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ARTICLE

In vivo Potential Antipsychotics: Synthesis, Characterization, Molecular Docking and Pharmacokinetic Properties of Multitarget Ligands

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ABSTRACT

A series of new 3,4-dihydroquinolin-2(1*H*)-one analogs of aripiprazole structural similarity compound was synthesized to explore the influence of structural features-replacement of 2,3-dichlorophenyl-4-piperazine/diazepane moiety with 3-methyl-2,7-diphenyl-1,4-diazepan-5-one. All the synthesized compounds are characterized by elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR, HSQC (2D NMR) and mass spectrometry. All the multitarget ligands have been docked against, human A_2A Adenosine receptor and human β_2-Adrenergic G-protein coupled receptor (GPCR), both receptor and ligand interaction shows an excellent dock score. Adsorption, distribution, metabolism and extraction (ADME) properties were also evaluated in the desirable range. Finally these compounds have orally drug-likeness property. In this event screening was performed for the neuroleptic activity of the synthesized compounds with different anti-psychotic animal models.

KEYWORDS

3,4-Dihydroquinolin-2(1*H*)-one, Aripiprazole, Antipsychotic, Molecular docking, ADME properties.

INTRODUCTION

Antipsychotics are drugs used to treat a variety of symptoms of psychosis, such as those caused by psychotic disorders or schizophrenia. There are two categories of antipsychotics: typical antipsychotics and atypical antipsychotics. Atypical antipsychotics are also used as mood stabilizers in the action of bipolar disorder, schizophrenia, autism and they can expand the action of antidepressants in major depressive disorder. Second-generation antipsychotics are well-known as atypical antipsychotics such as aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, zotepine, ziprasidone. Both generations of prescription tend to block receptors in the brain's dopamine pathways. Antipsychotics are occasionally referred to as neuroleptic drugs and some antipsychotics are recognized "major tranquilizers". Atypical antipsychotics are attention to be safer than typical antipsychotics; they still have rigorous side effects, together with tardive dyskinesia (a stern movement disorder), neuroleptic malignant syndrome and augmented risk of stroke, unexpected cardiac death, blood clots and diabetes [1].

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Schizophrenia is a composite neuropsychiatric disorder characterized by the progress of three different kinds of symptoms: positive (hallucinations, hyperactivity, delusions, disorganized speech), negative (anhedonia, avolition, social isolation) and cognitive (attentional impairment, memory deficits). For the behaviour of this disorder, the first generation of antipsychotic drugs was discovered about 50 years ago (*e.g.* chlorpromazine, haloperidol); described as selective D2 dopamine antagonists, today they are known as ''typical antipsychotics'' [2].

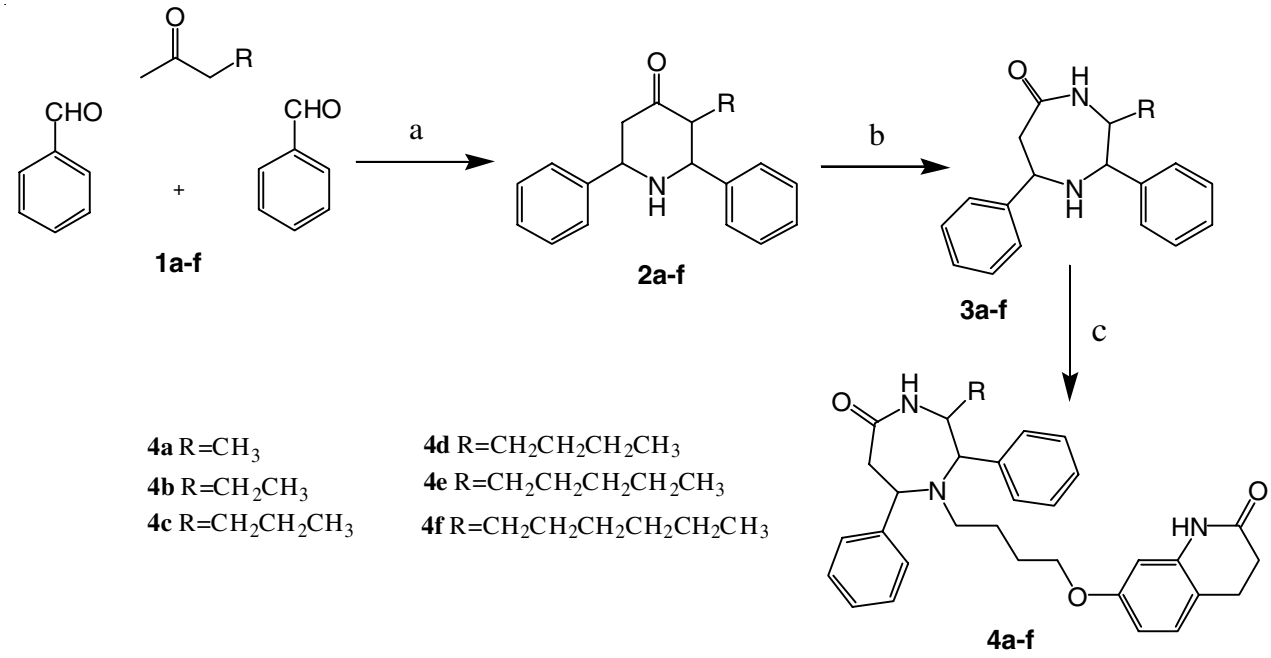
In a development of CNS active agents, the multitarget strategy seems to be one of the most valuable approaches. Accordingly, several launched antidepressant/antipsychotic drugs *e.g.* amisulpride and aripiprazole, or compounds investigated in clinical trials (vortioxetine) [3] display mixed serotonin (5-HT) and dopamine (D) receptor profile. It was freshly found that these drugs perform as 5-HT7 receptor antagonists and this mechanism is dependable for their antidepressant properties [4] Moreover, the multimodal receptor profile (5-HT1A, 5-HT2A, 5-HT7, D2, D3) of aripiprazole and its functional profile-partial agonist of D2 and 5-HT1A receptors and antagonist of 5-HT2A and 5-HT7 sites, might under line its board efficacy-antipsychotic, antidepressant and anxiolytic effects. The D receptor partial agonist's aripiprazole and the drug molecule cariprazine stand for promising options for the treatment of schizophrenia [5-7] because of their stabilizing effect on monoamine pathways, particularly the dopaminergic pathways and their atypical antipsychotic effect.

