptor potency decreased slightly (D_2, K_i = 185.2 ± 19.5 nM; 5-HT_{1A}, K_i = 169.2 ± 17.6 nM for **19**; D_2, K_i = 282.5 ± 30.6 nM; 5-HT_{1A}, K_i = 149.4 ± 16.7 nM for **20**), compared to compound **18**. The privileged structures in ziprasidone and risperidone revealed slightly different heterocycles (benzoisothiazole vs. benzoisoxazole), and compound **21** bearing benzoisothiazole showed increased affinity for the D_2 receptor (K_i = 91.4 ± 10.7 nM). In addition, both the replacement S with O atom for the heterocycles and the benzothiazole with a powerful electron-withdrawing substituent (fluorine atom) on the aromatic ring while benzoisoxazole without F at the same position may have made compound **22** more favorable for the three receptors compared with compound **21**. Substituting a hydrogen atom at the R_3 position for a methyl group (**23**) led to an

approximate three-fold decrease in activity for the D_2 receptor (K_i = 62.1 ± 7.2 nM), while the efficacy for the 5-HT receptors remained the same, compared with compound **22**. When a longer or shorter linker was introduced, the compounds displayed different affinities for the three receptors. The affinities remained the same as those of compound **22** when 4-chlorobutyryl chloride (**23**) was replaced with 5-chloropentanoyl chloride (**24**), indicating that the compound with a longer linker (5-unit) may fail to improve the affinities for the three receptors. Compound **8** containing 2-chloroacetyl chloride, a shorter linker (2-unit), resulted in significantly reduced activities at all three receptors.

Reducing the carbonyl groups and introducing more aliphatic linkers may be effcet physicochemical properties and drug-likeness. To evaluate the effects of these modifications, the carbonyl group of the linker was reduced to methylene and a hydroxymethyl group and the affinities for these compounds were determined (**Table 3**). When the carbonyl group was reduced by Et_3SiH in the presence of TFA, compounds containing the benzisoxazolepiperidine moiety with chain lengths of three (**29**) or four (**33**) carbons showed slightly reduced affinities for the receptors, compared with compound **22**. The same affinities were observed when the methyl group was substituted at the R_3 position (**34**). Introducing the privileged structures 2,3-dichlorophenylpiperazine (**30** and **31**) and 3-(piperazin-1-yl)benzo[d]isothiazole (**32**) led to a decrease in affinity for the D_2 receptor, while activity against the 5-HT_{2A} receptor was retained (albeit less than that of compound **22**). When the carbonyl group was reduced by sodium borohydride ($NaBH_4$), compounds **35** and **36** with OH

on the carbon chain resulted in a slight change in the D_2 and 5-HT_{2A} receptors affinities. These results indicate that introducing a carbonyl or hydroxymethyl group on the linker between the tricyclic heterocycle (containing 1,2,3,4-tetrahydroquinoline) and the privileged structure benzisoxazolepiperidine moiety moiety resulted in good activities for the three receptors.

Effect of the tricyclic heterocycle (containing indoline) on different privileged structures

We proceeded with our investigation by replacing 1,2,3,4-tetrahydroquinoline with different substituted indolines on the tricyclic heterocycles (**Table 4**). First, when indoline was introduced, the compounds showed moderate affinities for the D_2 receptor, regardless of whether the phenyl ring of the privileged structures was replaced by an electron-donating (**37**) or electron-withdrawing (**38**) group. Compound **39** with a cyano group on naked aromatic ring showed weaker affinities for the three receptors. Changing the phenyl ring to benzoisothiazole and benzoisoxazole resulted in increased affinity of the three receptors for compounds **40** and **41**.

Effect of the different linkers between the tricyclic heterocycles (containing indoline) and the privileged structures

The change of the different sapcer between the tricyclic heterocycle (containing indoline) and privileged structures was also determined (**Table 5**). Introducing 4-chlorobutyryl chloride and the linker changed the compound into a longer (4-unit) alkyl chain. Compounds with the privileged structures of aripiprazole, risperidone, and ziprasidone had significantly increased affinities for the three receptors. The

following order of the three receptors for the analogues with different modifications was observed: 2,3-dichlorophenylpiperazine (**42**) < 3-(piperazin-1-yl) benzo[d]isothiazole (**43**) < 6-fluoro-3-(4-piperidyl)-1,2-benzisoxazole (**44**). We then introduced fluorine substituents at different positions on the tricyclic heterocycle. The activities of the substitution of F at the seven (**45**) and nine (**46**) positions of the tricyclic heterocycle were retained, although it was little less than that of compound **44.** Notably, compound (**47**) bearing benzisoxazolepiperidine moiety, particularly those with a long (5-unit) linker, had significantly higher activties for D_2 receptor (K_i = 2.9 ± 0.3 nM), 5-HT_{1A} receptor (K_i = 8.6 ± 1.1 nM) and 5-HT_{2A} receptor (K_i = 0.72 ± 0.02 nM). In contrast, compound **48**, interposed with chain lengths of six carbons, showed significantly inactive to the three receptors.

To investigate further structure–activity relationships, the carbonyl group of the linker between the tricyclic heterocycle and benzisoxazolepiperidine moiety was reduced and the affinities for these compounds was investigated. When the carbonyl group was reduced to a methylene group, the 5-HT_{2A} receptor affinity of compounds with different chain lengths led a decrease but not the other two receptors. Compounds with chain lengths of four carbons (**50**) showed good activities for D_2 and 5-HT_{1A} receptor with K_i < 15 nM, whereas compounds with shorter (3-unit) (**49**) or longer (5-unit) (**51**) linker had slightly reduced affinities for the two receptors. When the carbonyl group was reduced by $NaBH_4$, compound **54,** with a chain length of five carbons, exhibited good binding activitie to the three receptors with K_i < 15 nM. Affinity for the D_2 receptor following modification of the chain length resulted in

analogues in the following order: chain lengths of three carbons (**52**) < four carbons (**53**) < five carbons (**54**). Compounds **52** and **53** had similar activties for the 5-HT_{1A} and 5-HT_{2A} receptors but weaker affinities than those of compound **54**.

Overall, compounds **44**, **47**, **50**, **53**, and **54** exhibited good activties for the three receptors. These five compounds especially compound **47** (K_i = 8.6 ± 1.1 nM) showed higher 5-HT_{1A} affinities than risperidone (K_i = 182 ± 15 nM). Moreover, compound 47 (K_i = 2.9 ± 0.3 nM) displayed a strong binding activity to D2 receptor compared with risperidone (K_i = 3.7 ± 0.3 nM). Compounds **47** (K_i = 0.72 ± 0.02 nM) showed similar 5-HT_{2A} activity to risperidone (K_i = 0.18 ± 0.02 nM). These relationships are summarized in **Figure 4.**

The atypical antipsychotics are less potent D_2 receptor antagonists than conventional antipsychotics and have the distinctive feature of being 5-HT_{2A} receptor antagonists, which improves their neurological safety.[31] Thus, the atypical antipsychotics have demonstrated superior effectiveness, with a diminished incidence of EPSs, but are associated with the development of metabolic disturbances.[32] They trigger many adverse events, such as excessive weight gain, which is primarily a result of treatment with clozapine and olanzapine, and to a lesser extent risperidone; the synergistic effects of histamine H_1 and serotonin 5-HT_{2C} antagonism have been postulated as the reason for the antipsychotic-induced weight gain. Many other adverse events may be induced by the administration of atypical antipsychotics. Glucose and lipid abnormalities may be caused by the treatment of clozapine and olanzapine, while the strong risk of QTc prolongation was tiggered by sertindole and

ziprasidone.[33] Treating schizophrenia with antipsychotic drugs may trigger orthostatic hypotension related to the antagonistic effect of the adrenergic α_1 receptor.[34] These adverse events have been suggested to be closely related to the three off-target receptors (5-HT_{2C}, histamine H_1, and adrenergic α_1). As shown in **Table 6**, compound **54** exhibited high binding activity to the two receptors compared to risperidone (**54**: 5-HT_{2C}, K_i = 33.7 ± 4.1 nM; H_1, K_i = 43.5 ± 5.2 nM; risperidone: 5-HT_{2C}, K_i = 28.2 ± 3.3 nM; H_1, K_i = 46.2 ± 5.1 nM). The other compounds may cause no or little treatment-associated weight gain because they have lower 5-HT_{2C} and histamine H_1 receptor affinities compared with risperidone. Due to their inactivity to the adrenergic α_1 receptor (K_i > 300 nM), the selected compounds except compound **50** (K_i = 99.3 ± 12.1 nM) may not cause orthostatic hypotension.

Furthermore, the 5-HT_6 receptor has high density in brain areas associated with learning and memory, predominantly in the hippocampus, striatum, nucleus accumbens, and prefrontal cortex. Its enrichment in those brain regions suggests an important role in memory and cognitive processes.[20] Given that blockade of the 5-HT_6 receptor induces glutamatergic and monoaminergic (e.g., dopaminergic and adrenergic) neurotransmitter release, it was reasonable to consider that 5-HT_6 receptor antagonism could be a promising approach for the improvement of cognitive abilities.[21] The dopamine D_3 receptor plays an important role in regulating cortical DA neurotransmission related to cognitive and motivational behaviors, due to its selective expression in the striatum and mesolimbic system.[23] Overall, the two desired target receptors (5-HT_6 and D_3 receptors) have been suggested to help improve

cognitive abilities. In **Table 6**, the 5-HT_6 receptor affinities of compounds **47**, **50**, **53**, and **54** are higher than risperidone (K_i = 1260 ± 150 nM). In particular, compounds **47** (K_i = 5.55 ± 0.6 nM) and **53** (K_i = 6.36 ± 0.8 nM) displayed significantly higher binding activities to the 5-HT_6 receptor than risperidone. According to **Table 6**, compound **47** (K_i = 1.66 ± 0.3 nM) showed higher binding activity to the D_3 receptor than risperidone (K_i = 31.9 ± 3.3 nM), while the other selected compounds had weak affinities for the D_3 receptor. Thus, these results suggest that compound **47** may alleviate cognitive impairment in patients.

Taken together, compounds **44**, **47**, and **53** showed low binding activity to the off-target receptors (5-HT_{2C}, histamine H_1, and adrenergic α_1 receptors [K_i > 300 nM]), while compound **47** exhibited excellent affinities for the desired target receptors (5-HT_6, K_i = 5.55 ± 0.6 nM; D_3, K_i = 1.66 ± 0.3 nM). Therefore, the three compounds were selected to evluate their safety profile.

hERG channel blockade

Cardiotoxicity is a serious side effect often caused by off-target interactions between drugs and various voltage-gated ion channels in the heart, particularly the hERG channel.[35] Unwanted interactions of drugs with this channel can trigger serious cardiac arrhythmias, such as long QT syndrome, which is characterized by prolongation of the QT interval and Torsades de pointes.[36] The possible lethal aftermath of drug-induced hERG blockade has significantly affected screening strategies, drug development, regulation, and approval procedures. Compounds **44**, **47**, and **53** were evaluated for their ability to block hERG in a patch-clamp assay.

Compound **47** (IC_{50} > 2000 nM) exhibited a lower hERG inhibition than the others.

Taken together, compound **47** exhibited excellent *in vitro* profiles with a higher affinity for the five desired targets and a lower affinity for the three off-target receptors and hERG.

Acute toxicity

The acute toxicity was investigated in terms of LD_{50} values. Compound **47** even at the highest tested dose (2000 mg/kg) was not lethal in more than half of the mice. It suggested that compound **47** displayed a good safety profile with a very low acute toxicity (LD_{50} > 2000 mg/kg).

Intrinsic activity of new multi-receptor compound 47

Compound **47** was selected for further functional characterization based on its excellent *in vitro* profiles and good safety properties. In **Table 7**, compound **47** stimulated the five receptors in an agonist assay and showed minimal agonist activity, displaying < 20% of the efficacy of the reference compounds, respectively. Compound **47** blocked five receptors by greater than 90% in an antagonist assay. Compound **47** functioned as an antagonist at the D_{2L} (IC_{50} = 9.20 nM), D_3 (IC_{50} = 25.6 nM), 5-HT_{1A} (IC_{50} = 587.8 nM), 5-HT_{2A} (IC_{50} = 257.4 nM) and 5-HT_6 (IC_{50} = 177.6 nM) receptors.

***In vivo* behavioral studies on selected analogues of compound 47**

Analysis of the data obtained from the receptor binding assays allowed compound **47** to be selected for testing in several mouse models sensitive to mesolimbic-mediated antipsychotic-like activity.

The antagonism of hyperlocomotion induced by dopamine receptor direct agonists (e.g., apomorphine) or compounds that facilitate dopaminergic tone (e.g., amphetamines and AMP) are used in murine models to assess antipsychotic efficacy.[37] The effects of apomorphine decrease significantly in response to D_2 receptor antagonists. Many of these compounds demonstrate a potent ability to attenuate climbing behavior induced by apomorphine in mice, which has been used as a model for identifying potential antipsychotic activity linked to behavioral agitation, one positive psychotic symptoms.[38] Treatment with Compound **47** can dose-dependently inhibit the apomorphine induced climbing behavior (**Figure 5**), with an ED_{50} value of 0.61 mg/kg (**Table 8**). In comparison, the apomorphine-induced climbing behavior was also attenuated by risperidone (ED_{50}, 0.028 mg/kg) and haloperidol (ED_{50}, 0.11 mg/kg), respectively. It indicate that compound **47** is a potent blocker of the D_2 receptor, which was also consistent with its potent D_2 receptor antagonistic activity.

It is well known that systemic administration of PCP or MK-801 increases the dopaminergic cell-firing rate in the brain.[39] The observation that uncompetitive NMDA receptor antagonists (e.g., PCP, MK801, and ketamine) induce schizophrenic symptoms (negative and cognitive symptoms) in healthy subjects and exacerbate existing psychoses in patients with schizophrenia suggests that endogenous dysfunction of NMDA receptor-mediated neurotransmission might play an important role in the pathophysiology of schizophrenia.[40] The compounds were also tested in the MK801-induced hyperactivity model. In this test, compound **47** significantly

dose-dependently decreased the increased locomotor activity induced by MK-801 (**Figure 6**) with an ED_{50} of 0.26 mg/kg (**Table 8**). In comparison, risperidone and haloperidol reversed the MK801-induced hyperactivity with an ED_{50} values of 0.011 and 0.16 mg/kg, respectively.

One of the major obstacles of the use of antipsychotics is their propensity to produce EPSs. The rodent catalepsy test has been often used to predict the incidence of EPSs in the antipsychotic drug discovery process.[41] Selected compounds were tested in mice using the horizontal bar test to evaluate the liability for striatal-mediated side effects and for cataleptogenic potential. This test is sensitive to catalepsy induced by D_2 receptor antagonist. In **Table 8**, haloperidol induced significant cataleptic effect (ED_{50}, 0.12 mg/kg), consistent with its strong antagonistic effect on D_2 receptor. In contrast, compound **47** produced a low potential cataleptogenic effect (ED_{50}, 78.62 mg/kg), while the ED_{50} of catalepsy induced by risperidone is 0.51 mg/kg. Compound **47** with a higher threshold for catalepsy might induce a lower incidence of extrapyramidal motor side-effects, compared with risperidone. Compound 47 exhibited a wider range of the therapeutic indices (128.88–302.38) based on its efficacy (apomorphine or MK-801 models) and its side effects (catalepsy), while the therapeutic index of risperidone was approximately 18.21–46.36.

The conditioned avoidance response (CAR) test has significant predictive validity, some construct validity, but little face validity. The CAR test has been used to assess the antipsychotic activity of potential agents that display high affinities for

dopamine receptors.[42] This test has long been considered an important preclinical animal model for the study of antipsychotic drugs.[43] Both compound **47** and risperidone effectively inhibited the avoidance response in the rat CAR model (**Figure 7**). A nonlinear regression analysis indicating risperidone's ED_{50} was 0.52 mg/kg, while treatment of compound **47** resulted an ED_{50} of 1.46 mg/kg (**Table 8**).

Weight gain and serum prolactin

The potential adverse effect profile of compound **47** was also assessed in terms of its ability to induce weight gain and high prolactin levels.[33] Negligible weight gain was detected by administering compound 47 in mice that experienced chronic dosing (28 days), whereas risperidone was associated with significantly more weight gain in the experienced chronic dosing (28 days) (**Figure 8**). The discrepancies was also consistent with their different affinities for the histamine H_1 (risperidone, K_i = 46.2 ± 5.1 nM; **47**, K_i = 630.3 ± 5.5 nM) and 5-HT_{2C} (risperidone, K_i = 28.2 ± 3.3 nM; **47**, K_i = 616.0 ± 65.1 nM) receptors. Moreover, compound **47** resulted nonsignificantly serum prolactin levels change compared with risperidone (**Figure 9**).

Besides the aforementioned functional profile, extended pharmacological *in vitro* profiling was conducted with compound **47** to investigate its potential off-target activity (**Table 6**). The results indicated that compound **47** behaved as an antagonist of the five receptors (**Table 7**) and showed weak affinities for off-target receptors (**Table 6**). Consequently, similar to other atypical antipsychotics, compound **47** displayed a complex pharmacology with the desired profile, but appeared to produce some potentially unwanted off-target effects. These effects, resulting from off-target

receptors (adrenergic α_1, histamine H_1, and 5-HT_{2C} receptors), suggest factors related to metabolic disturbances (weight gain), hypotension, and sedation; however, these states were not observed in this study. The pharmacokinetic properties of compound **47** have been extensively studied in rats, and good pharmacokinetic characteristics have been demonstrated.

Pharmacokinetic profile of compound 47

The pharmacokinetic properties of compound **47** have been extensively studied in rats, and the good pharmacokinetic characteristics are demonstrated in **Table 9**. Interestingly, two ways of administration showed similar half-life ($t_{1/2}$), $t_{1/2}$ of intravenous administration (1 mg/kg) was 2.15 ± 0.50 h, while oral administration (10 mg/kg) was associated with a $t_{1/2}$ of 2.02 ± 0.19 h. Compound **47** showed intravenous AUC (area under the curve) of 3151.2 ± 402.9 ng·h/mL and oral AUC of 18,539.5 ± 1584.6 ng·h/mL, respectively. Clearance was 15.4 mL/min/kg following intravenous administration. The T_{max} value was 1.00 ± 0.00 h and the peak serum concentration was 3733 ± 1635 ng/mL when dosed orally at 10 mg/kg. In sum, compound **47** exhibited a favorable drug-like pharmacokinetic properties with an oral bioavailability of 58.8 %.

Memory study

Given its promising profile, compound **47** exhibited excellent affinities for 5-HT_6 (K_i = 5.55 ± 0.6 nM) and D_3 (K_i = 1.66 ± 0.3 nM) receptors, so the effect of compound **47** on cognitive performance was evaluated in a novel object recognition (NOR) task in rats, predictive of potential procognitive activity of the drug.[22b, 44] The

NOR task is a widely-used behavioral task to assess visual recognition memory, and is based on an animal's innate preference for novelty.[45] The task consists of a training phase, where rats are presented with two identical objects to explore. Following a delay interval, memory was assessed by presenting the rats with a trained object and a novel object. Rats with a memory of the previously presented object will preferentially explore the novel object. Rats that receive a memory enhancing drug in conjunction with submaximal training are expected to exhibit improved memory performance similar to that of untreated animals that received stronger training (i.e., more exposure to objects during the training phase). In this study, compound **47** was orally administered 1 h prior to the acquisition trial and the exploration times for the two identical objects were recorded (**Figure 10A**). After a 24 h acquisition trial, one of the familiar objects was replaced with a novel object, the time spent investigating each of the objects was recorded (**Figure 10B**), and the novelty discrimination index (NDI) was calculated as the percentage of novel object interaction time relative to total interaction time during the retention trial (**Figure 10C**). As shown in **Figure 10A**, oral administration of compound **47** (0.03−0.3 mg/kg) did not significantly affect total exploration time during the acquisition trial. As shown in **Figure 10B**, Risperidone (0.2 mg/kg) failed to improve cognitive ability, while Rivastigmine can enhance recognition memory at 0.3 mg/kg. In contrast, rats treated with 0.1 or 0.3 mg/kg of compound **47** during the retention trial explored the novel object for a longer time, indicative of preserved memory for the familiar object presented during the acquisition trial, whereas rats under the vehicle condition or dosed with 0.03 mg/kg of

compound **47** did not exhibit differences between exploration times for the familiar and novel objects, indicating deterioration or loss of memory for the familiar object. In addition, a 0.3 mg/kg oral dose of compound **47** significantly increased the NDI (**Figure 10C**). These results suggest that compound **47** enhanced recognition memory during the NOR task in rats.