Later, the introduction of clozapine for treatment opposed to schizophrenia gave augment to a new group of ''atypical'' or ''non-classical'' antipsychotics that have no extra pyramidal symptoms (EPS) at the doses frequently used in therapy and are effective also against the negative symptoms [8-10]. A new generation of atypical antipsychotics (also known as ''dopamine stabilizers'') such as aripiprazole, with a concrete efficacy spectrum in different receptors (inverse agonist at 5-HT2B receptors, partial agonist at D2, D3, 5-HT2A and 5-HT2C receptors) [11] offered further advantage due to an improved efficacy in treating negative symptoms of schizophrenia and a decreased incidence and severity of central and peripheral side effects [12]. Now, while the treatment and maintenance of the positive symptoms of schizophrenia are largely addressed with current medications, the major challenge is to identify compounds showing clinically significant improvements in the treatment of negative symptoms and cognitive dysfunction. In addition, a major issue with many of the now prescribed atypical antipsychotic drugs remains the side-effect liabilities of weight gain, metabolic abnormalities, diabetes liabilities and potential cardiovascular safety concerns and so significant improvements can still be made. Consequently, much of the current focus in the design of new antipsychotic drugs has been centered on trying to improve upon these liabilities.

EXPERIMENTAL

The synthesis of all drug compounds is outlined in **Scheme-I**. A three-step synthetic strategy was adopted for the synthesis of substituted 1-[4-(3,4-dihydroquinolin-2(1*H*)-one-7-yloxy)butyl]-3-methyl-2,7-diphenyl-1,4-diazepan-5-one (**4a-f**). In the first step, compounds 3-alkyl-2,6-diarylpiperidin-4-one (**2a-f**) were prepared according to the reported literature [13] Schmidt reactions of azide with ketone when treated with Brønsted or Lewis acids at 0-5 °C were converted in to diazapine (**3a-f**) in good to excellent yields in the second step. The debromination reactions of 7-(4-bromobutoxy)-3,4-dihydro-2-(1*H*)-quinolinone with 3-alkyl-2,7-diphenyl-1,4-diazepan-5-one in aqueous medium to produced target compounds (**4a-f**).

All the reported melting points were taken in open capillaries. IR spectra was recorded in a Agilent Cary 650 FT-IR spectrophotometer by KBr pellet technique and only noteworthy absorption levels are listed. ^{1}H and ^{13}C NMR spectra



4a R=CH_3
4b R=CH_2CH_3
4c R=$CH_2CH_2CH_3$
4d R=$CH_2CH_2CH_2CH_3$
4e R=$CH_2CH_2CH_2CH_2CH_3$
4f R=$CH_2CH_2CH_2CH_2CH_2CH_3$

Scheme-I: Reagents and conditions: (a) EtOH, NH_4OAc warm: (b) conc. H_2SO_4, NaN_3, NaOH solution (20 %) (c) dichloromethane, 7-(4-bromobutoxy)-3,4-dihydroquinolin-2(1*H*)-one, N-ethyldiisopropylamine, reflux 2 h, 96 %

were recorded respectively at 400 and 100.6 MHz on a BRUKER AMX 400 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. HSQC were recorded on a BRUKER NMR spectrometer with standard parameters using 0.05 M solutions of the samples prepared in $CDCl_3$. The tubes used for recording NMR spectra are of 5 mm diameter. Mass Spectra (MS) was recorded on an API 3000 series mass spectrometer. Microanalysis was performed on a vario MICRO V2.2.0 CHN analyzer.

***In vivo* antipsychotic activity**

Evaluation of antipsychotic activity of wistar albino rat: Wistar albino rats of either sexes weighing 150-200 g were obtained from Sree Venkateshwara Entreprises Pvt Ltd, Bangalore. They were housed in the animal house of KMCH College of Pharmacy with the maintenance of 12 h day and night cycle. They were fed with normal pellet diet with sufficient water *ad libitum*. The study was approved by the Institutional animal ethics committee bearing the approval no KMCRET/PhD/01/2016-17. The rats were acclimatized for 7 days prior to the begin of the study.

Amphetamine induced stereotype in rats: Amphetamine is an oblique sympathomimetic agent. It induces licking, gnawing, grooming, sniffing (stereotype) in rats which can be effectively prevented by classical neuroleptic agents. This test is predictive of antipsychotic drug, for D2 receptor antagonism. Eight groups (n = 8) of adult Wistar rats were taken weighing between 180 to 220 g and were treated with either test or the standard drug (aripiprazole) and then placed in entity cages. They were injected with d amphetamine (5 mg/kg ip) after 30 min. The onset of stereotypic activities was evaluated at 30 min interval for 3 h. The reduction in mean stereotype score is indicative of antipsychotic effect [14].

Experimental design:

Group-1: Control (only distilled water)
Group-2: Amphetamine (5 mg/kg ip) + Aripiprazole (5 mg/kg, (Po)
Group-3: Amphetamine (5 mg/kg ip) + 4a 10 mg/kg (Po)
Group-4: Amphetamine (5 mg/kg ip) + 4b 10 mg/kg (Po)
Group-5: Amphetamine (5 mg/kg ip) +4c 10 mg/kg (Po)
Group-6: Amphetamine (5 mg/kg ip) +4d 10 mg/kg (Po)
Group-7: Amphetamine (5 mg/kg ip) + 4e 10 mg/kg (Po)
Group-8: Amphetamine (5 mg/kg ip) + 4f 10 mg/kg (Po)

Phencyclidine (PCP) induced bizarre pattern of locomotor activity: Phencyclidine is a glutamate receptor antagonist. Administration of phencyclidine has been found to induce locomotor hyperactivity in rodents and is antagonized by antipsychotic drugs. Male Wistar rats weighing 180-210 g were housed in a chamber. Animals were alienated into 8 groups (n = 8), for test or the reference drug. Before 0.5 h the start of the test, the animals were administered with the test and the standard drugs. Phencyclidine (2 mg/kg) was administered to the animals of all the groups just before the start of the experiment. Then the locomotor activity of the animals will be measured in photo-actometer for a session lasting for 90 min. Drugs antagonizing the phencyclidine induced activity are expected to act by some other receptor *viz.* glutamatergic and serotonergic rather than dopaminergic receptors [15].

Experimental design:

Group-1: Control (only distilled water)
Group-2: Phencyclidine (2 mg/kg sc) + aripiprazole (5 mg/kg, (Po)
Group-3: Phencyclidine (2 mg/kg sc) + 4a 10 mg/kg (Po)
Group-4: Phencyclidine (2 mg/kg sc) + 4b 10 mg/kg (Po)
Group-5: Phencyclidine (2 mg/kg sc) + 4c 10 mg/kg (Po)
Group-6: Phencyclidine (2 mg/kg sc) + 4d10 mg/kg (Po)
Group-7: Phencyclidine (2 mg/kg sc) + 4e 10 mg/kg (Po)
Group-8: Phencyclidine (2 mg/kg sc) + 4f 10 mg/kg (Po)

Phencyclidine (PCP) induced social withdrawal test: This investigation helps to show the efficiency of potential antipsychotic drugs against negative symptoms of schizophrenia. Phencyclidine decreases the time of social interaction in the rats. Naive male Wistar rats were housed in pairs for 10 days prior to the start of the experiment. During the test one, cage mate is removed and a new one is kept in the cage for 20 min. The amount of social interaction is measured as the total amount of time spent on various elements of interaction *i.e.* social exploration and genital investigation. Phencyclidine will be administered 5 min before the start of the experiment whereas the test or the standard drug will be given 30 min before the experiment.

Conditioned avoidance response in rats: In the trained reinforcement model, tentative animals are trained to perform a certain response *i.e.* to avoid a mild shock. Trained avoidance responses may be active (pressing a lever, climbing a pole, or jumping out of a box). Eight groups of rats (each having six rats) weighing 150-250 g were tested in this model for test drug and standard. Ten days of training period were carried out before the experiment and a total of 20 sessions of training were imparted to each rat before the experiment. Test and the standard drugs were administered 30 min before the start of the experiment [16].

Experimental design:

Group-1: Control (only distilled water)
Group-2: Aripiprazole (5 mg/kg, (Po)
Group-3: 4a 10 mg/kg (Po)
Group-4: 4b10 mg/kg (Po)
Group-5: 4c 10 mg/kg (Po)
Group-6: 4d 10 mg/kg (Po)
Group-7: 4e 10 mg/kg (Po)
Group-8: 4f 10 mg/kg (Po)

Induction of catalepsy in rats: Wistar rats weighing 180 to 200 g each are randomly divided in eight groups (test and standard). After an appropriate pretreatment time of the drug, each rat is tested for with respect to the right and left front paws which are first put on columns, first 3 cm and then 9 cm high. The cataleptic state was considered if the rat maintains the abnormal posture for 10 s or more [14,16].

The scoring was done according to the following: (1) 0-The rat moves usually when placed on a table. (2) 1-Rats move only when touched or pushed. (3) 1 + 1 = 2 – Rats placed on a table without paws set alternately on a 3 cm high block fails to correct the posture in 10 s, scored as 1 point for each paw, with a total of 2 for both paws. (4) 1 + 1 = 2 – Rats placed on a table with front paws set alternately on a 9 cm high block

fails to correct the posture in 10 secs, scored as 1 point for each paw, with a total of 2 for both paws. This model predicts the extra pyramidal side effects of the test drug.

Experimental design:

Group-1: Control (only distilled water)
Group-2: Aripiprazole (5 mg/kg, (Po)
Group-3: Aripiprazole (5 mg/kg, (Po) + 4a 10 mg/kg (Po)
Group-4: Aripiprazole (5 mg/kg, (Po) + 4b10 mg/kg (Po)
Group-5: Aripiprazole (5 mg/kg, (Po) + 4c 10 mg/kg (Po)
Group-6: Aripiprazole (5 mg/kg, (Po) + 4d 10 mg/kg (Po)
Group-7: Aripiprazole (5 mg/kg, (Po) + 4e 10 mg/kg (Po)
Group-8: Aripiprazole (5 mg/kg, (Po) + 4f 10 mg/kg (Po)

Synthesis of 3-alkyl-2,6-diphenylpiperidin-4-one (2a-f): The parent 2,6-diarylpiperidin-4-ones (**2a–2f**) were synthesized through Mannich reaction by adopting literature method [13].

Synthesis of 3-alkyl-2,7-diphenyl-1,4-diazepan-5-one (3a-f): To the acidic solution of 3-alkyl-2,6-diphenylpiperidin-4-one (2.65 g, 0.01 mol) in 5 mL conc. H_2SO_4 in ice cold conditions, (0.65 g, 0.01 mol) of sodium azide was added for 30 min with constant stirring. After the addition of azide the acidic solution was neutralized with 20 % sodium hydroxide solution. The neutralization was completed using litmus paper blue to yellow (pH = 7), the crude product was precipitated. The precipitate was filtered and washed with water to gives the pure titled compound. The above method was adopted for the synthesis of 3-alkyl-2,7-diphenyl-1,4-diazepan-5-one (**3b-f**).