Selectivity profile of compound 47

The interactions between compound **47** and other receptors related to central nervous system (CNS) disorders were evaluated, a selectivity profile was created using additional receptors (including the D_1, 5-HT_7, α_2, H_3, SERT, NET, DAT, sigma-1 [σ_1] and sigma-2 [σ_2], muscarinic M_1 and NMDA receptors). Moreover, anticholinergic side effects such as dry mouth, constipation and blurred vision were induced by the antitargeting muscarinic M_1 receptors.[12c] Compound **47** showed moderate affinities for D_1 and 5-HT_7 receptors (D_1, K_i = 76.9 ± 10.3 nM; 5-HT_7, K_i = 226.0 ± 33.2 nM), with no significant affinity (K_i > 1000 nM) for any other putative target. Futhurmore, Compound **47** inhibited D_1 receptor by greater than 90% in an antagonist assay and functioned as an antagonist at the D_1 receptor (IC_{50} = 366 nM), (Supporting Information).

CONCLUSIONS

A new series of fused tricyclic heterocycle piperazine (piperidine) derivatives was synthesized, and selected candidates were evaluated as potential new antipsychotic agents. Among this series, compound **47** was favorable for the binding

to the five (D_2, D_3, 5-HT_{1A}, 5-HT_{2A} and 5-HT_6) receptors. This compound has a desirable selectivity profile against other receptors, including 5-HT_{2C}, histamine H_1 and adrenergic α_1 receptors, which are known to be associated with the adverse effects of marketed antipsychotics. Compound **47** was a potent antagonist for those five receptors and was efficacious in animal models of psychoses. Because it reversed apomorphine- and MK-801-induced motor behavior, and avoidance behavior in the CAR test, compound **47** appears to be useful for addressing the positive symptoms of schizophrenia. Additionally, compound **47** displayed low hERG inhibitory activity, and no tendency to induce catalepsy. Furthermore, compound **47** was evaluated in the rat NOR test, and improved visual recognition memory was observed 24 h after training. Compound **47** may promote the development of a unique CNS-active drug candidate due to its suitable physicochemical, biophysical, and pharmacokinetic properties. A thorough preclinical profiling of compound **47** and its analogues is currently ongoing in our lab and further pharmacological details will be reported soon.

EXPERIMENTAL SECTION

Chemistry. All commercially available chemicals and reagents were used without further purification. Reagents were all of analytical grade or of chemical purity (>95%). Melting points were determined in open capillary tubes and uncorrected. ^{1}H NMR spectra was recorded on a Bruker Avance III 600 spectrometer at 600 MHz (^{1}H) using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts were given in

d values (ppm), using tetramethylsilane (TMS) as the internal standard; coupling constants (*J*) were given in Hz. Signal multiplicities were characterized as s (singlet), d (doublet), t(triplet), q (quartet), m (multiplet), br (broad signal). Analytical thin layer chromatography (TLC) was performed on silica gel GF254. Column chromatographic purification was carried out using silica gel. Compound purity is determined by high performance liquid chromatography (HPLC), and all final test compounds display purity higher than 95%. HPLC methods used the following: Shimadzu LC-20AD spectrometer; column, Waters XBridge^{TM} Sheild RP18 (150×4.6mm， 3.5μm); mobile phase, 0.01mol/L KH_2PO_4 (0.2 % Et_3N, pH = 3.5) aq./acetonitrile (Merck Company, Germany) 20/80; flow rate, 1.0 mL/min; column temperature, 35 ^oC. UV detection was performed at 210 nm.

General Procedures for the Preparation of Intermediates 3.

1,2,6,7-tetrahydro pyrido[3,2,1-ij]quinolin-3(5H)-one (3a). Conpound **3a** was synthesized by the followed two step reactions according the literatures with modifications.[26, 27] Step 1: To 1,2,3,4-tetrahydroquinoline (5.0 g, 37.5 mmol) was added acetone (50 ml), and then 3-chloropropionyl chloride (5.1g, 40.5mmol) was added slowly. The mixture was heated to reflux for 4 h. Then, it was cooled down and concentrated. The residue was diluted with water (50 mL) and extracted with 75 mL ethyl acetate by three times. The ethyl acetate layer was dried with anhydrous $MgSO_4$, the filtrate was removed under reduced pressure. The obtained crude product was recrystallized from ethyl acetate to give 3-chloro-1-(3,4-dihydroquinolin -1(2H)-yl)propan-1-one as pale white solid. M.P. 79 – 80 ^oC. Yield: 96.4%; ^1H NMR

(600 MHz, $CDCl_3$) δ 7.24 – 7.05 (m, 4H), 3.87 (t, *J* = 6.7 Hz, 4H), 3.00 (t, *J* = 6.7 Hz, 2H), 2.74 (s, 2H), 2.00 (p, *J* = 6.6 Hz, 2H). MS (ESI) m/z 224.2 (calcd 224.1 for $C_{12}H_{15}ClNO^+$ $[M+H]^+$). Step 2: The product (8 g, 35.8 mmol) from the first step was heated at 100 °C to melt, and then added anhydrous aluminum chloride (7.2 g, 54.1 mmol) by partions. The reaction was then stirred at 100 °C for 3 h. 100 mL ice water was added to quench the reaction, until the reaction temperature was cooled down. The reaction mixture was extracted with 75 mL ethyl acetate by three times. The ethyl acetate layer was dried with anhydrous $MgSO_4$, and then removed under reduced pressure after filtration. The crude product was purified via chromatography (petroleum ether/EtOAc = 6/1) to afford 1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin -3(5H)-one **(3a)**, as a pale white solid. M.P. 68 – 70 °C.Yield: 80.0%; ^1H NMR (600 MHz, $CDCl_3$) δ 7.02 (t, *J* = 6.9 Hz, 2H), 6.93 (t, *J* = 7.5 Hz, 1H), 3.95 – 3.84 (m, 2H), 2.94 – 2.86 (m, 2H), 2.81 (t, *J* = 6.3 Hz, 2H), 2.67 (dd, *J* = 8.4, 6.5 Hz, 2H), 2.02 – 1.91 (m, 2H). MS (ESI) m/z 188.2 (calcd 188.1 for $C_{12}H_{14}NO^+$ $[M+H]^+$).

5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (3b). A pale white solid. M.P. 74 – 76 °C. Yield: 75.0%; ^1H NMR (600 MHz, $CDCl_3$) δ 7.09 (d, *J* = 6.9 Hz, 1H), 7.00 (dd, *J* = 7.4, 0.7 Hz, 1H), 6.93 (td, *J* = 7.4, 1.7 Hz, 1H), 4.09 (dd, *J* = 11.5, 5.3 Hz, 2H), 3.20 (t, *J* = 8.4 Hz, 2H), 2.98 (t, *J* = 7.7 Hz, 2H), 2.69 (dd, *J* = 10.6, 4.9 Hz, 2H). MS (ESI) m/z 174.2 (calcd 174.1 for $C_{11}H_{12}NO^+$ $[M+H]^+$).

7-fluoro-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-2(4H)-one (3c). A pale white solid. M.P. 72 – 73 °C. Yield: 72.1%; ^1H NMR (600 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.4, 1H), 6.63 (d, *J* = 7.4, 1H), 4.11 (t, *J* = 8.4 Hz, 2H), 3.20 (t, *J* = 8.4 Hz, 2H), 2.98 (t, *J*

= 7.7 Hz, 2H), 2.69 (dd, *J* = 10.6, 4.9 Hz, 2H). MS (ESI) m/z 192.2 (calcd 192.1 for $C_{11}H_{11}FNO^+$ $[M+H]^+$).

9-fluoro-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-2(4H)-one (3d). A pale white solid. M.P. 80 – 81 °C. Yield: 70.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (d, *J* = 6.9 Hz, 1H), 6.65 (d, *J* = 7.4, 1H), 4.12 (t, *J* = 8.4 Hz, 2H), 3.18 (t, *J* = 8.4 Hz, 2H), 2.98 (t, *J* = 7.7 Hz, 2H), 2.69 (dd, *J* = 10.6, 4.9 Hz, 2H). MS (ESI) m/z 192.2 (calcd 192.1 for $C_{11}H_{11}FNO^+$ $[M+H]^+$).

General Procedures for the Preparation of Intermediates 4 , 6 and 7.

9-(2-chloroacetyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (4a).[46] To a suspension of 1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (3a) (5.0 g, 26.7 mmol) in 25mL 1,2-dichloroethane was added 2-chloroacetyl chloride (3.5 g, 23.9 mmol). Anhydrous aluminium trichloride (7.2g, 54.1 mmol) was added by portions under ice-cooling. The reaction mixture was kept at 0-5 °C for 30 min after all $AlCl_3$ addition and then the reaction was performed at room temperature for 2 h. Then the reaction was quenched with 100 mL ice water. The mixture was extracted with 75 mL dichloromethane by three times. After being dried over $MgSO_4$, dichloromethane was removed by evaporation. The crude mixture was purified by chromatography (petroleum ether: EtOAc = 4: 1) to yield 9-(2-chloroacetyl)-1,2,6,7-tetrahydro pyrido[3,2,1-ij]quinolin-3(5H)-one (**4a**). A pale white solid. M.P. 68 – 70 °C. Yield: 70.3 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.64 (s, 1H), 4.66 (s, 2H), 4.03 – 3.81 (m, 2H), 3.06 – 2.94 (m, 2H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.71 (dd, *J* = 8.5, 6.6 Hz, 2H), 1.99 (dt, *J* = 12.2, 6.1 Hz, 2H). MS (ESI)

m/z 264.2 (calcd 264.1 for $C_{14}H_{15}ClNO_2^+$ $[M+H]^+$).

9-(3-chloropropanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (4b). A pale white solid. M.P. 67 – 68 °C. Yield: 73.5%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.64 (s, 1H), 3.93 (dt, *J* = 12.9, 6.4 Hz, 4H), 3.42 (t, *J* = 6.8 Hz, 2H), 3.05 – 2.89 (m, 2H), 2.87 (d, *J* = 6.2 Hz, 2H), 2.79 – 2.65 (m, 2H), 2.05 – 1.92 (m, 2H). MS (ESI) m/z 278.1 (calcd 278.1 for $C_{15}H_{17}ClNO_2^+$ $[M+H]^+$).

9-(4-chlorobutanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (4c). A pale white solid. M.P. 70 – 71°C. Yield: 73.2%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.64 (s, 1H), 3.97 – 3.86 (m, 2H), 3.69 (t, *J* = 6.2 Hz, 2H), 3.14 (t, *J* = 7.0 Hz, 2H), 2.98 – 2.93 (m, 2H), 2.86 (t, *J* = 6.2 Hz, 2H), 2.70 (dd, *J* = 8.4, 6.7 Hz, 2H), 2.23 (p, *J* = 6.7 Hz, 2H), 1.98 (dt, *J* = 12.2, 6.1 Hz, 2H). MS (ESI) m/z 292.2 (calcd 292.1 for $C_{16}H_{19}ClNO_2^+$ $[M+H]^+$).

9-(5-chloropentanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (4d). A pale white solid. M.P. 71 – 72 °C. Yield: 71.2%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.63 (s, 1H), 4.03 – 3.93 (m, 2H), 3.91 – 3.81 (m, 2H), 3.70 (t, *J* = 6.2 Hz, 2H), 3.27 – 3.11 (m, 2H), 2.94 – 2.82 (m, 2H), 2.78 (dd, *J* = 15.9, 5.6 Hz, 2H), 2.57 – 2.44 (m, 2H), 2.31 – 2.15 (m, 2H), 2.06 – 1.95 (m, 2H). MS (ESI) m/z 306.2 (calcd 306.1 for $C_{17}H_{21}ClNO_2^+$ $[M+H]^+$).

8-(3-chloropropanoyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (6a). A pale white solid. M.P. 74 – 76 °C. Yield: 83.4%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.70 (s, 1H), 4.16 (t, *J* = 8.5 Hz, 2H), 3.66 (t, *J* = 6.2 Hz, 2H), 3.25 (t, *J* =

8.5 Hz, 2H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.74 (t, *J* = 7.8 Hz, 2H). MS (ESI) m/z 264.2 (calcd 264.1 for $C_{14}H_{15}ClNO_2^+$ $[M+H]^+$).

8-(4-chlorobutanoyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (6b). A pale white solid. M.P. 75 – 76 °C. Yield: 80.3 %. ^1H NMR (600 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.70 (s, 1H), 4.16 (t, *J* = 8.5 Hz, 2H), 3.71 (t, *J* = 6.2 Hz, 2H), 3.32 – 3.22 (m, 2H), 3.20 – 3.11 (m, 2H), 2.82 – 2.78 (m, 2H), 2.56 – 2.42 (m, 2H), 2.32 – 2.20 (m, 2H). MS (ESI) m/z 278.2 (calcd 278.1 for $C_{15}H_{17}ClNO_2^+$ $[M+H]^+$).

8-(5-chloropentanoyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (6c). A pale white solid. M.P. 72 – 75 °C.Yield: 65.2 %. ^1H NMR (600 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.70 (s, 1H), 4.16 (t, *J* = 8.4 Hz, 2H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.25 (t, *J* = 8.0 Hz, 2H), 3.05 (t, *J* = 7.8 Hz, 2H), 3.05-2.98 (m, 2H), 2.74 – 2.67 (m, 2H), 1.95 – 1.83 (m, 4H). MS (ESI) m/z 292.2 (calcd 292.1 for $C_{16}H_{19}ClNO_2^+$ $[M+H]^+$).

8-(6-chlorohexanoyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (6d). A pale white solid. M.P. 69 – 71 °C. Yield: 45.9 %. ^1H NMR (600 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.72 (s, 1H), 4.17 – 4.13 (m, 2H), 3.64 (t, *J* = 6.2 Hz, 2H), 3.20 (t, *J* = 8.4 Hz, 2H), 2.98 (t, *J* = 7.7 Hz, 4H), 2.69 (dd, *J* = 10.6, 4.9 Hz, 2H), 1.86 – 1.73 (m, 4H), 1.59 – 1.46 (m, 2H). MS (ESI) m/z 306.20 (calcd 306.13 for $C_{17}H_{21}ClNO_2^+$ $[M+H]^+$).

8-(4-chlorobutanoyl)-7-fluoro-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (6e). Pale white solid. M.P. 70 – 72 °C. Yield: 64.9 %. ^1H NMR (600 MHz, $CDCl_3$) δ 7.75 (s, 1H), 4.16 (t, *J* = 8.0 Hz, 2H), 3.72-3.67 (m, 2H), 3.25 (t, *J* = 8.5 Hz, 2H), 3.18 – 3.14 (m, 2H), 3.08 – 3.02 (m, 2H), 2.74 (t, *J* = 7.8 Hz, 2H), 2.25 – 2.20 (m, 2H). MS (ESI) m/z 296.2 (calcd 296.1 for $C_{15}H_{16}ClFNO_2^+$ $[M+H]^+$).

8-(4-chlorobutanoyl)-9-fluoro-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (6f). A pale white solid. M.P. 72 – 74 °C. Yield: 63.4 %. ^1H NMR (600 MHz, $CDCl_3$)

δ 7.69 (s, 1H), 4.15 (t, *J* = 8.5 Hz, 2H), 3.69 (t, *J* = 6.0 Hz, 2H), 3.27-3.21 (m, 2H), 3.15 (t, *J* = 6.8 Hz, 2H), 3.00 (t, *J* = 7.8 Hz, 2H), 2.73 (t, *J* = 7.8 Hz, 2H), 2.26 – 2.20 (m, 2H). MS (ESI) m/z 296.2 (calcd 296.1 for $C_{15}H_{16}ClFNO_2^+$ $[M+H]^+$).

8-(4-chlorobutyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij] quinolin-4(2H)-one (7a). To a suspension of **6b** (3.2 g, 11 mmol) in 60 mL CF_3COOH was added Et_3SiH (3.82 g, 33 mmol). After reaction at room temperature overnight, the mixture solvent was removed under reduced pressure, and the residue was dissolved in 100 mL dichloromethane, and then washed by saturated $NaHCO_3$ and brine. The dichloromethane layer was dried with anhydrous $MgSO_4$, and then removed by evaporation, and the crude product was purified by chromatography (petroleum ether: EtOAc = 4: 1) to give **7a**. Pale yellow oil; yield 81.2 %; ^1H NMR (600 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.83 (s, 1H), 4.09 (dd, *J* = 11.1, 5.8 Hz, 2H), 3.57 (t, *J* = 6.5 Hz, 2H), 3.18 (t, *J* = 8.4 Hz, 2H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.69 (t, *J* = 7.8 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 1.90 – 1.71 (m, 4H). MS (ESI) m/z 264.2 (calcd 264.1 for $C_{15}H_{19}ClNO^+$ $[M+H]^+$).

8-(5-chloropentyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (7b). Pale yellow oil; yield 80.5 %; ^1H NMR (600 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.70 (s, 1H), 4.16 (t, *J* = 8.5 Hz, 2H), 3.61 (t, *J* = 6.2 Hz, 2H), 3.25 (t, *J* = 8.5 Hz, 2H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.74 (t, *J* = 7.8 Hz, 2H), 1.95 – 1.83 (m, 4H), 1.63 (s, 2H). MS (ESI) m/z 278.2 (calcd 278.1 for $C_{16}H_{21}ClNO^+$ $[M+H]^+$).

General Procedures for the Preparation of Compounds 8–22 and 24

Arylpiperazine (piperidine) (0.32 mmol) and a catalytic amount of KI were added to the suspension of compounds **4** (1 eq) and K_2CO_3 (4 eq) in CH_3CN (5.0 mL),

and then the mixture was refluxed for 7-9 h. After filtering, CH_3CN was evaporated to dryness under reduced pressure. The residue was extracted with 75 mL dichloromethane by three times, after it was diluted with 10.0 mL water. After be dried over $MgSO_4$, dichloromethane was removed under reduced pressure, and the crude product was purified by chromatography (MeOH: $CHCl_3$ = 10:1) to yield target compounds.

9-(2-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)acetyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (8). Pale yellow oil; yield 72.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.77 (s, 1H), 7.72 (dd, *J* = 8.7, 5.1 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.05 (ddd, *J* = 9.0, 7.9, 2.0 Hz, 1H), 5.31 (s, 2H), 4.14 (t, *J* = 8.5 Hz, 3H), 3.84 (s, 2H), 3.24 (t, *J* = 8.5 Hz, 2H), 3.16 (d, *J* = 11.5 Hz, 2H), 3.04 (t, *J* = 7.8 Hz, 2H), 2.73 (t, *J* = 7.8 Hz, 2H), 2.45 – 2.38 (m, 2H), 2.24 – 2.15 (m, 2H), 2.09 (d, *J* = 12.6 Hz, 2H). HRMS (ESI) m/z 448.2023 (calcd 448.2031 for $C_{26}H_{27}FN_3O_3^+$ $[M+H]^+$).

9-(3-(4-phenylpiperazin-1-yl)propanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (9). Pale yellow oil; yield 73.6%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.66 (s, 1H), 7.33 – 7.26 (m, 2H), 6.96 (d, *J* = 7.9 Hz, 2H), 6.88 (t, *J* = 7.3 Hz, 1H), 3.95 – 3.88 (m, 2H), 3.26 – 3.22 (m, 4H), 3.20 (dd, *J* = 9.4, 5.4 Hz, 2H), 2.99 – 2.95 (m, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.76 – 2.64 (m, 6H), 1.99 (dt, *J* = 12.2, 6.1 Hz, 2H). HRMS (ESI) m/z 404.2342 (calcd 404.2333 for $C_{25}H_{30}N_3O_2^+$ $[M+H]^+$).