Synthesis of 1-[4-(3,4-dihydroquinolin-2(1*H*)-one-7-yloxy)butyl]-3-methyl-2,7-diphenyl-1,4-diazepan-5-one (4a): To a solution of 3-methyl-2,7-diphenyl-1,4-diazepan-5-one (1.40 g, 0.005 mmol) and 7-(4-bromobutoxy)-3,4-dihydro-2-(1*H*)-quinolinone (1.50 g, 0.005 mmol) in dichloromethane (30 mL) was refluxed for 2 h in N-ethyldiisopropylamine (0.65 mL, 0.005 mmol) and then completion of the reaction is monitored by TLC, the content of the flask was quenched in ice-cold water. A white crystalline precipitate was formed, filtered and dried: m.p. 140 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3428 (N-H stretching), 3085 (aromatic C-H stretching) 2932 (aliphatic C–H stretching), 1670, 1629 (C=O stretching),1520 (C=C stretching); ^{1}H NMR (δ ppm): 0.83 (s,3H CH_3), 2.68 (d, 1H 6ax), 3.15(d, 1H 6eq), 3.71 (d, 1H H_2), 4.13 (dd, 1H H_7), 3.84 (m, 1H H_3), 3.48 (t, 2H –N-CH_2), 3.96 (t, 2H quinolione attached O-CH_2), 2.05 (m, 2H CH_2), 1.93 (m, 2H CH_2), 2.61 (t, 2H O=C-CH_2 quinolinone), 2.89 (t, quinolione CH_2), 6.35–7.42 (m, 13H) aryl protons, 6.04 (s, diazepan-5-one N-H), 8.49 (s, quinolinone N-H) : ^{13}C NMR (δ ppm): 19.82 (3-methyl carbon), 24.61, 27.86, 29.44, 31.10, 33.48, 47.52, 54.83, 59.64, 67.03, 71.12, 102.23-158.50 (aromatic carbon), 172.03(C=O, quinolinone), 175.96(C=O, diazepan-5-one): GC-MS (*m/z*): 498.3 (M+1), (m.f: $C_{31}H_{35}N_3O_3$), yield 96 %.

1-[4-(3,4-Dihydroquinolin-2(1*H*)-one-7-yloxy)butyl]-3-ethyl-2,7-diphenyl-1,4-diazepan-5-one (4b): Compound **4b** was synthesized as described for **4a**, from 3-ethyl-2,7-diphenyl-1,4-diazepan-5-one. m.p.: 128 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3411 (N-H stretching), 3083 (aromatic C-H stretching) 2930, 2873 (aliphatic C–H stretching), 1703, 1676 (C=O stretching), 1629 (C=C stretching); ^{1}H NMR (δ ppm): 0.86, (t,3H CH_3), 1.12 (m,2H CH_2), 3.16 (d, 1H H_6ax), 2.66(d, 1H H_5eq), 3.65 (d, 1H H_2), 4.14 (dd, 1H H_7), 3.78 (m, 1H H_3), 3.47 (t, 2H –N-CH_2), 3.95 (t, 2H quinolione attached O-CH_2), 2.04 (m, 2H CH_2), 1.91 (m, 2H CH_2), 2.62(t, 2H O=C-CH_2 quinolinone), 2.87 (t, quinolione CH_2) 6.42-7.42 (m, 13H aryl protons), 6.35 (s, diazepan-5-one N-H), 9.32 (s, quinolinone N-H): ^{13}C NMR (δ ppm): 10.20, 25.65 (3-alkyl carbon), 24.60, 27.87, 29.44, 31.09, 33.53, 47.43, 54.12, 59.75, 67.02, 70.14, 102.27-158.50 (aromatic carbon), 172.25 (C=O, quinolinone), 176.39 (C=O, diazepan-5-one): GC-MS (*m/z*): 512.7 (M+1), (m.f: $C_{32}H_{37}N_3O_3$), yield 95 %.

1-[4-(3,4-Dihydroquinolin-2(1*H*)-one-7-yloxy)butyl]-3-propyl-2,7-diphenyl-1,4-diazepan-5-one (4c): Compound **4c** was synthesized as described for **4a**, from 3-propyl-2,7-diphenyl-1,4-diazepan-5-one. m.p.: 116 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3411 (N-H stretching), 3083 (aromatic C-H stretching) 2958 (aliphatic C–H stretching), 1676, 1628 (C=O Stretching), 1593 (C=C stretching); ^{1}H NMR (δ ppm): 0.75, (t,3H CH_3), 0.99, (m,2H CH_2), 1.11 (m, 2H CH_2), 3.15 (d, 1H H_6ax), 2.66(d, 1H H_6eq), 3.70 (d, 1H H_2), 4.14 (dd, 1H H_7), 3.76 (m, 1H H_3), 3.40 (t, 2H –N-CH_2), 3.96 (t, 2H quinolione attached O-CH_2), 2.05 (m, 2H CH_2), 1.92 (m, 2H CH_2), 2.61 (t, 2H O=C-CH_2 quinolinone), 2.89 (t, quinolione CH_2), 6.37-7.41 (m, 13H aryl protons), 6.08 (s, diazepan-5-one N-H), 8.75 (s, quinolinone N-H): ^{13}C NMR (δ ppm): 13.55, 18.60, 34.59 (3-alkyl carbon), 24.61, 27.87, 29.44, 31.10, 33.49, 47.44,58.80, 59.75, 67.03, 70.33, 102.25-158.51 (aromatic carbon), 171.64 (C=O, quinolinone),, 176.24(C=O, diazepan-5-one): GC-MS (*m/z*): 526.8 (M+1), (m.f: $C_{33}H_{39}N_3O_3$), yield 97 %.

1-[4-(3,4-Dihydroquinolin-2(1*H*)-one-7-yloxy)butyl]-3-butyl-2,7-diphenyl-1,4-diazepan-5-one (4d): Compound **4d** was synthesized as described for **4a**, from 3-butyl-2,7-diphenyl-1,4-diazepan-5-one. m.p.: 105 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3416 (N-H stretching), 3033 (aromatic C-H stretching) 2930, 2869 (aliphatic C–H stretching), 1709, 1677 (C=O Stretching), 1627 (C=C stretching); ^{1}H NMR (δ ppm): 0.76, (t,3H CH_3), 1.06-1.25, (m,6H CH_2, CH_2, CH_2), 2.63(d, 1H H_6ax), 3.16(d, 1H H_6eq), 3.75 (d, 1H H_2), 4.14 (dd, 1H H_7), 3.94 (m, 1H H_3), 3.48 (t, 2H –N-CH_2), 3.96 (t, 2H quinolione attached O-CH_2), 2.05 (m, 2H CH_2), 1.93 (m, 2H CH_2), 2.61(t, 2H O=C-CH_2 quinolinone), 2.89 (t, quinolione CH_2), 6.31-7.41 (m, 13H aryl protons), 5.90 (s, diazepan-5-one N-H), 8.04 (s, quinolinone N-H): ^{13}C NMR (δ ppm): 13.77, 22.11, 27.43, 32.26 (3-alkyl carbon), 24.61, 27.85, 29.43, 31.10, 33.46, 47.46, 58.92, 59.75, 67.05, 102.15-158.49 (aromatic carbon), 171.64 (C=O, quinolinone), 176.06(C=O, diazepan-5-one) : GC-MS (*m/z*): 540.3 (M+1), (m.f: $C_{34}H_{41}N_3O_3$), yield 98.5 %.

1-[4-(3,4-Dihydroquinolin-2(1*H*)-one-7-yloxy)butyl]-3-pentyl-2,7-diphenyl-1,4-diazepan-5-one (4e): Compound **4e** was synthesized as described for **4a**, from 3-pentyl-2,7-diphenyl-1,4-diazepan-5-one. m.p.: 105 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3411 (N-H stretching), 3033 (aromatic C-H stretching) 2924 (aliphatic C–H stretching), 1675, 1628 (C=O Stretching), 1593 (C=C stretching); ^{1}H NMR (δ ppm): 0.80, 1.00-1.25, (m,11H 3-pentyl), 2.66 (d, 1H H_6ax), 3.15(d, 1H H_6 eq), 3.71 (d, 1H H_2), 4.14 (dd, 1H H_7), 3.77(m, 1H H_3), 3.48 (t, 2H –N-CH_2), 3.96 (t, 2H quinolione attached O-CH_2), 2.05 (m, 2H CH_2), 1.93

(m, 2H CH_2), 2.63 (t, 2H O=C-CH_2 quinolinone), 2.89 (t, quinolione CH_2), 6.36-7.41 (m, 13H aryl protons), 6.01 (s, diazepan-5-one N-H), 8.68 (s, quinolinone N-H),: ^{13}C NMR (δ ppm): 13.94, 22.41, 25.07, 29.73, 32.55 (3-alkyl carbon), 24.60, 27.86, 29.44, 31.10, 33.50, 47.46, 59.04,59.75, 67.03, 70.32, 102.23-158.50 (aromatic carbon), 172.06(C=O, quinolinone), 176.21(C=O, diazepan-5-one): GC-MS (*m/z*): 554.6 (M+1), (m.f: $C_{35}H_{43}N_3O_3$), yield 96.8 %.

1-[4-(3,4-Dihydroquinolin-2(1*H*)-one-7-yloxy)butyl]-3-hexyl-2,7-diphenyl-1,4-diazepan-5-one (4f): Compound **4f** was synthesized as described for **4a**, from 3-hexyl-2,7-diphenyl-1,4-diazepan-5-one. m.p.: 105 °C; FT-IR (KBr, ν_{max}, cm^{-1}): 3437 (N-H stretching), 3061 (aromatic C-H stretching) 2925 (aliphatic C–H stretching), 1676, 1625 (C=O Stretching), 1593 (C=C stretching); ^{1}H NMR (δ ppm): 0.82, 1.04-1.25 (m,13H 3-hexyl), 2.62 (d, 1H H_6ax), 3.15 (d, 1H H_6eq), 3.71 (d, 1H H_2), 4.15 (dd, 1H H_7), 3.75 (m, 1H H_3), 3.61 (t, 2H –N-CH_2), 3.97 (t, 2H quinolione attached O-CH_2), 2.05 (m, 2H CH_2), 1.92 (m, 2H CH_2), 2.62 (t, 2H O=C-CH_2 quinolinone), 2.88 (t, quinolione CH_2), 6.37-7.44 (m, 13H aryl protons), 6.00 (s, diazepan-5-one N-H), 8.60 (s, quinolinone N-H),: ^{13}C NMR (δ ppm): 14.04, 22.44, 25.32, 26.63, 28.85, 32.54 (3-alkyl carbon), 24.59, 28.50, 29.44, 31.09, 33.41, 47.44, 59.06, 59.73, 67.03, 70.28, 102.28-158.51 (aromatic carbon), 172.20(C=O, quinolinone), 176.30(C=O, diazepan-5-one): GC-MS (*m/z*): 568.5 (M+1), (m.f: $C_{36}H_{45}N_3O_3$), yield 98.3 %.