9-(3-(4-(pyridin-2-yl)piperazin-1-yl)propanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij] quinolin-3(5H)-one (10). Pale yellow oil; yield 70.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 4.0 Hz, 1H), 7.73 (s, 1H), 7.71 (s, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 6.79 (dd, *J* = 6.8, 5.2 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 4.26 – 3.99 (m, 4H), 3.95 – 3.84 (m, 4H), 3.57 (t, *J* = 6.4 Hz, 2H), 3.46-3.26 (m, 4H), 3.05 – 2.94 (m, 2H), 2.87 (t, *J* = 6.0 Hz, 2H), 2.75 – 2.65 (m, 2H), 2.03 – 1.93 (m, 2H). HRMS (ESI) m/z 405.2272 (calcd 405.2285 for $C_{24}H_{29}N_4O_2^+$ $[M+H]^+$).

9-(3-(4-(pyrimidin-2-yl)piperazin-1-yl)propanoyl)-1,2,6,7-tetrahydropyrido[3,2,1 -ij]quinolin-3(5H)-one (11). Pale yellow oil; yield 65.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (d, *J* = 4.7 Hz, 2H), 7.66 (s, 1H), 7.65 (s, 1H), 6.51 (t, *J* = 4.7 Hz, 1H), 4.08 – 3.78 (m, 6H), 3.23 (t, *J* = 7.3 Hz, 2H), 2.97 – 2.92 (m, 4H), 2.86 (t, *J* = 6.2 Hz, 2H), 2.73 – 2.67 (m, 2H), 2.66 – 2.62 (m, 4H), 2.00-1.96 (m, 2H). HRMS (ESI) m/z 406.2246 (calcd 406.2238 for $C_{23}H_{28}N_5O_2^+$ $[M+H]^+$).

9-(3-(4-(2-methoxyphenyl)piperazin-1-yl)propanoyl)-1,2,6,7-tetrahydropyrido[3, 2,1-ij]quinolin-3(5H)-one (12). Pale yellow oil; yield 62.5%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.66 (s, 1H), 7.33 – 7.26 (m, 1H), 6.96 (d, *J* = 7.9 Hz, 2H), 6.88 (t, *J* = 7.3 Hz, 1H), 3.95 – 3.88 (m, 5H), 3.26 – 3.22 (m, 4H), 3.20 (dd, *J* = 9.4, 5.4 Hz, 2H), 2.99 – 2.95 (m, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.76 – 2.64 (m, 6H), 1.99 (dt, *J* = 12.2, 6.1 Hz, 2H). HRMS (ESI) m/z 434.2430 (calcd 434.2438 for $C_{26}H_{32}N_3O_3^+$ $[M+H]^+$)

9-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (13). Pale yellow oil; yield 67.2%; ^{1}H NMR (600 MHz,

$CDCl_3$) δ 7.68 (s, 1H), 7.67 (s, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 6.97 – 6.91 (m, 2H), 3.95 – 3.89 (m, 2H), 3.23 (t, *J* = 7.4 Hz, 2H), 3.02 – 2.91 (m, 8H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.80 – 2.67 (m, 6H), 2.29 (s, 3H), 2.24 (s, 3H),1.99 (dt, *J* = 12.1, 6.1 Hz, 2H). HRMS (ESI) m/z 432.3653 (calcd 432.2646 for $C_{27}H_{34}N_3O_2^+$ $[M+H]^+$).

9-(3-(4-(4-chlorophenyl)piperazin-1-yl)propanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (14). Pale yellow oil; yield 68.8%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.65 (s, 1H), 7.21 (d, *J* = 9.0 Hz, 2H), 6.91 – 6.81 (d, *J* = 9.0 Hz , 2H), 3.95 – 3.85 (m, 2H), 3.19 (dd, *J* = 8.9, 4.2 Hz, 6H), 2.98 – 2.94 (m, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.86 (t, *J* = 6.2 Hz, 2H), 2.75 – 2.66 (m, 6H), 1.98 (m, 2H). HRMS (ESI) m/z 438.1957 (calcd 438.1943 for $C_{25}H_{29}ClN_3O_2^+$ $[M+H]^+$).

9-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (15). Pale yellow oil; yield 76.1%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.65 (s, 1H), 7.21 – 7.10 (m, 2H), 6.98 (dd, *J* = 7.3, 2.3 Hz, 1H), 4.01 – 3.83 (m, 2H), 3.20 (t, *J* = 7.4 Hz, 2H), 3.11 (s, 4H), 2.96 (dt, *J* = 10.5, 7.2 Hz, 4H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.79 – 2.66 (m, 6H), 1.99 (dt, *J* = 12.2, 6.1 Hz, 2H). HRMS (ESI) m/z 472.1562 (calcd 472.1553 for $C_{25}H_{28}Cl_2N_3O_2^+$ $[M+H]^+$).

9-(3-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)propanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (16). Pale yellow solid; M.P. 145 – 147 ^{o}C. Yield 72.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 9.5 Hz, 2H), 7.49 – 7.45 (m, 1H), 7.38 – 7.32 (m, 1H), 3.93 – 3.87 (m, 2H), 3.63 – 3.53 (m, 4H), 3.21 (t, *J* = 7.4 Hz, 2H), 2.95 (q, *J* = 7.1 Hz, 4H), 2.85 (t, *J* = 6.2 Hz, 2H), 2.79 – 2.75 (m, 4H), 2.72 – 2.65 (m, 2H), 1.97 (dt, *J* = 12.2, 6.1 Hz,

2H). HRMS (ESI) m/z 461.2012 (calcd 461.2006 for $C_{26}H_{29}N_4O_2S^+$ $[M+H]^+$).

9-(3-(4-(benzo[d]thiazol-2-yl)piperidin-1-yl)propanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (17). Pale yellow solid; M.P. 165 – 166 °C. Yield 75.2%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 9.6 Hz, 2H), 7.51 – 7.42 (m, 1H), 7.40 – 7.32 (m, 1H), 3.96 – 3.83 (m, 2H), 3.31 – 3.04 (m, 5H), 3.00 – 2.81 (m, 6H), 2.78 – 2.63 (m, 2H), 2.37 – 2.18 (m, 4H), 2.10 – 1.91 (m, 4H). HRMS (ESI) m/z 460.2060 (calcd 460.2053 for $C_{27}H_{30}N_3O_2S^+$ $[M+H]^+$).

9-(3-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)propanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (18). Pale yellow oil; yield 78.2%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.72 (s, 1H), 7.21 – 7.11 (m, 2H), 7.03 – 6.86 (m, 1H), 3.93 (dt, *J* = 12.9, 6.4 Hz, 3H), 3.42 (t, *J* = 6.8 Hz, 2H),3.20 (t, *J* = 7.3 Hz, 2H), 3.11 (s, 4H), 3.05 – 2.89 (m, 2H), 2.87 (d, *J* = 6.2 Hz, 2H), 2.79 – 2.65 (m, 2H), 2.05 – 1.92 (m, 6H). HRMS (ESI) m/z 462.2188 (calcd 462.2187 for $C_{27}H_{29}N_3O_3^+$ $[M+H]^+$).

9-(4-(4-(2,3-dimethylphenyl)piperazin-1-yl)butanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (19). Pale yellow oil; yield 60.8%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.67 (s, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 2H), 3.95 – 3.88 (m, 2H), 3.01 (t, *J* = 7.2 Hz, 4H), 2.98 – 2.95 (m, 2H), 2.91 (s, 2H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.69 (dd, *J* = 17.7, 10.5 Hz, 6H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.28 (s, 3H), 2.23 (s, 3H), 2.06 – 1.95 (m, 4H). HRMS (ESI) m/z 446.2813 (calcd 462.2802 for $C_{28}H_{36}N_3O_2^+$ $[M+H]^+$).

9-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butanoyl)-1,2,6,7-tetrahydropyrido[3,

2,1-ij]quinolin-3(5H)-one (20). Pale yellow oil; yield 58.2%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.65 (s, 1H), 7.20 – 7.13 (m, 2H), 6.95 (dd, *J* = 7.1, 2.4 Hz, 1H), 3.95 – 3.88 (m, 2H), 3.03 (d, *J* = 27.0 Hz, 4H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.98 – 2.94 (m, 2H), 2.86 (t, *J* = 6.2 Hz, 2H), 2.69 (dd, *J* = 15.4, 8.2 Hz, 6H), 2.52 (t, *J* = 7.2 Hz, 2H), 2.07 – 1.89 (m, 4H). HRMS (ESI) m/z 486.1723 (calcd 486.1710 for $C_{26}H_{30}Cl_2N_3O_2^+$ $[M+H]^+$).

9-(4-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)butanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (21). Pale yellow oil; yield 62.1%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.67 (s, 1H), 7.66 (s, 1H), 7.51 – 7.46 (m, 1H), 7.41 – 7.34 (m, 1H), 3.95 – 3.87 (m, 2H), 3.56 (d, *J* = 4.0 Hz, 4H), 3.02 (t, *J* = 7.1 Hz, 2H), 2.98 – 2.94 (m, 2H), 2.86 (t, *J* = 6.2 Hz, 2H), 2.75 – 2.68 (m, 6H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.08 – 1.95 (m, 4H). HRMS (ESI) m/z 475.2168 (calcd 475.2162 for $C_{27}H_{31}N_4O_2S^+$ $[M+H]^+$).

9-(4-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)butanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (22). Pale yellow oil; yield 63.8%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.65 (s, 1H), 7.29 (s, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.14 (tt, *J* = 12.4, 6.2 Hz, 1H), 3.95 – 3.87 (m, 2H), 3.49 – 3.40 (m, 3H), 3.21 (t, *J* = 6.2 Hz, 2H), 3.07 – 3.00 (m, 2H), 3.00 – 2.92 (m, 4H), 2.86 (t, *J* = 6.1 Hz, 2H), 2.72 – 2.65 (m, 4H), 2.33-2.30 (m, 4H), 1.98 – 19.5 (m, 2H). HRMS (ESI) m/z 476.2353 (calcd 476.2344 for $C_{28}H_{31}FN_3O_3^+$ $[M+H]^+$).

9-(5-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)pentanoyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (24). Pale yellow oil; yield 65.5%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.7, 5.1 Hz, 1H), 7.64 (s, 1H), 7.63 (s, 1H), 7.24 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.10 – 7.02 (m, 1H), 3.99 – 3.84 (m, 2H), 3.50 – 3.42 (m,

3H), 3.26 – 3.23 (m, 2H), 3.08 (d, *J* = 10.0 Hz, 2H), 3.01 – 2.93 (m, 4H), 2.85 (t, *J* = 6.2 Hz, 2H), 2.72 – 2.66 (m, 2H), 2.49 – 2.43 (m, 2H), 2.14 (dt, *J* = 21.2, 8.7 Hz, 2H), 2.10 – 2.03 (m, 4H), 1.97 (dt, *J* = 12.1, 6.1 Hz, 2H). HRMS (ESI) m/z 490.2510 (calcd 490.2500 for $C_{29}H_{33}FN_3O_3^+$ $[M+H]^+$).

General Procedure for the Preparation of Compound 23 and 34

Ethyl Acetoacetate (13.0 g, 100 mmol) was added to 1,2,3,4-tetrahydro quinoline (14.6 g, 110 mmol) in toluene (150 mL), and it was heated at 100 °C overnight. After the reaction completion, the solutions were removed under reduced pressure and the residues were purified by chromatography (petroleum ether : EtOAc = 1 : 1) to yield 1-(3,4-dihydroquinolin-1(2H)-yl)butane -1,3-dione **(25).**[47] Pale yellow oil; yield 89.5%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.1 Hz, 1H), 7.23 (dd, *J* = 14.5, 7.2 Hz, 2H), 7.08 – 7.02 (m, 1H), 4.08 (t, *J* = 8.5 Hz, 2H), 3.23 (t, *J* = 8.4 Hz, 2H), 2.38 (s, 2H), 2.10 (dt, *J* = 12.1, 6.1 Hz, 2H), 2.04 (s, 3H). MS (ESI) m/z 218.2 (calcd 218.1 for $C_{13}H_{16}NO_2^+$ $[M+H]^+$).

Concentrated sulfuric acid (20 mL) was added to **25** (10 g, 46.1 mmol), then it was heated at 100 °C for 6 h. After its cooling, the mixture was poured into 100 mL ice water. The precipitate thus formed was neutralized to pH=8 with saturated $NaHCO_3$. After filtered and washed with water resulting 1-methyl-6,7-dihydro pyrido[3,2,1-ij]quinolin-3(5H)-one **(26).** Pale white solid; M.P. 82 – 84 °C. Yield 69.3%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.61 (s, 1H), 4.67 – 3.92 (m, 2H), 3.02 (t, *J* = 6.2 Hz, 2H), 2.48 (d, *J* = 0.7 Hz, 3H), 2.13 (dt, *J* = 12.1, 6.1 Hz, 2H). MS (ESI) m/z 200.2 (calcd 200.1 for $C_{13}H_{14}NO_2^+$ $[M+H]^+$).

A suspension of **26** (6.0 g, 30.1 mmol) in 50 mL MeOH was hydrogenated at room temperature under 3 MPa in the presence of 10% palladized charcoal (0.12 g) for 6 h. The mixture was filtered and MeOH was evaporated. The residue was purified by chromatography (petroleum ether : EtOAc = 6 : 1) to yield 1-methyl-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one **(27).**[50] Pale white solid; M.P. 71 – 72 °C. Yield 94.3%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 4.17 – 4.01 (m, 2H), 3.21 (ddd, *J* = 18.4, 12.6, 5.0 Hz, 1H), 2.76 (dd, *J* = 16.5, 6.4 Hz, 2H), 2.44 – 2.40 (m, 2H), 2.13 (dt, *J* = 12.1, 6.1 Hz, 2H), 1.34 (d, *J* = 7.0 Hz, 3H). MS (ESI) m/z 202.2 (calcd 202.1 for $C_{13}H_{16}NO_2^+$ $[M+H]^+$).

To a suspension of **27** (5.0 g, 24.9 mmol) in 25mL 1,2-dichloroethane was added 4-chlorobutanoyl chloride (3.2 g, 22.3 mmol). Anhydrous aluminium trichloride (6.7 g, 50.5 mmol) was added by portions under ice-cooling. The mixture was kept at 0-5 °C for 30 min after all $AlCl_3$ addition and then the reaction was performed at room temperature for 2 hours. Then the reaction was quenched with 100 mL ice water. The mixture was extracted with 75 mL dichloromethane by three times. After dichloromethane layer was dried over $MgSO_4$, it was removed by evaporation. The crude product was purified by chromatography (petroleum ether: EtOAc = 4: 1) to yield 9-(4-chlorobutanoyl)-1-methyl-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin -3(5H)-one **(28).** Pale white solid; M.P. 71 – 72 °C. Yield 80.2%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.68 (s, 1H), 3.97 – 3.86 (m, 2H), 3.70 (t, *J* = 6.2 Hz, 2H), 3.22 – 3.09 (m, 3H), 2.88 (t, *J* = 6.2 Hz, 2H), 2.52 (dd, *J* = 15.9, 7.3 Hz, 2H), 2.27 – 2.19

(m, 2H), 2.04 – 1.95 (m, 2H), 1.33 (d, *J* = 7.0 Hz, 3H). MS (ESI) m/z 306.2 (calcd 306.1 for $C_{17}H_{21}ClNO_2^+$ $[M+H]^+$).

6-Fluoro-3-(piperidin-4-yl)benzo[d]isoxazole hydrochloride (0.32 mmol) and a catalytic amount of KI were added to the mixture of compounds **28** (1 eq) and K_2CO_3 (4 eq) in CH_3CN (5.0 mL), and then was refluxed for 7-9 h. After cooling, the filtrate was evaporated to dryness under reduced pressure. The residue was extracted with 75 mL dichloromethane by three times, after it was diluted with 10.0 mL water. After dried, dichloromethane was removed under reduced pressure, the crude product was purified by (MeOH: $CHCl_3$ = 10 : 1) to afford 9-(4-(4-(6-fluorobenzo[d]isoxazol -3-yl)piperidin-1-yl)butanoyl)-1-methyl-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one **(23)**. Pale yellow oil; yield 60.2%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 3H), 7.26 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.06 (td, *J* = 8.8, 2.1 Hz, 1H), 4.06 – 3.93 (m, 1H), 3.92 – 3.83 (m, 1H), 3.18 – 3.03 (m, 4H), 3.01 (t, *J* = 7.1 Hz, 2H), 2.88 (t, *J* = 6.2 Hz, 2H), 2.55 – 2.46 (m, 4H), 2.18 (t, *J* = 10.9 Hz, 2H), 2.10 – 1.96 (m, 8H), 1.32 (d, *J* = 7.0 Hz, 3H). HRMS (ESI) m/z 490.2508 (calcd 490.2500 for $C_{29}H_{33}FN_3O_3^+$ $[M+H]^+$).

General Procedure for the Preparation of Compounds 29, 30 and 34.

According method A. 9-(3-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl) propyl)-1,2,6,7-tetrahydropyrido [3,2,1-ij]quinolin-3(5H)-one **(29).** To a suspension of **22** (0.5 g, 1.1 mmol) in 20 mL CF_3COOH was added Et_3SiH (0.38 g, 3 eq). After reacted at room temperature overnight, the mixture was evaporated, and the residue was dissolved in 100 mL dichloromethane, and then washed by saturated $NaHCO_3$

and brine. The dichloromethane layer was dried with anhydrous $MgSO_4$, and then removed under reduced pressure. The crude product was purified by chromatography (MeOH: $CHCl_3$ = 10: 1) to afford **29**. Pale yellow oil; yield 81.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 11.6, 5.8 Hz, 1H), 7.68 (s, 1H), 7.66 (s, 1H), 7.26 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.12 – 7.02 (m, 1H), 3.94 – 3.88 (m, 2H), 3.20 (t, *J* = 7.3 Hz, 2H), 3.10 (dd, *J* = 15.3, 7.3 Hz, 3H), 3.00 – 2.95 (m, 2H), 2.92 (t, *J* = 7.3 Hz, 2H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.73 – 2.69 (m, 2H), 2.30 (t, *J* = 12.5 Hz, 2H), 2.14 – 2.05 (m, 4H), 1.99 (dt, *J* = 12.1, 6.1 Hz, 2H),1.86-1.80(m, 2H). HRMS (ESI) m/z 448.2401 (calcd 448.2395 for $C_{27}H_{31}FN_3O_2^+$ $[M+H]^+$).

9-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (30). Pale yellow oil; yield 83.1%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.63 (s, 1H), 7.18 – 7.11 (m, 2H), 6.98 – 6.93 (m, 1H), 3.93 – 3.87 (m, 2H), 3.26 – 3.17 (m, 2H), 3.10 (s, 2H), 2.99 – 2.91 (m, 4H), 2.83 (dd, *J* = 16.6, 10.0 Hz, 4H), 2.76 (dd, *J* = 13.5, 7.0 Hz, 4H), 2.67 (dd, *J* = 15.4, 8.1 Hz, 2H), 1.99 – 1.86 (m, 4H). HRMS (ESI) m/z 458.1751 (calcd 458.1760 for $C_{29}H_{30}FN_3O_3^+$ $[M+H]^+$).

According Method B. 9-(4-chlorobutyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij] quinolin-3(5H)-one **(5).** To a suspension of **4c** (3.2 g, 11 mmol) in 60 mL CF_3COOH was added Et_3SiH (3.82 g, 3 eq). After reacted at room temperature overnight, the mixture solvent was removed under reduced pressure, and the residue was dissolved in 150 mL dichloromethane, and then washed by saturated $NaHCO_3$ and brine. The dichloromethane layer was dried with anhydrous $MgSO_4$, and then removed by

evaporation, and the crude product was purified by (petroleum ether: EtOAc = 4: 1) to give **5**. Pale yellow oil; yield 79.7 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.83 (d, *J* = 2.5 Hz, 2H), 3.92 – 3.85 (m, 2H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.89 – 2.82 (m, 2H), 2.78 (t, *J* = 6.3 Hz, 2H), 2.66 (dd, *J* = 8.4, 6.5 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 1.95 (dt, *J* = 12.2, 6.1 Hz, 2H), 1.87 – 1.81 (m, 2H), 1.79 – 1.73 (m, 2H). MS (ESI) m/z 278.2 (calcd 278.1 for $C_{16}H_{21}ClNO^+$ $[M+H]^+$).