HSQC spectral analysis of synthesized compound 1-[4-(3,4-dihydroquinolin-2(1*H*)-one-7-yloxy)butyl]-3-methyl-2,7-diphenyl-1,4-diazepan-5-one (4a): The synthesized compound **4a** was further analyzed by HSQC spectral analysis for confirmation of its structure. In the HSQC spectrum of compound **4a** it is seen that the carbon signal at 175.96 and 172.03 ppm have no correlation with any carbon signals and hence it is due to the carbonyl group of diazepan-5-one and quinolinone moiety. The proton signals 6.35-7.42 ppm have correlation with carbon signals at 102.23-158.50 ppm is due to aromatic ring. The carbon resonance at 19.82 ppm correlates with the proton signal centered at 0.83 ppm and this correlation confirms that the carbon signal at 19.82 ppm is due to methyl carbon of piperidin-4-one ring. The carbon resonance at 71.12 and 59.64 ppm correlates with the proton signal at 3.71 and 4.13 ppm is due to C2 and C7 carbon of the diazepan-5-one ring and the proton signal at 3.84 ppm have been correlation with carbon signal at 54.83 ppm is due to C3 carbon of the diazepan-5-one ring. The axial and equatorial proton signal at 3.15 and 2.68 ppm is due to C6 position of the diazepan-5-one ring correlates with the carbon signal at 47.52 ppm. The proton signals at 2.61 and 2.89 ppm correlates with the carbon signal at 31.10 and 24.61 ppm is due to alkyl carbon of the quinolinone ring and the proton signal at 6.04 and 8.49 ppm have no correlation with any carbon signal and hence it is due to the N-H proton of the diazepan-5-one and quinolinone moiety. The proton signals appeared at 1.93, 2.05, 3.48 and 3.96 ppm have correlation with the carbon signals at 27.86, 29.44, 33.48 and 67.03 ppm is due to linker chain between the diazepan-5-one and quinolinone ring.

RESULTS AND DISCUSSION

Molecular docking studies: The docking results reveal that all the compounds inside 2RH1 protein showed good binding energy toward the target protein ranging from -7.458 to -3.655 kcal/mol. The docking results revealed that compound **4a** showed minimum binding energy of -7.458 kcal/mol, which are due to dipole and vander wall interactions with amino acids of target protein. It was observed that the most active compound of the series, *i.e.*, compound **4a** was predicted to the most active *in silico* too. The other compounds like **4c** and **4e** having significant antipsychotic activity is also found to have good docking scores. The acting force of binding mode is mainly depends on hydrogen bonding, van-der Walls force hydrophobic interaction due to non-polar residue interactions of the ligand molecule. The observed docking glide score presented in Table-1.

Binding mode of compound **4b** this hit compound revealed glide score 6.558 kcal/mol and glide energy 29.109 kcal/mol. Totally three hydrogen bond interaction were formed between 3EML into **4b**. The side chain hydrogen atom of negative charged residue Asn 253 were strongly interacted with oxygen atom of diazapine-5-one with bond distance (1.622 Å), the side chain hydrogen atom of the polar residue of Phe 168 were well interacted with oxygen atom of the linker chain with bond length (2.083 Å). The quinolinone amide group was strongly interacted with oxygen atom of the Tyr 271 residue with the bond distance (2.408 Å) respectively. Interestingly the following residues Leu 267, Met 270, Leu 85, Ile 66, Ala 81 and Ile 274 are mainly involved in hydrophobic interactions. The other synthesized compounds **4c**, **4d** and **4e** shows moderate docking score against the receptor. Remaining compounds **4a** and **4f** have poor Glide score values and there is no number of hydrogen bonding interactions occurred in **4a**. The observed docking glide score presented in Table-2.

ADME property: Lipinski's rule of five also known as the Pfizer's rule of five or simply the rule of five (RO5) is a rule of thumb to evaluate drug-likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Lipinski *et al.* [18], based on the observation that most orally administered drugs are relatively small and moderately lipophilic

TABLE-1
MOLECULAR DOCKING STUDIES OF 2RH1 PROTEIN WITH SYNTHESIZED COMPOUNDS

Entry	Glide score	Glide energy	N. of HB interactions	Interacting residues	Distance (Å)
4a	-7.429	-51.649	1	Asp 300	2.232
4b	-6.433	-60.776	2	His 178,Phe 193	1.868, 2.650
4c	-7.214	-48.747	2	Trp 313, Ser 204	2.039, 2.551
4d	-3.718	-43.284	1	His 296	1.963
4e	-5.538	-54.757	2	Asn 301,Asp 300	1.870, 2.002
4f	-4.285	-47.945	1	Glu 180	2.070

TABLE-2
MOLECULAR DOCKING STUDIES OF 3EML PROTEIN WITH SYNTHESIZED COMPOUNDS

Entry	Glide score	Glide energy	N. of HB interactions	Interacting residues	Distance (Å)
1	-3.452	-42.509	–	–	–
2	-6.558	-29.109	3	Tyr 271, Phe 168, Asn 253	2.408, 2.083, 1.622
3	-4.012	-29.935	3	Asn 253, Phe 168, Tyr 271,	1.707, 2.173, 2.610
4	-4.952	-33.717	3	Tyr 271, Phe 168, Asn 253	2.435, 2.079, 2.055
5	-4.876	-46.620	2	Asn 253, Phe 168	1.759, 2.167
6	-3.748	-45.722	1	Asn 253	1.842

molecules [17,18]. A preliminary test of the drug-likeness of the compounds was calculated in accordance with Lipinski's rule of five [17,19]. All the newly synthesized compounds were subjected to a computational program using QIKPROP 3.7 [20] module of Schrödinger software for the in combo determination of pharmacokinetic properties such as absorption, distribution, metabolism and excretion (ADME).

The Lipinski's rule of five values of compounds indicates that the compounds are endowed with drug like properties. To obey the Lipinski's rule of five, the compounds required molecular weight (mol_MW) of less than 500 amu, not more than 5 and 10 hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA) respectively and the partition coefficient between octanol and water (QP logPo/w) is less than 6.5. The compounds which have more than one violation of these rules are not considered as orally active drug candidates.

The predicted ADME properties have been calculated in particular; eight descriptors were determined and analyzed such as MW, HBD, HBA, QP logPo/w, QP logPBB, QPPCaco2, QP logHERG and QP logS (Table-3). Compound **4a** shows an excellent drug-likeness property compared to other compounds, because of there is no violations. All the other compounds **4b-4f** obey the Lipinski's rule of five with one violation, therefore molecular weight having more than 500. The predicted octanol/water partition coefficient (QP logPo/w) was lower than that of 6.5, so its obey the Lipinski's rule of five because the partition coefficient of the lead compounds **4a-f** to give the predicted values from 4.189 to 6.000 permissible range for the ADME property. The pharmacokinetic property have suggested that oral bioavailability is influenced by a compound's, emphasized that this approach should be considered with caution with respect to choice of descriptor algorithm used and also because other factors can have a significant influence on bioavailability. However, along with the polar surface area criterion, a total sum of H-bond donors and acceptor's criterion (≥ 12) can be used, which is algorithm independent [21]. Similarly, molecules obeying Lipinski's rule of 5 could be more likely to have good intestinal absorption or permeation, which is confirmed by the predicted Caco-2 cell permeability (QPPCaco), used in a model for the gut–blood barrier [22]. QPPCaco predictions for all the test compounds showed very good values for Caco-2 cell permeability, Also, the QikProp descriptor for the brain/blood partition coefficient (QPlogBB) and the blood–brain barrier mimicked MDCK cell permeability (QPPMDCK). Show satisfactory predictions for all the test compounds, because the predicted brain/blood partition coefficient ranges from-1.439 to –1.096 in all the test compounds. For examples, dopamine and serotonin are CNS negative because they are too polar to cross the blood-brain barrier (-3.0 to 1.2). In addition, the aqueous solubility (QP logS) parameter with respect to lead compound **4a-f** assessed and all the compounds were predicted to have QP logS values in the permissible range. Furthermore, the QP log HERG descriptor for the prediction about the IC_{50} value of HERG K+ channel blockage was predicted for the test compounds.

In vivo antipschotic activity

Inhibition of amphetamine induced stereotype: Results from this study shows that all the stereotypic activities like sniffing, rearing and licking were reduced significantly in all the treatment groups ($P < 0.05$) compared to the control groups, but the degree of reduction varied differently among the treatment groups with small significant difference in all the different compounds **4a-f**. The standard drug aripiprazole reduced sniffing, rearing and licking activity by 51, 39 and 25 %, respectively. The synthesized compounds reduced sniffing, rearing and licking activity by 64, 71 and 75 %, respectively, compared to the control groups as shows in Table-4. Aripiprazole and synthesized compounds **4a-f** showed decrease in amphetamine-induced stereotype compared to the control (Fig. 1). However, the extent of decrease of the stereotypic activity for aripiprazole was less as compared to the synthesized compounds. This kind of outcome was indicative of a possibility that the test compounds may be decreasing the labels of dopamine levels in the brain as is the case for the standard drug aripiprazole.

Phencyclidine induced bizarre pattern of locomotor activity: The central nervous system locomotor activity of the synthesized compounds **4a-f** ware tested by using act photometer and the results are shown in Table-5. The locomotor

TABLE-3
ADME PROPERTIES OF SYNTHESIZED COMPOUNDS

Entry	MW	HBD	HBA	QP logPo/w	QP logPBB	QPPCaco2	QP logHERG	QP logS
1	497.636	2.000	7.750	4.189	-1.096	39	-6.555	-5.416
2	511.663	2.000	7.750	4.497	-1.034	48	-6.474	-5.127
3	525.689	2.000	7.750	4.869	-1.134	48	-6.637	-5.535
4	539.716	2.000	7.750	5.244	-1.236	48	-6.794	-5.949
5	553.743	2.000	7.750	5.621	-1.338	48	-6.552	-6.373
6	567.770	2.000	7.750	6.000	-1.439	48	-7.089	-6.798

TABLE-4
INHIBITION OF AMPHETAMINE INDUCED STEREOTYPE IN RATS

Groups	Sniffing	Rearing	Licking
Control	17 ± 0.730297	7.00000 ± 0.730297	4 ± 0.365148
Amphetamine + Aripiprazole	8.33333 ± 0.760117***	4.33333 ± 0.557773	1 ± 0.365148***
Amphetamine + **4a**	10.5767 ± 0.918937*	4.66667 ± 0.557773	4.66667 ± 0.210819^{ns}
Amphetamine + **4b**	10.6739 ± 0.760117**	5.36770 ± 0.365180	4.33333 ± 0.210819^{ns}
Amphetamine + **3c**	11.1893 ± 0.78476^{ns}	5.87370 ± 0.895800	3.33333 ± 0.210819*
Amphetamine + **4d**	11.2873 ± 1.83773**	6.00000 ± 0.123330	3.66667 ± 0.210819
Amphetamine + **4e**	12.4576 ± 0.87654*	6.35780 ± 0.918937	2.3337 ± 0.210819
Amphetamine + **4f**	12.6667 ± 0.760117^{ns}	6.66730 ± 1.115550	2.66667 ± 0.421637^{ns}

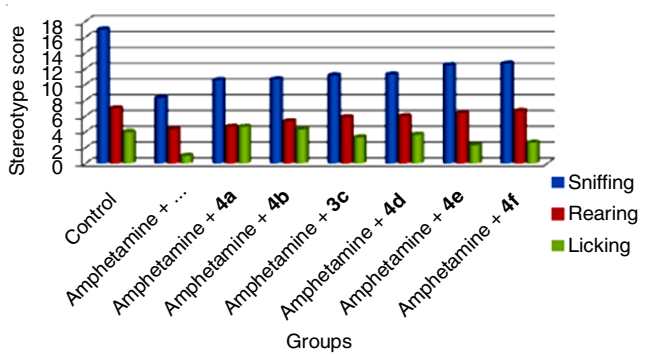


Fig. 1. Amphetamine induced stereotype activity of synthesized compounds

activity noticed that most of the compounds showed excellent of reducing locomotor activities against control group observed at 10 mg/kg concentrations. The most of the quinoline compounds produce significant depressant activity at all the tested compounds in 10 mg/kg concentrations. In this experiment, all the synthesized drug candidates **4a-f** were expressed higher depressant activity when compared to standard CNS depressant drug aripiprazole are shows in Fig. 2.