Compounds **5** (0.32 mmol), K_2CO_3 (1.28 mmol) in acetonitrile (5.0 mL), arylpiperazine (piperidine) (0.32 mmol) and a catalytic amount of KI were added in CH_3CN (5.0 mL), and then refluxed for 27-30 h. After cooling, the filtrate was evaporated to dryness under reduced pressure. 75 mL dichloromethane was used extracted by three times, after the residue was diluted with 10.0 mL water. After dried over $MgSO_4$, dichloromethane were removed by evaporation. The crude product was purified by chromatography (MeOH: $CHCl_3$ = 50:1) to give target compounds. 9-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one **(31).** Pale yellow oil; yield 71.2 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 – 7.12 (m, 2H), 7.02 – 6.95 (m, 1H), 6.84 (d, *J* = 2.3 Hz, 2H), 3.93 – 3.83 (m, 2H), 3.18-3.07 (m, 4H), 2.92 – 2.85 (m, 2H), 2.78 (t, *J* = 6.2 Hz, 2H) , 2.66 (dd, *J* = 8.4, 6.5 Hz, 6H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.50 – 2.45 (m, 2H), 1.97-1.93 (m, 2H), 1.69 – 1.56 (m, 4H). HRMS (ESI) m/z 472.1926 (calcd 472.1917 for $C_{26}H_{32}Cl_2N_3O^+$ $[M+H]^+$).

9-(4-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)butyl)-1,2,6,7-tetrahydropyrido [3,2,1-ij]quinolin-3(5H)-one (32). Pale yellow oil; yield 72.5 %; ^{1}H NMR (600 MHz,

$CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.41 – 7.34 (m, 1H), 6.85 (d, *J* = 2.6 Hz, 2H), 3.94 – 3.82 (m, 2H), 3.69 – 3.54 (m, 4H), 2.91 – 2.83 (m, 2H), 2.79 (t, *J* = 6.2 Hz, 2H), 2.73 – 2.68 (m, 4H), 2.66 (dd, *J* = 8.4, 6.5 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.51 – 2.46 (m, 2H), 1.95 (dt, *J* = 12.2, 6.1 Hz, 2H), 1.71 – 1.57 (m, 4H). HRMS (ESI) m/z 461.2378 (calcd 461.2370 for $C_{27}H_{33}N_4OS^+$ $[M+H]^+$).

9-(4-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)butyl)-1,2,6,7-tetrahydro pyrido[3,2,1-ij]quinolin-3(5H)-one (33). Pale yellow oil; yield 71.1 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.5, 5.1 Hz, 1H), 7.26 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.07 (td, *J* = 8.8, 1.7 Hz, 1H), 6.84 (d, *J* = 1.9 Hz, 2H), 3.91 – 3.85 (m, 2H), 3.09 (d, *J* = 9.2 Hz, 3H), 2.90 – 2.84 (m, 2H), 2.78 (t, *J* = 6.2 Hz, 2H), 2.68 – 2.64 (m, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.46 – 2.41 (m, 2H), 2.19 – 2.03 (m, 6H), 1.95 (dt, *J* = 12.1, 6.2 Hz, 2H), 1.66 – 1.60 (m, 19.0 Hz, 4H). HRMS (ESI) m/z 462.2541 (calcd 462.2551 for $C_{28}H_{33}FN_3O_2^+$ $[M+H]^+$).

According method A. **9-(4-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin -1-yl)butyl)-1-methyl-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (34).** Pale yellow oil; yield 83.3%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.6, 5.1 Hz, 1H), 7.26 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.08 (td, *J* = 8.8, 2.1 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 2H), 3.89 – 3.87 (m, 2H), 3.16 (d, *J* = 10.8 Hz, 3H), 2.89 – 2.84 (m, 2H), 2.78 (t, *J* = 6.2 Hz, 2H), 2.67 – 2.63 (m, 2H), 2.57 (dd, *J* = 19.0, 12.1 Hz, 6H), 2.24 – 2.07 (m, 4H), 1.94 (dt, *J* = 12.1, 6.1 Hz, 2H), 1.65 (s, 6H). HRMS (ESI) m/z 476.2715 (calcd 476.2708 for $C_{29}H_{35}FN_3O_2^+$ $[M+H]^+$).

General Procedure for the Preparation of Compound 35 and 36.

To a suspension of **22** (3 mmol) in 30 mL methol, $NaBH_4$ (3.1 mmol) was added by portions under the room temperature. After stirred for 6−8 h, the reaction was quenched by 100 mL ice water, 75 mL dichloromethane was used to extracte the mixture by three times. The dichloromethane layer was dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was purified chromatography (MeOH: $CHCl_3$ = 10:1) to give 9-(3-(4-(6-fluoro benzo[d]isoxazol-3-yl)piperidin-1-yl)-1-hydroxypropyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one **35**. Pale yellow oil; yield 92.2 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 11.6, 5.8 Hz, 1H), 7.68 (s, 1H), 7.66 (s, 1H), 7.26 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.12 – 7.02 (m, 1H), 3.94 – 3.88 (m, 2H), 3.20 (t, *J* = 7.3 Hz, 2H), 3.10 (dd, *J* = 15.3, 7.3 Hz, 3H), 3.00 – 2.95 (m, 2H), 2.92 (t, *J* = 7.3 Hz, 2H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.73 – 2.69 (m, 2H), 2.30 (t, *J* = 12.5 Hz, 2H), 2.14 – 2.05 (m, 4H), 1.99 (dt, *J* = 12.1, 6.1 Hz, 2H), 1.86 – 1.80(m, 2H). HRMS (ESI) m/z 464.2344 (calcd 464.2344 for $C_{27}H_{31}FN_3O_3^+$ $[M+H]^+$).

9-(4-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)-1-hydroxybutyl)-1,2,6,7-tetrahydropyrido[3,2,1-ij]quinolin-3(5H)-one (36). Pale yellow oil; yield 93.8 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 8.5, 5.1 Hz, 1H), 7.26 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.07 (td, *J* = 8.8, 1.7 Hz, 1H), 6.84 (d, *J* = 1.9 Hz, 2H), 3.94 – 3.82 (m, 2H), 3.09 (d, *J* = 9.2 Hz, 3H), 2.93 – 2.84 (m, 2H), 2.78 (t, *J* = 6.2 Hz, 2H), 2.69 – 2.62 (m, 2H), 2.58 (t, *J* = 7.4 Hz, 2H), 2.52 – 2.41 (m, 2H), 2.23 – 2.04 (m, 6H), 1.95 (dt, *J* = 12.1, 6.2 Hz, 2H), 1.69 – 1.57 (m, 4H). HRMS (ESI) m/z 478.2505 (calcd 478.2500 for $C_{28}H_{33}FN_3O_3^+$ $[M+H]^+$).

General Procedures for the Preparation of Compounds 37 – 48.

Compounds **6** (0.32 mmol), K_2CO_3 (3 eq), arylpiperazine (piperidine) (1 eq) and a catalytic amount of KI were added in 5.0 mL CH_3CN, and then refluxed for 7-9 h. After reaction, the filtrate was evaporated to dryness under reduced pressure. The residue was extracted with 75 mL dichloromethane by three times, after it was diluted with 10.0 mL water. After dried over $MgSO_4$, dichloromethane were removed by evaporation. The crude product was purified by chromatography (MeOH: $CHCl_3$ = 10:1) to give target compounds.

8-(3-(4-(2,3-dimethylphenyl)piperazin-1-yl)propanoyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (37). Pale yellow oil; yield 88.2 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.73 (s, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.93 (dd, *J* = 10.1, 8.1 Hz, 2H), 4.15 (t, *J* = 8.5 Hz, 2H), 3.25 (t, *J* = 8.5 Hz, 2H), 3.21 (t, *J* = 7.4 Hz, 2H), 3.05 (t, *J* = 7.8 Hz, 2H), 3.00 – 2.90 (m, 6H), 2.74 (t, *J* = 7.8 Hz, 6H), 2.28 (s, 3H), 2.24 (s, 3H). HRMS (ESI) m/z 418.2478 (calcd 418.2489 for $C_{26}H_{32}N_3O_2^+$ $[M+H]^+$).

8-(3-(4-(2,3-dichlorophenyl)piperazin-1-yl)propanoyl)-5,6-dihydro-1H-pyrrolo [3,2,1-ij]quinolin-4(2H)-one (38). Pale yellow oil; yield 89.1 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.71 (s, 1H), 7.21 – 7.14 (m, 2H), 7.02 – 6.95 (m, 1H), 4.15 (t, *J* = 8.5 Hz, 2H), 3.27 – 3.20 (m, 4H), 3.12 (s, 2H), 3.04 (t, *J* = 7.8 Hz, 2H), 2.99 (t, *J* = 7.3 Hz, 2H), 2.77 (d, *J* = 21.4 Hz, 4H), 2.74 (t, *J* = 7.8 Hz, 4H). HRMS (ESI) m/z 458.1388 (calcd 458.1397 for $C_{24}H_{26}Cl_2N_3O_2^+$ $[M+H]^+$).

3-fluoro-4-(4-(3-oxo-3-(4-oxo-2,4,5,6-tetrahydro-1H-pyrrolo[3,2,1-ij]quinolin-8-yl)propyl)piperazin-1-yl)benzonitrile (39). Pale yellow oil; yield 91.1 %;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.71 (s, 1H), 7.39-7.35 (m, *J* = 8.4, 1.4 Hz, 1H), 7.32 – 7.25 (m, 1H), 6.93 (t, *J* = 8.5 Hz, 1H), 4.15 (t, *J* = 8.4 Hz, 2H), 3.25 (dd, *J* = 9.3, 5.5

Hz, 6H), 3.17 (t, *J* = 7.3 Hz, 2H), 3.04 (t, *J* = 7.8 Hz, 2H), 2.92 (t, *J* = 7.3 Hz, 2H), 2.74 (t, *J* = 7.8 Hz, 2H), 2.72 – 2.70 (m, 4H). HRMS (ESI) m/z 433.2030 (calcd 433.2034 for $C_{25}H_{26}FN_4O_2^+$ $[M+H]^+$).

8-(3-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)propanoyl)-5,6-dihydro-1H-pyrrolo [3,2,1-ij]quinolin-4(2H)-one (40). Pale yellow oil; yield 92.3 %;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.77 (s, 1H), 7.72 (s, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 4.15 (t, *J* = 8.5 Hz, 2H), 3.63 – 3.55 (m, 4H), 3.25 (t, *J* = 8.5 Hz, 2H), 3.21 (t, *J* = 7.4 Hz, 2H), 3.04 (t, *J* = 7.8 Hz, 2H), 2.95 (t, *J* = 7.4 Hz, 2H), 2.79 – 2.76 (m, 4H), 2.74 (t, *J* = 7.8 Hz, 2H). HRMS (ESI) m/z 477.1856 (calcd 447.1849 for $C_{25}H_{27}N_4O_2S^+$ $[M+H]^+$).

8-(3-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)propanoyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (41). Pale yellow oil; yield 89.9 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.74 – 7.69 (m, 2H), 7.26 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.07 (td, *J* = 8.8, 2.1 Hz, 1H), 4.16 (t, *J* = 8.5 Hz, 2H), 3.26 (t, *J* = 8.5 Hz, 2H), 3.20 (t, *J* = 7.4 Hz, 2H), 3.13 (d, *J* = 11.4 Hz, 3H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.74 (t, *J* = 7.8 Hz, 2H), 2.29 (dd, *J* = 14.0, 11.4 Hz, 2H), 2.18 – 2.04 (m, 4H). HRMS (ESI) m/z 448.2030 (calcd 448.2031 for $C_{26}H_{27}FN_3O_3^+$ $[M+H]^+$).

8-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butanoyl)-5,6-dihydro-1H-pyrrolo [3,2,1-ij]quinolin-4(2H)-one (42). Pale yellow oil; yield 75.3 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.71 (d, *J* = 12.1 Hz, 1H), 7.22 – 7.12 (m, 2H), 7.01 – 6.91 (m, 1H), 4.51 (t, *J* = 8.5 Hz, 2H), 4.15 (t, *J* = 8.5 Hz, 2H), 3.78 (t, *J* = 8.5 Hz, 2H), 3.25 (t, *J* = 8.5 Hz, 2H), 3.13 – 3.06 (m, 4H), 3.03 (m, 4H), 2.75 (t, *J* = 8.5 Hz, 4H), 2.10 – 1.95 (m, 2H). HRMS (ESI) m/z 472.1559 (calcd 472.1553 for $C_{25}H_{28}Cl_2N_3O_2^+$

$[M+H]^+$).

8-(4-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)butanoyl)-5,6-dihydro-1H-pyrrolo [3,2,1-ij]quinolin-4(2H)-one (43). Pale yellow oil; yield 72.5 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.75 (s, 1H), 7.71 (s, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 4.14 (td, *J* = 8.5, 3.8 Hz, 2H), 3.89 (d, *J* = 12.5 Hz, 2H), 3.75 (dd, *J* = 10.8, 4.8 Hz, 2H), 3.47 (t, *J* = 6.1 Hz, 2H), 3.23 (dt, *J* = 23.0, 11.6 Hz, 2H), 3.13 (t, *J* = 7.0 Hz, 2H), 3.03 (dd, *J* = 14.7, 7.5 Hz, 4H), 2.73 (td, *J* = 7.8, 3.5 Hz, 2H), 2.23 (dt, *J* = 13.2, 6.7 Hz, 2H), 2.06 – 1.98 (m, 2H). HRMS (ESI) m/z 461.2018 (calcd 461.2006 for $C_{26}H_{29}N_4O_2S^+$ $[M+H]^+$).

8-(4-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)butanoyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (44). Pale yellow oil; yield 71.4 %;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 17.1 Hz, 1H), 7.67 (s, 1H), 7.62 (dt, *J* = 9.3, 4.7 Hz, 1H), 7.17 (dt, *J* = 8.3, 4.1 Hz, 1H), 7.00 (ddd, *J* = 8.6, 6.4, 1.8 Hz, 1H), 4.08 (t, *J* = 8.2 Hz, 2H), 3.19 (t, *J* = 8.0 Hz, 2H), 3.05 – 2.90 (m, 7H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.44 (t, *J* = 6.5 Hz, 2H), 2.12 (t, *J* = 10.3 Hz, 2H), 2.04 – 1.89 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.84, 167.84, 165.28, 163.83, 163.69, 162.79, 161.14, 145.46, 133.08, 129.15, 126.66, 123.96, 122.55, 122.44, 119.61, 117.33, 117.32, 112.38, 112.13, 97.51, 97.25, 57.93, 53.45, 45.70, 36.16, 34.52, 31.44, 30.51, 27.33, 24.24, 21.97. HRMS (ESI) m/z 462.2188 (calcd 462.2187 for $C_{27}H_{29}FN_3O_3^+$ $[M+H]^+$).

7-fluoro-8-(4-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)butanoyl)-5,6-dihydro -1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (45). Pale yellow oil; yield 73.2 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.64 – 7.60 (m, 1H), 7.19 – 7.10 (m, 1H), 7.06 – 6.98 (m, 1H), 4.10 (t, *J* = 8.2 Hz, 2H), 3.18 (t, *J* = 8.0 Hz, 2H), 3.05 – 2.90 (m, 7H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 6.5 Hz, 2H), 2.13 (t, *J* = 10.3 Hz, 2H), 2.05 –

1.89 (m, 6H). HRMS (ESI) m/z 480.2099 (calcd 480.2093 for $C_{27}H_{28}F_2N_3O_3^+$ $[M+H]^+$).

9-fluoro-8-(4-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)butanoyl)-5,6-dihydro -1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (46). Pale yellow oil; yield 72.6 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.62 (dt, *J* = 9.3, 4.7 Hz, 1H), 7.17 (dt, *J* = 8.3, 4.1 Hz, 1H), 7.00 (ddd, *J* = 8.6, 6.4, 1.8 Hz, 1H), 4.08 (t, *J* = 8.2 Hz, 2H), 3.19 (t, *J* = 8.0 Hz, 2H), 3.05 – 2.90 (m, 7H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.44 (t, *J* = 6.5 Hz, 2H), 2.12 (t, *J* = 10.3 Hz, 2H), 2.04 – 1.89 (m, 6H). HRMS (ESI) m/z 480.2100 (calcd 480.2093 for $C_{27}H_{28}F_2N_3O_3^+$ $[M+H]^+$).

8-(5-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)pentanoyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (47). Pale yellow oil; yield 70.4 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 3H), 7.21 – 7.18 (m, 1H), 7.05 – 7.00 (m, 1H), 4.13 – 4.10 (m, 2H), 3.21 (dd, *J* = 10.9, 5.4 Hz, 2H), 3.06 – 2.93 (m, 7H), 2.69 (dd, *J* = 11.3, 7.5 Hz, 2H), 2.43 (d, *J* = 7.5 Hz, 2H), 2.11 – 2.03 (m, 6H), 1.76 (s, 2H), 1.61 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.90, 167.81, 165.25, 163.84, 163.71, 162.76, 161.09, 145.50, 132.86, 129.17, 126.62, 123.92, 122.64, 122.53, 119.62, 117.29, 117.28, 112.37, 112.12, 97.49, 97.22, 58.57, 53.56, 45.68, 38.27, 34.60, 31.42, 30.55, 27.32, 26.63, 24.22, 22.65. HRMS (ESI) m/z 476.2348 (calcd 476.2344 for $C_{28}H_{31}FN_3O_3^+$ $[M+H]^+$).

8-(6-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)hexanoyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (48). Pale yellow oil; yield 66.1 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 – 7.68 (m, 3H), 7.26 – 7.18 (m, 1H), 7.10 – 7.00 (m, 1H), 4.20 – 4.10 (m, 2H), 3.44 (t, *J* = 6.2 Hz, 2H), 3.20 – 2.90 (m, 9H) , 2.72 – 2.66 (m,

2H), 2.20 – 1.95 (m, 6H), 1.86 – 1.73 (m, 4H), 1.59 – 1.46 (m, 2H). HRMS (ESI) m/z 490.2506 (calcd 490.2500 for $C_{29}H_{33}FN_3O_3^+$ $[M+H]^+$).

General Procedure for the Preparation of Compounds 49 – 51.

According method A. 8-(3-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl) propyl)-5,6-dihydro-1H-pyrrolo [3,2,1-ij]quinolin-4(2H)-one **(49).** To a suspension of **41** (0.5 g, 1.1 mmol) in 20 mL CF_3COOH was added Et_3SiH (0.38 g, 3 eq). After reaction at room temperature overnight, the mixture solvent was removed under reduced pressure, and the residue was dissolved in 100 mL dichloromethane, and then washed by saturated $NaHCO_3$ and brine. The dichloromethane layer was dried with anhydrous $MgSO_4$, and then removed by evaporation, and the crude product was purified by chromatography (MeOH: $CHCl_3$ = 10: 1) to give **49**. Pale yellow oil; yield 92.2 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.72 (s, 1H), 7.71 – 7.68 (m, 1H), 7.29 – 7.20 (m, 1H), 7.06 (td, *J* = 8.8, 1.9 Hz, 1H), 4.15 (t, *J* = 8.5 Hz, 2H), 3.25 (t, *J* = 8.5 Hz, 2H), 3.18 (dt, *J* = 13.1, 7.8 Hz, 3H), 3.09 (dt, *J* = 22.0, 9.4 Hz, 4H), 3.04 (t, *J* = 7.8 Hz, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.74 (t, *J* = 7.8 Hz, 2H), 2.30 – 2.26 (m, 2H), 2.15 – 2.06 (m, 4H). HRMS (ESI) m/z 434.2230 (calcd 434.2238 for $C_{26}H_{29}FN_3O_2^+$ $[M+H]^+$).

According method B. Compounds **7** (0.32 mmol), K_2CO_3 (4 eq), arylpiperazine (piperidine) (1 eq) and a catalytic amount of KI were added in 5.0 mL CH_3CN, and then refluxed for 27-30 h. After reaction, the filtrate was evaporated to dryness under reduced pressure. The residue was extracted with 75 mL dichloromethane by three times, after it was diluted with 10.0 mL water. After dried over $MgSO_4$,

dichloromethane were removed by evaporation. The crude product was purified by chromatography (MeOH: $CHCl_3$ = 50:1) to give target compounds.

8-(4-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)butyl)-5,6-dihydro-1H-pyrrolo [3,2,1-ij]quinolin-4(2H)-one (50). Pale yellow oil; yield 70.2 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.2 Hz, 1H), 7.26 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.10 (td, *J* = 8.8, 2.0 Hz, 1H), 6.92 (s, 1H), 6.83 (s, 1H), 4.08 (t, *J* = 8.4 Hz, 2H), 3.42 – 3.23 (m, 3H), 3.18 (t, *J* = 8.4 Hz, 2H), 2.96 (t, *J* = 7.7 Hz, 2H), 2.68 (t, *J* = 7.7 Hz, 4H), 2.62 (t, *J* = 7.5 Hz, 4H), 2.33 (s, 4H), 1.76 (s, 2H), 1.71 – 1.57 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.46, 165.30, 163.91, 163.78, 162.81, 161.09, 139.32, 137.97, 128.91, 125.39, 123.25, 122.64, 122.53, 119.87, 117.29, 112.42, 112.17, 97.55, 97.28, 58.82, 53.61, 45.28, 35.70, 34.61, 31.71, 30.52, 30.03, 27.78, 26.64, 24.44. HRMS (ESI) m/z 448.2383 (calcd 448.2395 for $C_{27}H_{31}FN_3O_2^+$ $[M+H]^+$).

8-(5-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)pentyl)-5,6-dihydro-1H-pyrrolo [3,2,1-ij]quinolin-4(2H)-one (51). Pale yellow oil; yield 69.8 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.6, 5.1 Hz, 1H), 7.26 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.15 – 7.00 (m, 1H), 6.92 (s, 1H), 6.83 (s, 1H), 4.09 (t, *J* = 8.4 Hz, 2H), 3.29 – 3.09 (m, 5H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.69 (t, *J* = 7.7 Hz, 2H), 2.64 – 2.54 (m, 2H), 2.49 (s, 2H), 2.19 (dd, *J* = 43.3, 32.1 Hz, 6H), 1.64 (dt, *J* = 15.2, 7.7 Hz, 4H), 1.39 (dt, *J* = 15.3, 7.7 Hz, 2H). HRMS (ESI) m/z 462.2537 (calcd 462.2551 for $C_{28}H_{33}FN_3O_2^+$ $[M+H]^+$).

General Procedure for the Preparation of Compounds 52 - 54.

To a suspension of **41** (3 mmol) in 30 mL methol, $NaBH_4$ (3.1 mmol) was added by portions under the room temperature. After stirred for 6−8 h, the reaction was quenched by 100 mL ice water, 75 mL dichloromethane was used to extracte the mixture by three times. The organic layer was dried with anhydrous $MgSO_4$,

dichloromethane was evaporated under reduced pressure. The crude product was purified by means of chromatography (MeOH: $CHCl_3$ = 10:1) to yield 8-(3-(4-(6-fluorobenzo[d]isoxazol -3-yl)Piperidin-1-yl)-1-hydroxypropyl)-5,6-dihydro -1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one **(52).** Pale yellow oil; yield 93.1 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.7, 5.1 Hz, 1H), 7.27 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.14 (s, 1H), 7.11 – 7.04 (m, 2H), 4.91 (dd, *J* = 9.1, 2.3 Hz, 1H), 4.10 (t, *J* = 8.4 Hz, 2H), 3.34 (s, 1H), 3.19 (dd, *J* = 16.2, 7.7 Hz, 4H), 2.98 (t, *J* = 7.8 Hz, 2H), 2.89 – 2.76 (m, 1H), 2.69 (t, *J* = 7.7 Hz, 3H), 2.40 (s, 1H), 2.22 – 2.07 (m, 6H), 1.99 – 1.87 (m, 1H), 1.87 – 1.78 (m, 1H). HRMS (ESI) m/z 450.2181 (calcd 450.2187 for $C_{26}H_{29}FN_3O_3^+$ $[M+H]^+$).

8-(4-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)-1-hydroxybutyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (53). Pale yellow oil; yield 92.5 %; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 – 7.74 (m, 1H), 7.2 – 7.24 (m, 1H), 7.14 (s, 1H), 7.08 – 7.04 (m, , 2H), 4.66 – 4.63 (m, 1H), 4.08 (t, *J* = 8.4 Hz, 2H), 3.18 (t, *J* = 8.4 Hz, 4H), 2.97 (t, *J* = 7.7 Hz, 4H), 2.68 (t, *J* = 7.8 Hz, 2H), 2.59 (d, *J* = 5.0 Hz, 2H), 2.29 – 2.18 (m, 2H), 2.21 – 2.09 (m, 4H), 2.03 – 1.91 (m, 2H), 1.87 – 1.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.66, 165.35, 163.98, 163.85, 162.86, 160.54, 141.55, 140.16, 128.84, 123.00, 122.82, 122.71, 120.80, 119.80, 117.05, 112.65, 112.40, 97.57, 97.31, 73.87, 58.90, 53.45, 52.48, 45.37, 40.07, 31.68, 29.66, 27.78, 24.47, 24.10. HRMS (ESI) m/z 464.2335 (calcd 464.2344 for $C_{27}H_{31}FN_3O_3^+$ $[M+H]^+$).

8-(5-(4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-yl)-1-hydroxypentyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one (54). Pale yellow oil; yield 93.6 %; ^{1}H

NMR (600 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 1H), 7.26 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.12 (s, 1H), 7.06 (td, *J* = 8.8, 2.1 Hz, 1H), 7.03 (s, 1H), 4.66 (dd, *J* = 7.9, 5.4 Hz, 1H), 4.11 (t, *J* = 8.4 Hz, 2H), 3.26 – 3.18 (m, 2H), 3.16 – 3.06 (m, 2H), 3.04 – 2.94 (m, 2H), 2.70 (t, *J* = 7.8 Hz, 2H), 2.47 – 2.39 (m, 2H), 2.28 – 1.97 (m, 6H), 1.90 – 1.72 (m, 2H), 1.57 – 1.49 (m, 4H), 1.46 – 1.38 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.65, 165.28, 163.86, 163.73, 162.79, 161.01, 141.16, 140.41, 128.94, 123.24, 122.82, 122.71, 120.99, 119.84, 117.19, 117.18, 112.45, 112.19, 97.49, 97.22, 73.99, 58.53, 53.53, 53.41, 45.36, 39.07, 34.42, 31.55, 30.17, 27.72, 26.39, 24.37, 23.76. HRMS (ESI) m/z 478.2512 (calcd 478.2500 for $C_{28}H_{33}FN_3O_3^+$ $[M+H]^+$).

Receptor Binding Studies

Materials. The following specific radioligands and tissue sources were used: (a) the serotonin 5-HT_{1A} receptor, [^{3}H]8-OH-DPAT, from rat brain cortex; (b) the serotonin 5-HT_{2A} receptor, [^{3}H]ketanserin in the present of 4-dione hydrochloride hydrate (35 nM), from rat brain cortex; (c) the serotonin 5-HT_{2C} receptor, [^{3}H]mesulergine in the present of spiperone (40 nM), from rat brain cortex; (d) the serotonin 5-HT_6 receptor, [^{3}H]lysergic acid diethylamide, from 5-HT_6-C3 cells (CHO-K1); (e) the dopamine D2 receptor, [^{3}H]spiperone, from rat striatum; (f) the histamine H_1 receptor, [^{3}H]mepyramine, from guinea pig cerebellum; (g) the adrenergic α_1 receptor, [^{3}H]prazosin, from rat cerebral cortex; and (h) the dopaminergic D_3 Receptor, [^{3}H] 7-OH-DPAT, from rat olfactory tubercle.

General Procedures for the Binding Assays. All of the new compounds were solved in 50 % (v/v) DMSO, and the compound concentration is 2×10^{-3} M. Diluted to the

initial concentration of the new compound is 2×10^{-4} M contained 5% DMSO. For 5-HT_{1A} receptor binding assays, total binding (TB) was determined in the presence of the radioligand [^{3}H]8-OH-DPAT. Nonspecific binding (NB) was determined in the presence of the radioligand [^{3}H]8-OH-DPAT and serotonin, whereas compound binding (CB) was determined in the presence of the radioligand [^{3}H]8-OH-DPAT and the compound of interest. Each specific binding (SB) was calculated as the total binding (TB) minus the nonspecific binding (NB) at a particular concentration of radioligand. Each percentage of inhibition (%) was calculated as follows: percentage of inhibition (%) = [(TB - CB)/(TB - NB)] × 100.

Blank binding experiments contained 0.25% (v/v) DMSO were performed; DMSO had no effect. All compounds were tested at least three times over a six-fold concentration range (10^{-5}M to 10^{-10} M). IC_{50} values were determined by nonlinear regression analysis with fitting to the Hill equation curve. Ki values were calculated using the Cheng and Prussoff equation, $K_i = IC_{50}/(1 + C/K_d)$, where C represents the concentration of the hot ligand used, and K_d the receptor dissociation constant of each labeled ligand. The mean K_i values and SEM were derived in at least three independent experiments.

5-HT_{1A} receptor.[28b, 28c] Rat cerebral cortex was homogenized in 20 vol of ice-cold Tris-HCl buffer (50 mM, pH 7.4) using an ULTRA TURAX homogeniser, and was then centrifuged at 32,000 g for 10 min. The resulting pellet was then resuspended in the same buffer, incubated for 10 min at 37 ^{o}C, and centrifuged at 32,000 g for 10 min. The final pellet was resuspended in Tris-HCl buffer containing 10 mM Pargyline, 4

mM $CaCl_2$ and 0.1% ascorbic acid. Total binding each assay tube was added 900 μL of the tissue suspension, 50 μL of 0.5 nM [^{3}H] 8-OH-DPAT (187.4 Ci/mmol, Perkin Elmer Life Sciences, Boston, MA, USA), 50 μL Tris-HCl buffer containing 10mM Pargyline, 4 mM $CaCl_2$ and 0.1% ascorbic acid. Non-specific binding each assay tube was added 900 μL of the tissue suspension, 50 μL of [^{3}H] 8-OH-DPAT, 50 μL of 10 mM serotonin. Compound binding each assay tube was added 900 μL of the tissue suspension, 50 μL of [^{3}H] 8-OH-DPAT, 50 μL of new compounds or reference drug. The tubes were incubated at 37 ^{o}C for 30 min. The incubation was followed by a rapid vacuum filtration through Whatman GF/B glass filters, and the filtrates were washed twice with 5 mL cold buffer and transferred to scintillation vials. Scintillation fluid (1.0 mL) was added and the radioactivity bound was measured using a PE Microbeta 2450 liquid scintillation counter.

5-HT$_{2A}$ receptor.[28b, 28c] Rat cerebral cortex was homogenized in 20 vol of ice-cold Tris-HCl buffer (50 mM, pH 7.4) using an ULTRA TURAX homogeniser, and centrifuged at 32,000 g for 20 min. The resulting pellet was resuspended in the same quantity of the buffer centrifuged for 20 min. The final pelletwas resuspended in 50 vol of the Tris-HCl buffer. Total binding each assay tube was added 900 μL of the tissue suspension, 50 μL of 0.6 nM [^{3}H] ketanserine (60.0 Ci/mmol, Perkin Elmer Life Sciences, Boston, MA, USA), 50 μL of 4-dione hydrochloride hydrate and 50 μL Tris-HCl buffer. Nonspecific binding each assay tube was added 900 μL of the tissue suspension, 50 μL of [^{3}H] ketanserin, 50 μL of 4-dione hydrochloride hydrate and 50 μL of 10 mM methisergide. Compound binding each assay tube was added 900 μL of

the tissue suspension, 50 μL of [^{3}H] ketanserin, 50 μL of 4-dione hydrochloride hydrate and 50 μL of new compounds or reference drug. The tubes were incubated at 37 ^{o}C for 30 min. The incubation was followed by a rapid vacuum filtration through Whatman GF/B glass filters, and the filtrates were washed twice with 5 mL cold buffer and transferred to scintillation vials. Scintillation fluid (1.0 mL) was added and the radioactivity bound was measured using a PE Microbeta 2450 liquid scintillation counter.

Dopamine D2 receptor.[28b, 28c] Rat striatum was homogenized in 20 vol of ice-cold 50mM Tris-HCl buffer (pH 7.4) using an ULTRA TURAX homogeniser, and centrifuged twice for 10 min at 48,000 g with resuspension of the pellet in fresh buffer. The final pellet was resuspended in 50 mM ice-cold Tris-HCl containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% ascorbic acid and 5 mM pargyline. Total binding each assay tube was added 900 μL of the tissue suspension, 50 μL of 0.5 nM [3H] spiperone (16.2 Ci/mmol; Perkin Elmer Life Sciences, Boston, MA, USA), 50 μL Tris-HCl buffer containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% ascorbic acid and 5 mM pargyline. Non-specific binding each assay tube was added 900 μL of the tissue suspension, 50 μL of [^{3}H]spiperone, 50 μL of 10 mM (t)-butaclamol. Compound binding each assay tube was added 900 μL of the tissue suspension, 50 μL of [^{3}H] spiperone, 50 μL of new compounds or reference drug. The tubes were incubated at 37 ^{o}C for 30 min. The incubation was followed by a rapid vacuum filtration through Whatman GF/B glass filters, and the filtrates were washed twice with 5 mL cold buffer and transferred to scintillation vials.

Scintillation fluid (1.0 mL) was added and the radioactivity bound was measured using a PE Microbeta 2450 liquid scintillation counter.

Histamine H_1 receptor.[28b, 28c] Guinea pig cerebellum was homogenized in 20 vol of ice-cold 50 mM phosphate buffer (pH 7.7) using an ULTRA TURAX homogeniser, and centrifuged twice for 10 min at 50,000 g with resuspension of the pellet in fresh buffer. The final pellet was resuspended in phosphate buffer. Total binding each assay tube was added 900 μL of membranes 50 μL of 1 nM [^{3}H]mepyramine (20.0 Ci/mmol; Perkin Elmer Life Sciences, Boston, MA, USA), 50 μL phosphate buffer. Non-specific binding each assay tube was added 900 μL of membranes, 50 μL of [^{3}H]mepyramine, 50 μL of 1 mM promethazine. Compound binding each assay tube was added 900 μL of Membranes, 50 μL of [^{3}H]mepyramine, 50 μL of new compounds or reference drug. The tubes were incubated at 30 ^{o}C for 60 min. The incubationwas followed by a rapid vacuum filtration through Whatman GF/B glass filters, and the filtrates were washed twice with 5 mL cold buffer and transferred to scintillation vials. Scintillation fluid (1.0 mL) was added and the radioactivity bound was measured using a PE Microbeta 2450 liquid scintillation counter.

5-HT_{2C} receptor.[28b, 28c] Rat cerebral cortex was homogenized in 20 vol of ice-cold Tris-HCl buffer (50 mM, pH 7.4) using an ULTRA TURAX homogeniser and centrifuged at 32000g for 20 min. The resulting pellet was resuspended in the same quantity of the buffer centrifuged for 20 min. The final pellet was resuspended in 50 vol of the Tris-HCl buffer. For total binding, to each assay tube was added 900 μL of the tissue suspension, 50 μL of [^{3}H]mesulergine, 50 mL of spiperone and 50 μL of

Tris-HCl buffer. For nonspecific binding, to each assay tube was added 900 μL of the tissue suspension, 50 μL of 1 nM [^{3}H]mesulergine (85.4 Ci/mmol; Perkin-Elmer Life Sciences, Boston, MA, USA), 50 μL of spiperone and 50 μL of 10 mM mianserin. Compound binding, to each assay tube was added 900 μL of the tissue suspension, 50 μL of [^{3}H]mesulergine, 50 μL of spiperone and 50 μL of new compounds, or reference drug. The tubes were incubated at 37 ^{o}C for 15 min. The incubation was followed by rapid vacuum filtration through Whatman GF/B glass filters, and the filtrates were washed twice with 5 mL of cold buffer and transferred to scintillation vials. Scintillation fluid (1.0 mL) was added, and the radioactivity bound was measured using a PE Microbeta 2450 liquid scintillation counter.

Adrenergic α_1 receptor.[28b, 28c] Rat cerebral cortex was homogenized in 20 vol of ice-cold Tris-HCl buffer containing 5 mM EDTA (50 mM, pH 7.4) using an ULTRA TURAX homogeniser and centrifuged at 44000 g for 20 min at 4 ^{o}C. The resulting pellet was resuspended in the same quantity of the buffer centrifuged for 20 min. The final pellet was resuspended in 50 vol of the Tris-HCl buffer. For total binding, to each assay tube was added 900 μL of the tissue suspension, 50 μL of 1 nM [^{3}H]prazosin (85.4 Ci/mmol; Perkin-Elmer Life Sciences, Boston, MA, USA), and 50 μL of Tris-HCl buffer. For nonspecific binding, to each assay tube was added 900 μL of the tissue suspension, 50 μL of 1 nM [^{3}H]prazosin, and 50 μL of 10 mMprazosin. Compound binding, to each assay tube was added 900 μL of the tissue suspension, 50 μL of [^{3}H]prazosin, 50 μL of new compounds, or reference drug. The tubes were incubated at 25 ^{o}C for 60 min. The incubation was followed by rapid vacuum

filtration through Whatman GF/B glass filters, and the filtrates were washed twice with 5 mL of cold buffer and transferred to scintillation vials. Scintillation fluid (1.0 mL) was added, and the radioactivity bound was measured using a PE Microbeta 2450 liquid scintillation counter.

5-HT$_6$ receptor.[28b, 28c] Membranes were prepared from CHO-5-HT$_6$ cells stably transected with the human serotonin 5-HT$_6$ receptor cell. The harvested cells are suspended in 1 volume of fresh physiological phosphate buffered saline (PBS) solution and centrifugedat 1000 g. This homogenate was centrifuged at 100000 g for 60 min, the resulting pellet was suspended in Tris-HCl (pH 7.4) to obtain a concentration corresponding to 4×10^7 cells/ml and aliquots were stored at -80 ^{o}C. Total binding each assay tube was added 900 μL of the tissue suspension, 50 μL of 2 nM [^{3}H]lysergic acid diethylamide (84.0 Ci/mmol, Perkin Elmer Life Sciences, Boston, MA, USA), 50 μL Tris-HCl buffer. Non-specific binding each assay tube was added 900 μL of the tissue suspension, 50 μL of [^{3}H]lysergic acid diethylamide, 50 μL of 10 mM serotonin. Compound binding each assay tube was added 900 μL of the tissue suspension, 50 μL of [^{3}H]lysergic acid diethylamide, 50 μL of new compounds or reference drug. The tubes were incubated at 37 ^{o}C for 30 min. The incubation was followed by a rapid vacuum filtration through Whatman GF/B glass filters, and the filtrates were washed twice with 5 mL cold buffer and transferred to scintillation vials. Scintillation fluid (1.0 mL) was added and the radioactivity bound was measured using a PE Microbeta 2450 liquid scintillation counter.

Dopaminergic D$_3$ Receptor.[28b, 28c] A rat olfactory tubercle was homogenized in 20

volumes of ice-cold 50 mM Hepes Na (pH 7.5) using an ULTRA TURAX homogenizer and centrifuged twice for 10 min at 48,000 g with resuspension of the pellet in fresh buffer. The final pellet was resuspended in 50 mM Hepes Na, pH 7.5, containing 1 mM EDTA, 0.005% ascorbic acid, 0.1% albumin, and 200 nM eliprodil. For total binding, to each assay tube was added 900 μL of membranes, 50 μL of 0.6 nM [^{3}H] 7-OH-DPAT (50 Ci/mmol; Perkin-Elmer Life Sciences, Boston, MA, USA), and 50 μL of 50 mM Hepes Na, pH 7.5, containing 1 mM EDTA, 0.005% ascorbic acid, 0.1% albumin, and 200 nM eliprodil. For nonspecific binding, to each assay tube was added 900 μL of membranes, 50 μL of [^{3}H] 7-OH-DPAT (50 Ci/mmol; Perkin-Elmer Life Sciences, Boston, MA, USA), and 50 μL of 1 μM dopamine. For specific binding, to each assay tube was added 900 μL of membranes, 50 μL of [^{3}H] 7-OH-DPAT (50 Ci/mmol; Perkin-Elmer Life Sciences, Boston, MA, USA), 50 μL of new compounds, or reference drug. The tubes were incubated at 25 °C for 60 min. The incubation was followed by rapid vacuum filtration through Whatman GF/B glass filters, and the filtrates were washed twice with 5 mL of cold buffer and transferred to scintillation vials. Scintillation fluid (1.0 mL) was added, and the radioactivity bound was measured using a PE Microbeta 2450 liquid scintillation counter.

Experimental in Vitro Pharmacology for Intrinsic Activity Assessment.[22, 28b]

HEK cells expressing five receptors (HEK293/D_{2L}, HEK293/ACTOne D_3, HEK293/5-HT_{1A}, HEK293/5-HT_{2A}, HEK293T/h5-HT_6) were seeded in a 384-well black-walled, clearbottom plate at a density of 1.5×10^4 cells/well in cell seeding medium (90% DMEM and 10% dialyzed serum) and incubated in CO_2 incubator for

16-24 hours (at least overnight).

For the D_{2L} assay, all compounds were diluted with DMSO, 1/2 log dilution (3.162 fold) , 11 points and triplicate to get the compounds dose, then added the assay buffer to get the working concentration and did the test. Agonist mode: 1: Diluted the reference compound Dopamine to 50 μM (11 points, 5X) 2: Diluted the test compounds to working concentration (11 points, 5X); Antagonist mode: 1: Diluted the reference compound SCH23390 to 600 μM (11 points, 6X) 2: Diluted the test compounds to working concentration (11 points, 6X). Assay buffer: 1x HBSS, 20 mM HEPES, 2.5 mM Probenecid (Probenecid is 400 mM stock in 1 M NaOH, add freshly). Assay buffer was used as dye loading buffer, compound dilution buffer, etc.

And then gently discarded the medium, and added 20 μL calcium dye loading solution into each well. Incubated the plate at 37°C in the dark for 60 min before calcium signal readout.

For the agonist assay, added 5 μL/well 5x working concentration of test compounds into cell plate using FLIPR. Read with FLIPR (FLIPR Calcium 4, Molecular Devices) using the specified settings and saved data. The total assay volume was 25 μL including 20 μL/well dye loading buffer and 5 μL/well 5x working concentration of test compounds.

For the antagonist assay, added 6x working concentration of antagonist compound at 5 μL/well to cells and incubated plate at room temperature in the dark for 15 mins. Transferred assay plate to FLIPR and added 5 μL/well 6x working concentration of antagonist compound using FLIPR. Read with FLIPR using the

specified settings and saved data. The total assay volume was 30 μL including 20 μL/well dye loading buffer, 5 μL/well 6x work concentration of test compounds and 5 μL/well 6x work concentration of agonist compound.

Data analysis: FLIPR read the plate and got the maximal fluorescence signal data from the Excitation light wavelength at 480 nm and Emission light wavelength at 520 nm. All results for test compounds were test three times. According to the positive control (HPE) and negative control (ZPE) results, calculated the Effcet (%) or Inhibition (%) of reference and the test compounds, used GraphPad Prism 5 to analyze the data, and got the dose response curve and the value of EC_{50} and IC_{50}.

Effcet (%) for agonist mode was calculated from the following equation:

$$\text{Effcet (\%)} = (\text{Value}_{(\text{Raw Data})} - \text{Average}_{(\text{ZPE})}) / (\text{Average}_{(\text{HPE})} - \text{Average}_{(\text{ZPE})}) \times 100$$

The % Effcet was then plotted as a function of the log of the cumulative doses of compounds.

Inhibition (%) for antagonist mode was calculated from the following equation:

$$\text{Inhibition (\%)} = (\text{Average}_{(\text{HPE})} - \text{Value}_{(\text{Raw Data})}) / (\text{Average}_{(\text{HPE})} - \text{Average}_{(\text{ZPE})}) \times 100$$

The % inhibition was then plotted as a function of the log of the cumulative doses of compounds.

hERG Affinity.

Ability to block hERG potassium channels was determined using the whole-cell patch clamp method and cloned hERG potassium channels (expressed in HEK 293 cells) as biological material.[49] For this purpose, the patch clamp amplifier (Axopatch

200B, Molecular Devices) and digital converter (Digidata 1440A, Molecular Devices) were used. Recording electrodes were made from borosilicate glass with filament (BF120-94-15, Sutter Instrument Company). Creation of voltage-clamp command pulse protocols and data acquisition were controlled by pCLAMP software (version 10.1, Molecular Devices). The bath solution consisted of 137 mM NaCl, 5.4 mM KCl, 10 mM glucose, 10 mM HEPES, and 2 mM $CaCl_2$. The pH was adjusted to 7.5 by addition of NaOH. The pipet filling solution consisted of 140 mM KCl, 1 mM $MgCl_2$, 5 mM EGTA, 10 mM HEPES, and 5 mM Na_2ATP. The pH was adjusted to 7.2 by addition of KOH. The test compound 47 was solved in 50 % (w/v) DMSO, and the initial concentration was 1 mM, and the test concentration for compound 47 was Diluted by the the bath solution.

To study voltage dependence of steady-state block of hERG channels on different drug concentrations (0.3, 1, 3, and 10 μM) in HEK cells, the holding membrane potential was switched from −80 to +50 mV for 2 s following return to −50 mV for 3 s (sampling rate of 4 kHz, low-pass filtered at 1 kHz) in intervals of 30 s. Tail currents were measured at −50 mV in control and in the presence of the drug at concentrations determined empirically. All raw measurements were performed using Clampfit (version 10.2), a part of pCLAMP software (version 10.1). The hERG inhibition experiments were tested three independent experiments. Results were transferred to the program Statistical Package for the Social Sciences (SPSS) spreadsheets for further analysis.

***In Vivo* Test.**

Animals. Chinese Kun Ming (KM) mice (20 ± 2.0 g) and Sprague-Dawley (SD) rats (250 ± 5.0 g) were used as experimental animals in this study. All the animals were housed under standardized conditions for light, temperature, and humidity and received standard rat chow and tap water and libitum. Animals were assigned to different experimental groups randomly, each kept in a separate cage. In the test, the drug was administered p.o. in a vehicle of 10:90 PEG400/H_2O at a volume of 0.1 mL/10g. All studies involving animals in this research follow the guidelines of the bylaw of experiments on animals and have been approved by the Ethics and Experimental Animal Committee of Jiangsu Nhwa Pharmaceutical Co., Ltd.

Acute toxicity.

Mice (10 mice in each group) were orally dosed with increasing doses of the compound **47** (250, 500, 1000, 1500 and 2000 mg/kg). The number of surviving animals was recorded after 24 h of drug administration, and the percent mortality in each groupwas calculated. The LD_{50} values were calculated by using the program SPSS (Statistical Package for the Social Science).

MK-801-induced hyperactivity.[28b, 28c]

Mice (10 mice in each group) were orally dosed with vehicle or increasing doses of the haloperidol (0.1, 0.3, 1, 3.0 and 10 mg/kg), risperidone (0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg) and compound 47 (0.03, 0.1, 0.3 and 1 mg/kg). Animals were placed in Plexiglas cages for evaluating locomotor activity. After 60 min, the animals were challenged with 0.3 mg/kg (sc) of MK-801 and the locomotor activity of each animal was recorded for 90 min. Statistical evaluation was performed by two-way

ANOVA followed by Tukey test for multiple comparisons. #, $p < 0.05$ versus vehicle treatment; **, $p < 0.01$, *, $p < 0.05$ versus MK-801 treatment.

Apomorphine-induced climbing.[28b, 28c]

Mice (10 mice in each group) were orally dosed with vehicle or increasing doses of the haloperidol (0.1, 0.3, 1 and 3 mg/kg), risperidone (0.01, 0.03, 0.1 and 0.3 mg/kg), compound **47** (0.1, 0.3, 1 and 3 mg/kg). Animals were then challenged at 30 min post-injection with 1.0 mg/kg of the apomorphine in 0.9% NaCl + 0.1% ascorbic acid, placed in cylindrical wire cages (12 cm in diameter, 14 cm in height), and observed for climbing behavior at 10, 20 and 30 min post dose. The climbing behavior was scored as follows: 3, 4 paws on the cage floor = 0 score; 2 and 3 paws on the cage = 1 score; 4 paws on the cage = 2 score. The statistical significances of drug effects were analyzed by the nonparametric two-tailed-Manne-Whitney U test: #, $p < 0.05$ versus vehicle treatment; **, $p < 0.01$, *, $p < 0.05$ versus apomorphine treatment.

Catalepsy test.[28b, 28c]

Mice (10 mice in each group) were orally dosed with vehicle or increasing doses of the haloperidol (0.1, 0.3, 1, 1.5 and 3.0 mg/kg), risperidone (0.1, 0.4, 0.75, 1.5, 3 and 6.0 mg/kg), compound **47** (1, 5, 15, 45 and 100 mg/kg). 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; the endpoint was 60 s and an all-or-none criterion was used. A mean immobility score of 30 s was used as the criterion for the

presence of catalepsy.

Conditioned Avoidance Response (CAR).[28b, 28c, 48]

Rats were trained daily and tested in a computer-assisted two-way active avoidance apparatus (shuttle box) equipped with a tilting grid floor with microswitch detection and connected to a high resistant power supply. These boxes are divided into two compartments of equal size by a partition with one opening. Upon presentation of the light-conditioned stimulus (CS), the animal had 3 s to move from one compartment of the shuttle box into the other. If the rat remained in the same compartment for more than 3 s, the unconditioned stimulus (UCS) was presented as an electric shock in the grid floor, until the rat escaped. If it did not respond within 7 s, including the first 3 s, the trial was terminated (failure). The interval between trials was 45 s. The following variables were recorded: avoidance (response to CS within 3 s); escape (response to CS UCS); failure (failure to respond to CS and CS UCS); and intertrial crossing. The animals were trained on consecutive days until they achieved about 70% conditioned avoidance. The selected animals were given the different oral doses of either **47** (0.6, 1.2 and 2 mg/kg, po) or risperidone (0.06, 0.2 and 0.6 mg/kg, po). CAR was then tested 60 min later. While the training phase consisted of 40 trials each day (in one session), the testing phase consisted of 20 trials each session (one session at each of the time points). The number of trials in which an avoidance response occurred was divided by the total number of trials per session to give the percentage avoidance response.

Weight Gain and Serum Prolactin.[28b, 28c, 48]

Mice (10 mice in each group) were orally dosed with vehicle or increasing doses as follows: risperidone (0.03, 0.09, and 0.27 mg/kg) and **47** (0.6, 1.8 and 5.4 mg/kg). The animals received multiple doses (28 day) of each compound. The weight of mice was tested every day. The mice were killed by decapitation 180 min after the last treatment. Blood samples (2 mL) were collected and centrifuged (300 g for 30 min), and the resulting serum samples were stored at −20 °C until analyzed for prolactin (PRL). Serum PRL was determined by an EIA-kit from Amersham. Data were analyzed by Student's t test (##, $p < 0.01$).

Pharmacokinetics Study in Rats.

The HPLC conditions were as follows: column, XSELECT CSH XP C18 (2.1 mm × 50 mm, 2.5 μm); mobile phase, 0.025% FA and 1 mM NH4OAc (ROE SCIENTIFIC INC, USA) in water/acetonitrile (Merck Company, Germany) (v:v, 45:55); flow rate, 0.6 mL/min; column temperature, 50 °C. UV detection was performed at 210 nm. For routine compound **47** screening, rats (n = 6/group) were dosed via the lateral tail vein at the indicated dose for iv administration (1 mg/kg, 100% saline) or *via* oral gavage (10 mg/kg, suspension in 0.5% methylcellulose). At 30 min and 1, 2, 3, 4, 5, 6, 8 and 24 h after administration, serial blood samples were collected from the lateral tail vein into heparinized collection tubes (approximately 0.25 mL). The plasma was separated by centrifugation, and the sample was prepared for LC/MS analysis by protein precipitation with acetonitrile. The plasma samples were analyzed for drug and internal standard via the LC−MS/MS protocol.

Novel Object Recognition Training and Testing.[22b, 44, 45]

Rats were acclimated for 1 week prior to the experiment. The rats were housed in groups of two /cage in a light-controlled room (12 h light/dark cycles with lights on at 07:00). Food and water were provided ad libitum. Rats were habituated to handling and an empty test arena (a gray-colored polyvinyl chloride box (40 × 40 × 50 cm^3)) for 7 min on each of 3 consecutive days. On the training day, the drug was administered p.o. in a vehicle of physiological saline at a volume of 1 mL/kg. 1h after dosing, each rat was placed in the test arena, which now contained two identical objects located centrally in the arena. Rats were given either 3 min explore the arena and objects. Memory retention was tested 24 h after training. Rats were placed back in the arena with one "familiar" (previously trained) and one "novel" object and given 5 min to explore. The spatial position of objects left−right position) and which object was novel (ball or cube) was counterbalanced across subjects. Objects and arenas were cleaned with diluted 75% alcohol solution between trials to remove rat feces and urine. To determine memory performance, the novelty discrimination index (NDI) was calculated using the following equation: novel object interaction time/total interaction time ×100 (%). Rats were excluded from the analysis if total exploration time in the acquisition trial was less than 10 s. Numbers of rats treated with vehicle and those treated with 0.03, 0.1, and 0.3 mg/kg of compound **47** were n = 9 for 0.03 mg/kg and n = 10 for the other groups.

Statistics

To estimate the potency of test and reference compounds, the ED_{50} values and their 95% confidence limits were calculated by using the program SPSS (Statistical

Package for the Social Science).

ASSOCIATED CONTENT

Supporting Information

Additional receptors binding affinities of compound **47**; ^{1}H NMR, ^{13}C NMR, HRMS, and HPLC of compound **47**; ^{13}C NMR and HPLC of Compound **44**, **50**, **53** and **54**; LR-MS of the intermediates **3b**, **4b**, **5**, **6c** and **7a**; The D_1, D_{2L}, D_3, 5-HT_{1A}, 5-HT_{2A} and 5-HT_6 receptors functional activity of Compound **47**; The dose-response curve of hERG of compound **47**. Molecular Formula Strings: jmcmar_mfs.csv

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Notes

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ABBREVIATIONS USED

D_2, dopamine-2; D_3, dopamine-3; 5-HT_{1A}, serotonin-1A; 5-HT_{2A}, serotonin-2A; 5-HT_{2C}, serotonin-2C; H_1, histamine-1; α_1, adrenergic-1; EPS, extrapyramidal symptoms; hERG, ether-a-gogo-related gene; CNS, central nervous system; NMDA, N-methyl-D-aspartate; ED_{50}, 50% effective dose; LD_{50}, median lethal dose.

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Figure Captions

Figure 1. Reprensant of antipyschotics

Figure 2. Structure of **1** highlighting common dopaminergic D_2 structural characteristics: a motif containing features of common privileged structures, an aliphatic spacer/linker, and a heterocyclic group.

Figure 3. Design of multifunctional ligands. Based on the compound **1**, the privileged structures (phenylpiperazines and heterocyclicpiperazines(piperidines)) were introduced by replacement of 3-(piperidin-4-yl)-1H-indole. The appropriate linker between the merged fragments and the substituent of fused tricyclic heterocycles was investigation for the binding to the multi recpetors.

Figure 4. Summary of the results of SAR studies performed on different regions of the synthesized derivatives.

Figure 5. Effect of compound **47** administered po on APO (apomorphine)-induced climbing in mice (10/group). Results are expressed as means ± SEM of the score. Statistical significances of drug effects were analyzed by the nonparametric two-tailed Mann−Whitney U-test: #, $p < 0.05$ versus vehicle treatment; **, $p < 0.01$ and *, $p < 0.05$ versus apomorphine treatment.

Figure 6. Effect of compound **47** administered po on MK-801-induced hyperactivity in mice (10/group). Results are expressed as the means ± SEM of distance traveled. Statistical evaluation was performed by two-way ANOVA followed by Tukey's test for multiple comparisons. #, $p < 0.05$ versus vehicle treatment; **, $p < 0.01$ and *, $p < 0.05$ versus MK-801 treatment.

Figure 7. Effect of Risperidone (10/group) and compound **47** (10/group) on the performance of conditioned avoidance response in rats 90 min after single subcutaneous administration. The animals served as their own controls using a within-subject design. Values of percentage inhibition of avoidance are expressed as Mean±SEM. The avoidance values were analyzed in a repeated measures analysis of variance with dose (vehicle, resperidone and compound **47**) as a within-subjects factor for each drug separately. Post hoc comparisons were performed using the Bonferroni adjustment for multiple comparisons and the level of significance indicated in the figure is that with respect to vehicle treatment (**, $P < 0.05$) and all statistical analysis were carried out using SPSS software.

Figure 8. Influence of **47** and risperidone on weight gain. Each value is the mean ± SEM of 10 mice per group. Student's t test: ##, $p < 0.01$ versus vehicle group.

Figure 9. Serum prolactin (PRL) multiple (28 days) administration of compound **47** and risperidone in mice. Each value is the mean ± SEM of 10 mice per group. Student's t test: ##, $p < 0.01$ versus vehicle group.

Figure 10. Effects of **47** on a novel object recognition task in rats. Vehicle or **47** (0.03, 0.1, and 0.3 mg/kg), rivastigmine (0.3 mg/kg), risperidone (0.2 mg/kg) was orally administered 2 h prior to the acquisition trials. (A) Exploration times in the acquisition trial and (B) the retention trial (performed 48 h after the acquisition trial) were scored. (C) Novelty discrimination index (NDI) in the retention trial was calculated as novel object interaction time/total interaction time × 100 (%). Data are presented as the mean ± SEM, n = 9 for 0.03 mg/kg and n = 10 for the other groups;

**, $p < 0.01$ vs familiar object by paired t test; #, $p < 0.025$ vs vehicle by one-tailed Williams' test.

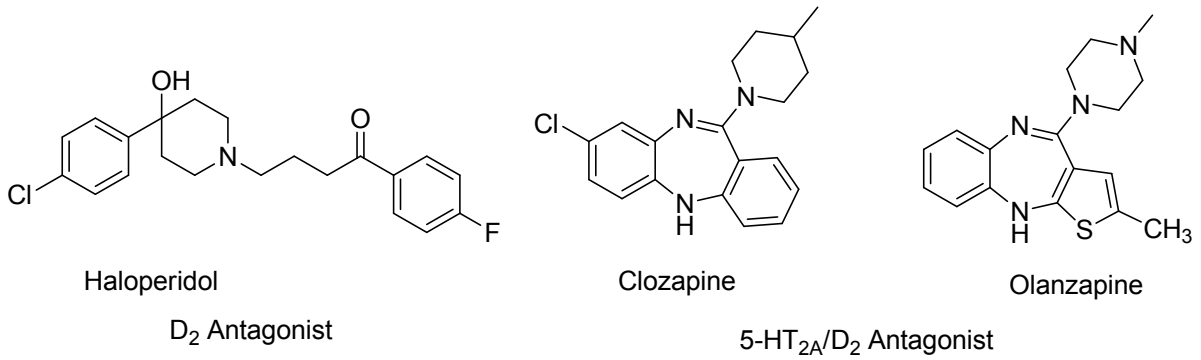
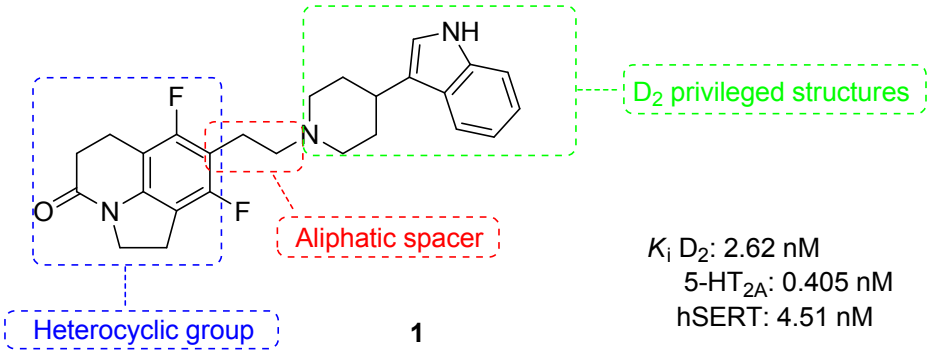


Figure 1. Reprensant of antipyschotics



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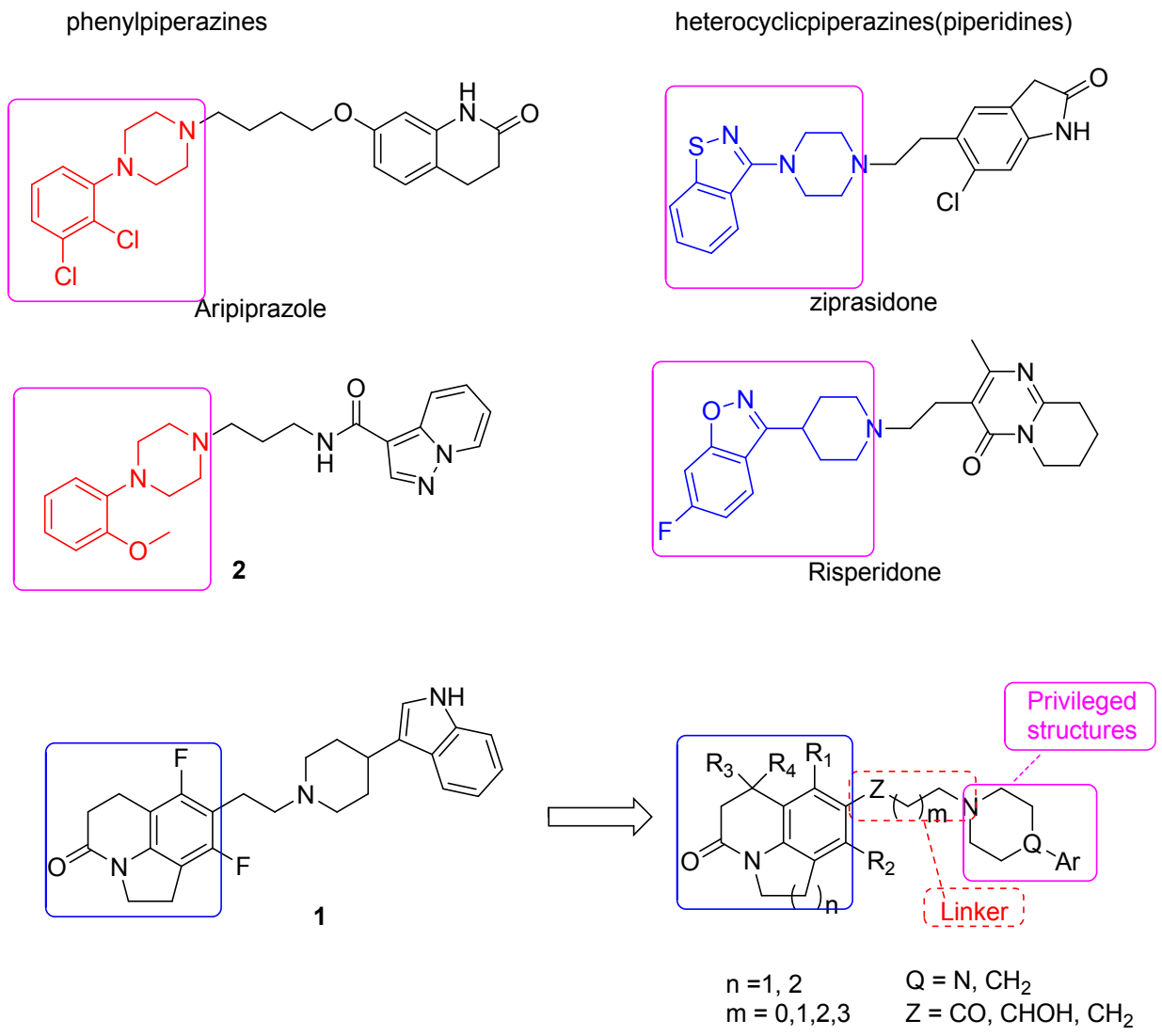

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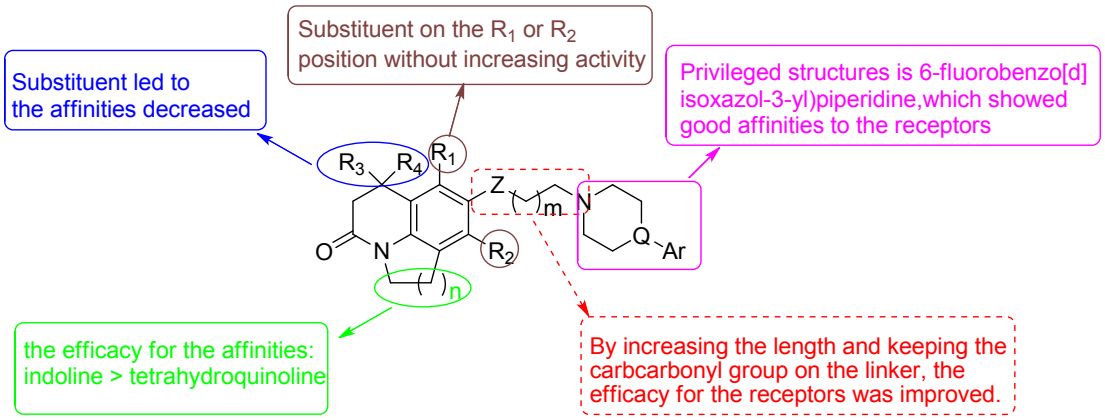

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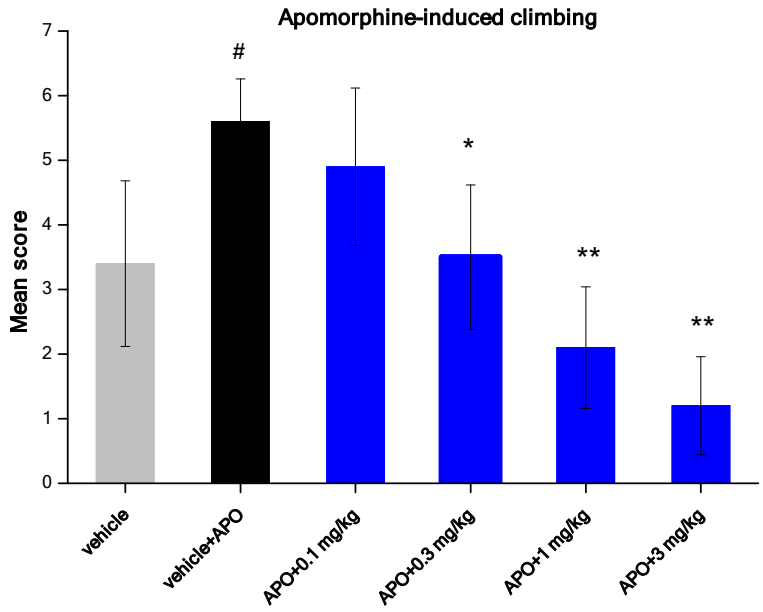

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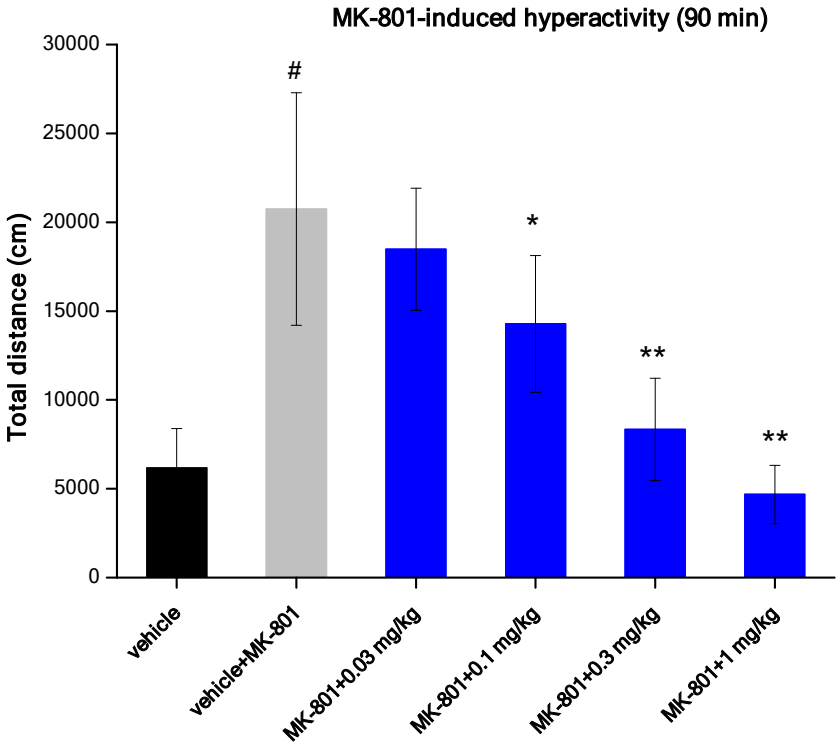

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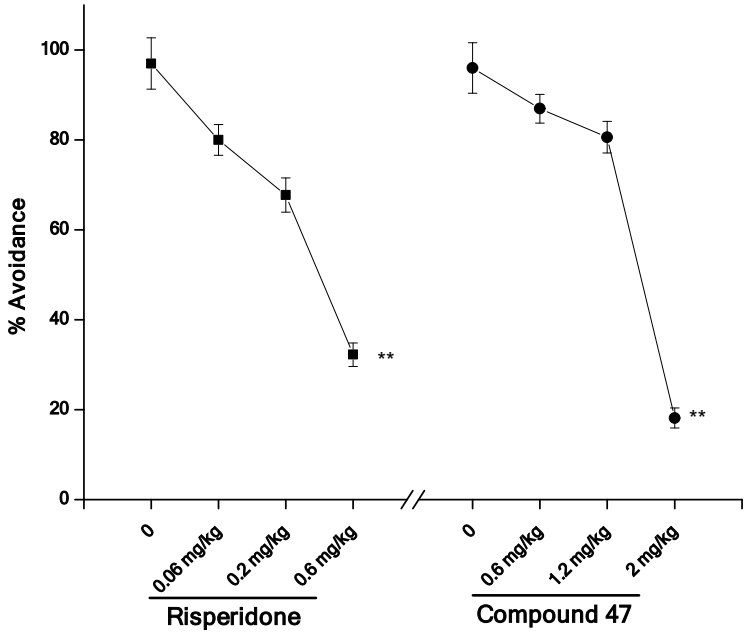

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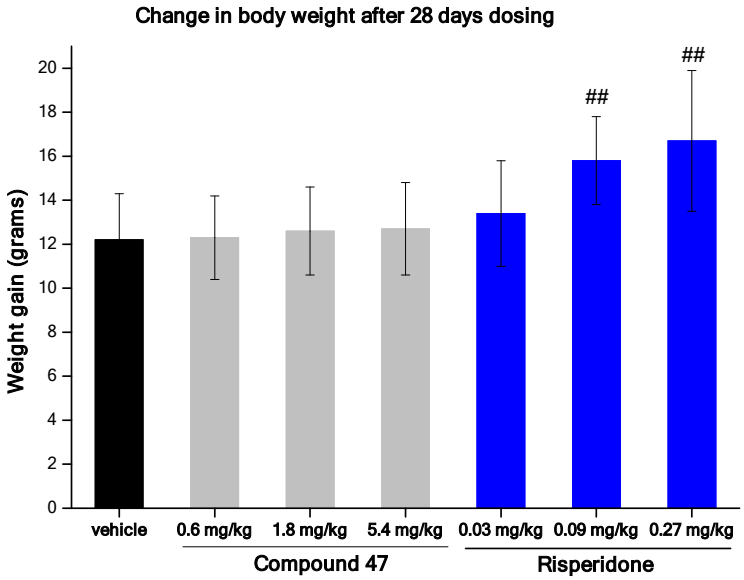

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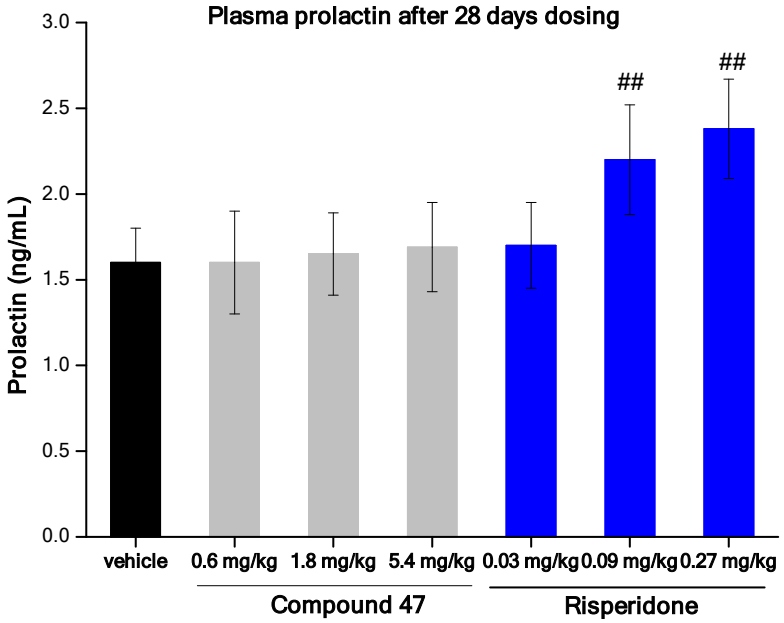

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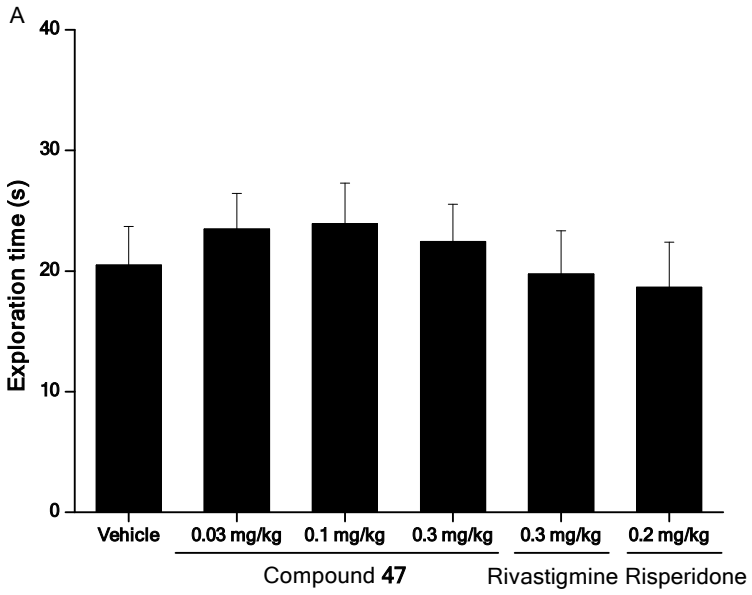
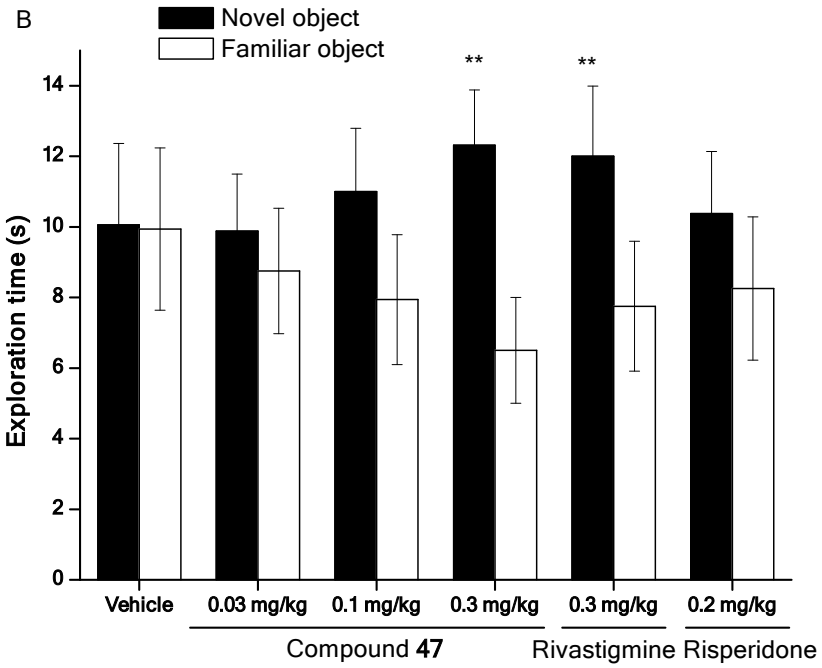
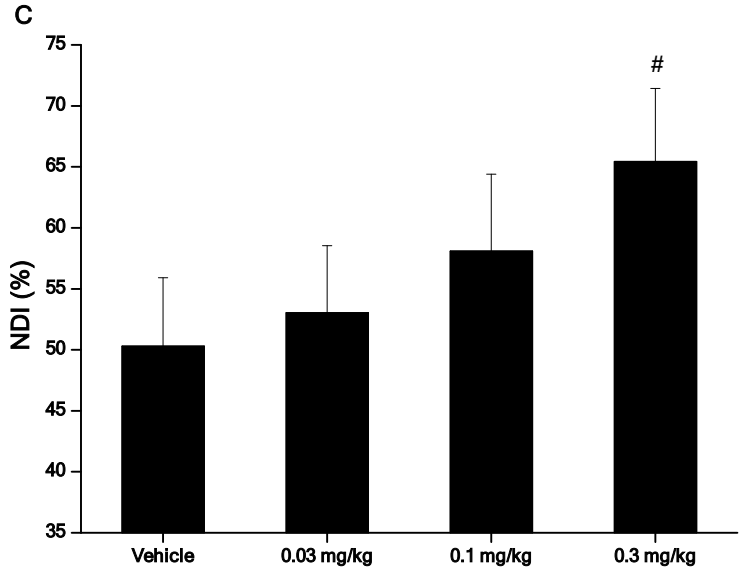

A
Exploration time (s)
40
30
20
10
0
Vehicle
0.03 mg/kg
0.1 mg/kg
0.3 mg/kg
0.3 mg/kg
0.2 mg/kg
Compound 47
Rivastigmine
Risperidone


B
Novel object
Familiar object
**
**
Exploration time (s)
14
12
10
8
6
4
2
0
Vehicle
0.03 mg/kg
0.1 mg/kg
0.3 mg/kg
0.3 mg/kg
0.2 mg/kg
Compound 47
Rivastigmine
Risperidone



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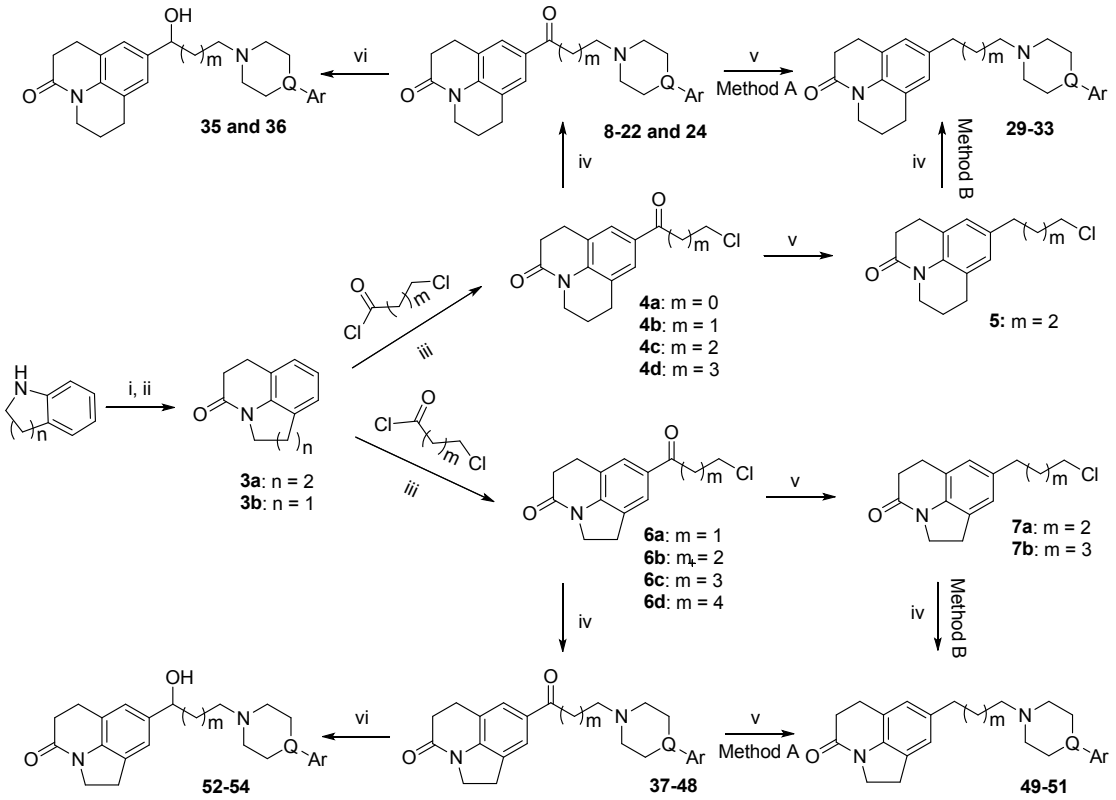
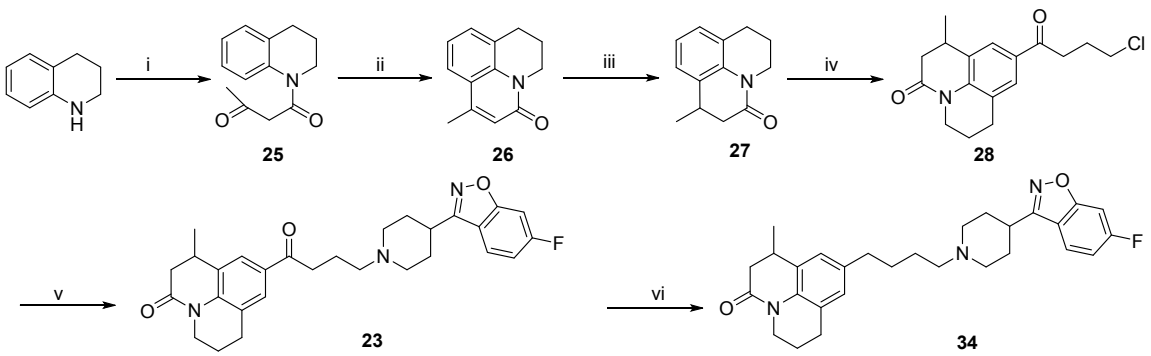
Scheme 1[a]



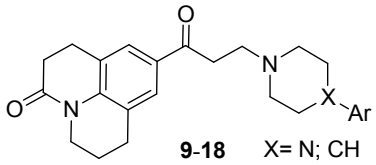
[a]**Reagents and conditions**: (i) 3-chloropropanoyl chloride, acetone, reflux; (ii) $AlCl_3$, 110 ^oC; (iii) appropriate chloroalkyl chloride, $AlCl_3$, DCE; (iv) appropriate phenylpiperazines or heterocyclicpiperazines(piperidines), K_2CO_3, KI, acetonitrile, reflux; (v) Et_3SiH, TFA, room tempreture; (vi) $NaBH_4$, MeOH, room tempreture.

Scheme 2[a]

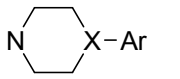
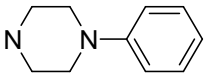
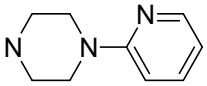
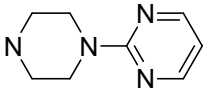
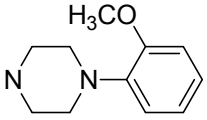
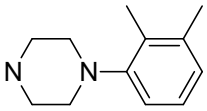
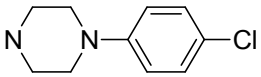
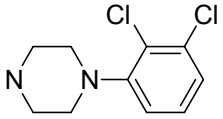
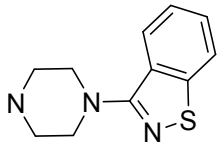
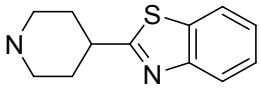
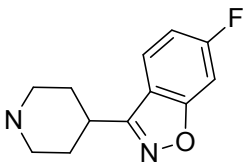


[a]**Reagents and conditions**: (i) ethyl acetoacetate, toluene, reflux overnight; (ii) H_2SO_4 (con.), 100 °C, 6h; (iii) Pd/C, H_2; (iv) 4-chlorobutanoyl chloride, $AlCl_3$, DCE; (v) 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole hydrochloride, K_2CO_3, KI, acetonitrile, reflux; (vi) Et_3SiH, TFA, room tempreture.

Table 1. Binding Affinities for D_2, 5-HT_{1A}, and 5-HT_{2A} Receptors of Compounds **9-18** and Reference Antipsychotics

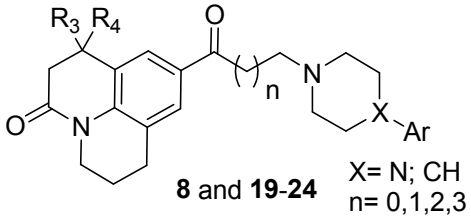


9-18 X= N; CH

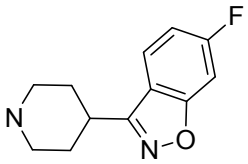
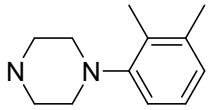
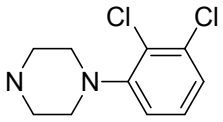
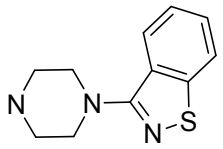
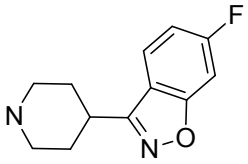
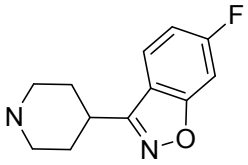
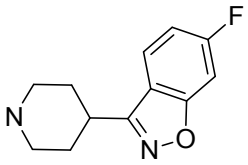
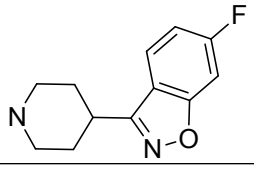
Compd		Receptor affinity K_i ± SE (nM)[a]		
		D_2	5-HT_{1A}	5-HT_{2A}
9		1764.8±212.4	1856.2±208.1	752.3±121.2
10		1660.8±181.3	1656.2±171.9	675.2±102.4
11		>2000	1965.4±127.1	557.4±84.6
12		>2000	964.8±125.3	178.2±28.5
13		1852.9±223.6	196.1±21.3	207.3±23.4
14		>2000	1628.8±121.1	720.4±83.2
15		1217.6±124.3	268.6±30.1	207.4±28.3
16		182.1±14.2	128.7±13.0	72.0±8.2
17		861. 2±54.6	392.0±43.2	173.0±28.1
18		58.2±6.4	62.9±7.3	52.3±5.8
Risperidone		3.7 ± 0.3	181.9 ± 15	0.18 ± 0.02

[a] K_i values are taken from three experiments, expressed as means ± SEM.

Table 2. Binding Affinities for D_2, 5-HT_{1A}, and 5-HT_{2A} Receptors of Compounds **8** and **19-24**



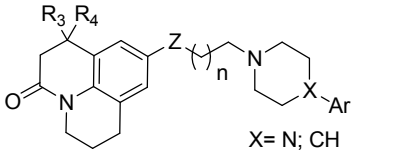
8 and **19-24**

Compd	R_3	R_4	n	N–X–Ar	Receptor affinity K_i ± SE (nM)[a]		
					D_2	5-HT_{1A}	5-HT_{2A}
18	H	H	1		58.2±6.4	62.9±7.3	52.3±5.8
19	H	H	2		185.2±19.5	169.2±17.6	58.9±5. 2
20	H	H	2		282.5±30.6	149.4±16.7	79.8±9.5
21	H	H	2		91.4±10.7	152.8±15. 9	87.9±9.2
22	H	H	2		18.2±2.4	32.9±4.3	22.3±2.8
23	H	CH_3	2		62.1±7.2	42.3±5.5	32.2±3.2
24	H	H	3		31.8±2.3	32.6±3.6	19.1±2.4
8	H	H	0		900.3±129.7	>2000	765.4±113.2

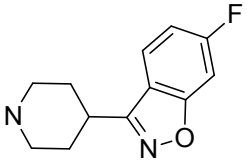
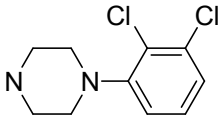
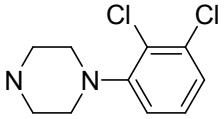
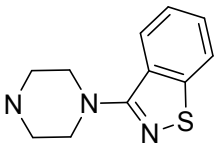
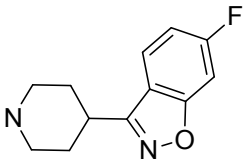
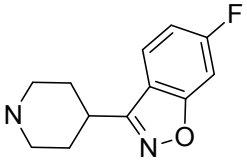
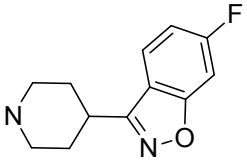
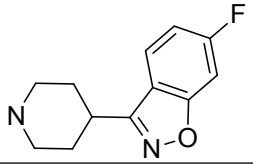
[a] K_i values are taken from three experiments, expressed as means ± SEM.

Table 3. Binding Affinities for D_2, 5-HT_{1A}, and 5-HT_{2A} Receptors of Compounds

29-36



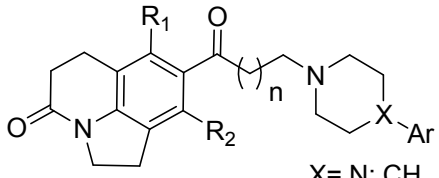
29-36

Compd	R_3	R_4	n	Z	N X−Ar	Receptor affinity K_i ± SE (nM)[a]		
						D_2	5-HT_{1A}	5-HT_{2A}
29	H	H	1	CH_2		44.2±5.2	58.6±9.3	73.9±9.8
30	H	H	1	CH_2		582.1±64.2	196.2±22.1	186.1±23.1
31	H	H	2	CH_2		394.3±41.5	193.9±19.8	97.8±9.6
32	H	H	2	CH_2		154.2±15.7	98.0±10.9	83.9±10.1
33	H	H	2	CH_2		74.3±6.2	69.1±5. 6	59.3±6.2
34	H	CH_3	2	CH_2		85.8±8.6	82.9±9.4	83.4±10.5
35	H	H	1	CHOH		28.4±3.5	19.6±2.1	19.9±2.2
36	H	H	2	CHOH		29.7±3.7	79.1±6.2	24.2±2.5

[a] K_i values are taken from three experiments, expressed as means ± SEM.

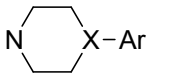
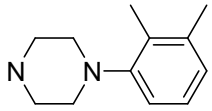
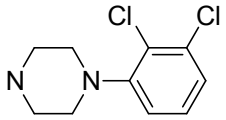
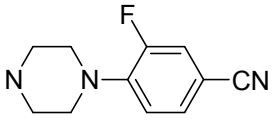
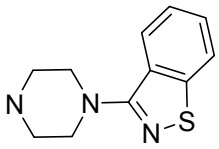
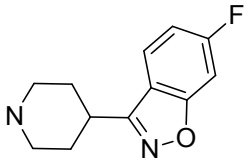
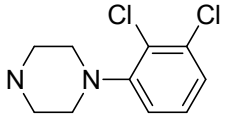
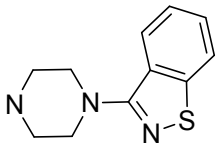
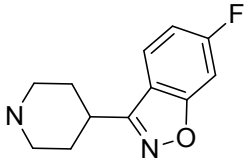
Table 4. Binding Affinities for D_2, 5-HT_{1A}, and 5-HT_{2A} Receptors of Compounds

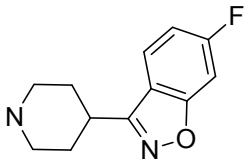
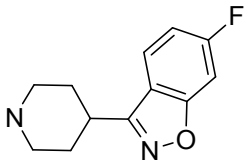
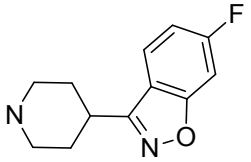
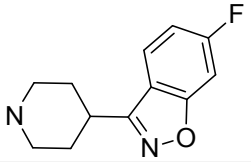
37-48



37-48

X= N; CH
n= 0,1,2,3,4

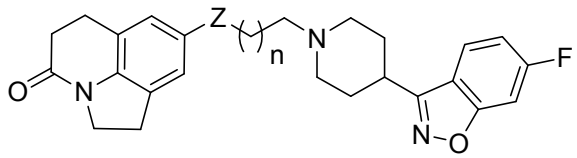
Compd	R_1	R_2	n		Receptor affinity K_i ± SE (nM)[a]		
					D_2	5-HT_{1A}	5-HT_{2A}
37	H	H	1		188.8±20.5	84.6±10.2	174.9±21.3
38	H	H	1		187.6±17.2	81.6±12.1	92.5±14.2
39	H	H	1		574.3±67.3	473.9±49.8	387.7±40.6
40	H	H	1		88.8±9.5	54.6±7.2	68.4±9.3
41	H	H	1		19.7±1.5	16.4±1.9	17.4±1.6
42	H	H	2		104.3±13.1	53.9±5.8	37.8±4.5
43	H	H	2		49.9±5.2	31.8±3.5	50.3±5.9
44	H	H	2		10.3±1.3	12.0±1.7	9.9±1.2

45	F	H	2		19.2±2.1	25.3±2.8	17.9±1.8
46	H	F	2		18.3±1.2	19.1±2.3	21.9±2.3
47	H	H	3		2.9±0.3	8.6±1.1	0.72±0.02
48	H	H	4		89.1±9.3	168.2±20.3	34.7±4.0

[a] K_i values are taken from three experiments, expressed as means ± SEM.

Table 5. Binding Affinities for D_2, 5-HT_{1A}, and 5-HT_{2A} Receptors of Compounds

49-54



49-54 Z= CH_2; CHOH
n= 1,2,3

Compd	Z	n	Receptor affinity K_i ± SE (nM)[a]		
			D_2	5-HT_{1A}	5-HT_{2A}
49	CH_2	1	46.5±4.9	38.7±4.0	29.3±3.2
50	CH_2	2	9.9±1.7	11.7±1.8	19.3±2.1
51	CH_2	3	43.2±5.1	54.0±6.1	58.3±6.0
52	CHOH	1	19.6±1.8	29.3±3.8	59.6±6.8
53	CHOH	2	13.4±1.5	22.5±3.5	69.5±7.2
54	CHOH	3	8.4±1.5	12.0±1.3	0.4±0.05

[a] K_i values are taken from three experiments, expressed as means ±SEM.

Table 6. Binding affinities for the 5-HT_{2C}、H_1 an α_1 receptors (K_i nM) and hERG Channels (IC_{50} (nM)) of Selected Compounds and Reference Antipsychotics

Compd	Receptor affinity K_i ± SE (nM)[a]					hERG
	5-HT_{2C}	H_1	α_1	5-HT_6	D_3	IC_{50} (nM)
44	610.3±61.3	421.0±45.7	491.3±1.9	241.0±25.2	61.3±6.3	823.7
47	616.0±65.1	630.3±5.5	431.0±62.2	5.55±0.6	1.66±0.3	2905.4
50	539.9±54.7	711.7±81.2	99.3±12.1	17.7±1. 8	54.9±5.7	--
53	742.0±78.0	339.0±35.4	339±34.8	6.36±0.8	45.37±5.4	1899.6
54	33.7±4.1	43.5±5.2	596±60.2	29.46±0.4	116.32±12.8	--
Risperidone	28.2±3.3	46.2±5.1	54.7±2.1	1260±150	31.9±3.3	167.1

[a] K_i values are taken from three experiments, expressed as means ± SEM.

Table 7. Activities of Compound **47** and Reference Compounds to D_{2L}, D_3, 5-HT_{1A}, 5-HT_{2A} and 5-HT_6 Receptors

Receptor	**Compd**	**Activation (10 μM, %) (n = 3)**	**EC_{50} (nM)**	**Inhibition (10 μM, %) (n = 3)**	**IC_{50} (nM)**
D_{2L}	Dopamine	101.1±3.1	19.0		
	SCH23390			99.0±1.0	31.0
	47	9.8±8.4		93.3±1.3	9.02
D_3	Dopamine	100.1±8.5	2.1		
	spiperone			99.2±2.4	93.2
	47	5.2±1.2		100.6±3.3	25.6
5-HT_{1A}	5-HT	102.5±0.5	19.0		
	WAY-100635			95.5±0.5	11.3
	47	8.6±0.5		94±3.2	587.8
5-HT_{2A}	5-HT	94.5±2.3	1.6		
	Ketanserin			100±2.1	83.7
	47	0.6±0.2		100±3.2	257.4
5-HT_6	5-HT	98.0±1.6	43.6		
	Clozapine			103.5±2.1	20.0
	47	6.0±0.1		91.3±3.5	177.6

Table 8 *In vivo* pharmacological profile of compound **47**

Compd	APO[a]	MK-801[b]	CAT[c]	CAR[d]	CAT/APO	CAT/MK-801
47	0.61(0.34-1.08)[e]	0.26(0.14-0.51)	78.62 (35.65-189.74)	1.46 (1.15-3.94)	128.88	302.38
risperidone	0.028(0.017-0.048)	0.011(0.003-0.051)	0.51(0.26-2.04)	0.52 (0.28-0.66)	18.21	46.36
Haloperidol	0.11 (0.084-0.13)	0.16(0.064-0.37)	0.12(0.030-1.03)		1.09	0.75

[a] APO: apomorphine-induced climbing ($ED_{50,}$ mg/kg, po).

[b] MK-801: MK-801-induced hyperactivity ($ED_{50,}$ mg/kg, po).

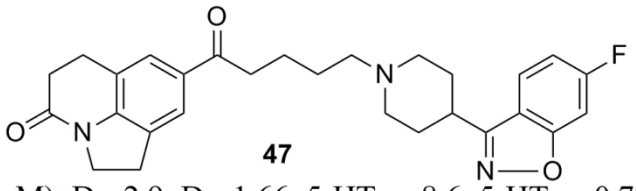
[c] CAT: catalepsy ($ED_{50,}$ mg/kg, po).

[d] CAR: conditioned avoidance response ($ED_{50,}$ mg/kg, po).

[e] 95% confidence limits.

Table 9. Pharmacokinetic Profile of Compound **47** in Rats (n = 6/Group)

Dose (mg/kg)	**Cmax (ng/mL)**	**$t_{1/2}$ (h)**	**Tmax (h)**	**CL(mL/min/kg)**	**AUC(0-t) (ng × h/mL)**	**AUC(0-∞) (ng × h/mL)**	**F(%)**
1 (iv)		2.15±0.50		15.4±0.74	3141.3±397.6	3151.2±402.9	
10 (po)	3733±1635	2.02±0.19	1.00±0.00		18532.7±1588.6	18539.5±1584.6	58.8



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In vitro (k_i, nM): D_2, 2.9; D_3, 1.66; 5-HT_{1A}, 8.6; 5-HT_{2A}, 0.72; 5-HT_6, 5.55; 5-HT_{2C}, 616.0; H_1, 630.3; α_1, 431.0

In vivo (ED_{50}, mg/kg): APO, 0.61; MK-801, 0.26; CAR,1.46; CAT, 78.62

Pharmacokinetic: $t_{1/2}$, 2.02; F%, 58.8

Table of Contents Graphic

130x46mm (300 x 300 DPI)