TABLE-5
PHENCYCLIDINE INDUCED BIZARRE PATTERN OF LOCOMOTOR ACTIVITY

Groups	Locomotor activity scores
Control	302.333 ± 3.47051
Phencyclidine + Aripiprazole	311.667 ± 3.93842^{ns}
Phencyclidine + **4a**	277.000 ± 2.39444***
Phencyclidine + **4b**	279.333 ± 0.918937^{ns}
Phencyclidine + **4c**	284.333 ± 3.47051***
Phencyclidine + **4d**	287.637 ± 4.69515***
Phencyclidine + **4e**	290.000 ± 2.38544**
Phencyclidine + **4f**	295.333 ± 1.17379^{ns}

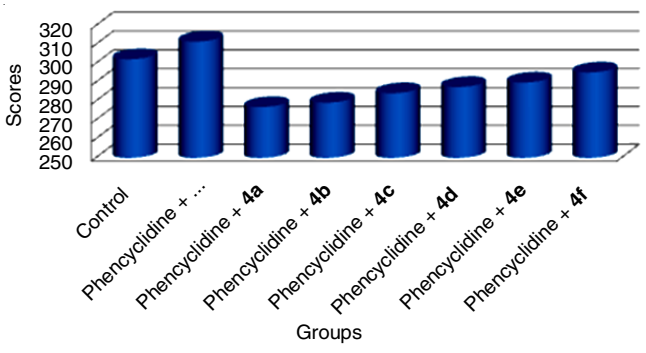


Fig. 2. Locomotor activity of synthesized compounds against control and reference drug

Phencyclidine induced social withdrawl test: No animals from the test groups or the standard group altered the social exploration and the anogenital inspection activity compared with the control group significantly (P > 0.05). This model is suggestive of the absence of negative symptoms alleviating property of all the treatment groups (Table-6). Phencyclidine induced social withdrawal test along with the standard drug did not have any impact on the phencyclidine-induced social interaction test. This particular model was suggestive of the ineffectiveness of the test compounds to alleviate the negative symptoms of schizophrenia. It is once again established that aripiprazole has no effect on the negative symptoms of schizophrenia (Fig. 3).

TABLE-6
PHENCYCLIDINE INDUCED SOCIAL WITHDRAWAL TEST

Groups	Social exploration	Anogenital inspection
Control	7.345 ± 0.558	4.000 ± 0.632
Phencyclidine + Aripiprazole	5.677 ± 0.557*	3.000 ± 0.365*
Phencyclidine + **4a**	6.09 ± 0.365	3.290 ± 0.365*
Phencyclidine + **4b**	6.68 ± 0.558	3.333 ± 0.558
Phencyclidine + **4c**	7.19 ± 0.365	3.489 ± 0.421
Phencyclidine + **4d**	7.67 ± 0.557	3.674 ± 0.557
Phencyclidine + **4e**	8.28 ± 0.730	3.790 ± 0.558
Phencyclidine + **4f**	8.87 ± 0.365	4.000 ± 0.365

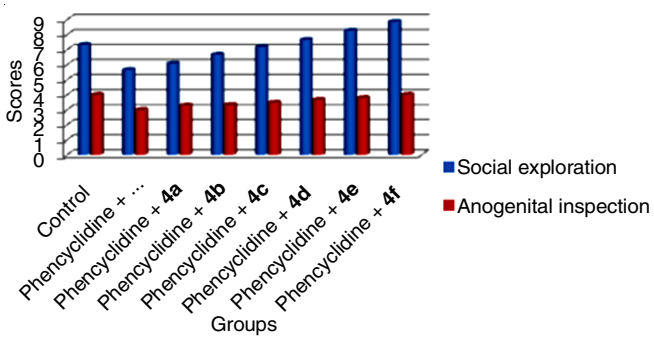


Fig. 3. Social exploration and anogenital inspection activity of synthesized compounds

Conditioned avoidance response in rats: All the groups significantly decreased the escape response compared to the control group (P < 0.05). Group II reduced the escape response by almost 53 %, Group III-31 %, Group IV and V by 25 %, Group VI-18 %, Group VII-16 %, Group VIII-12 % respectively (Fig. 4). However, there was no dose-dependent reduction of escape response for the synthesized compounds. In this

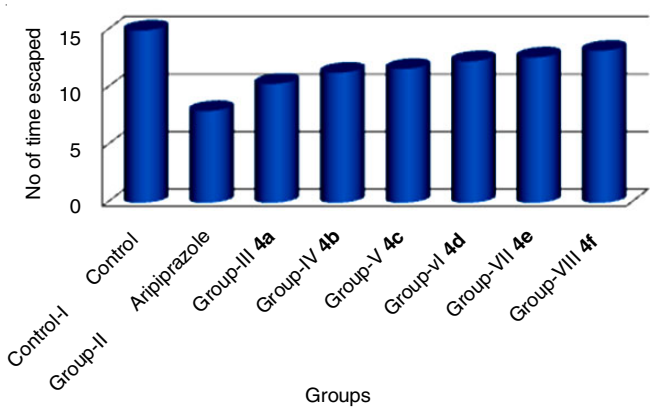


Fig. 4. Effect of aripiprazole alone and synthesized compounds in albino rats dose response

study the no of escaping time increases is depended upon substitution because, the alkyl chains increase from methyl to hexyl substituents. Both the synthesized compounds as well as the standard drug reduced the conditioned avoidance response; however, the magnitude of reduction was less for the test compounds than the standard drug when they were compared with the control group. This kind of results for the standard and the test compounds again indicated the alleviating effects of positive symptoms of schizophrenia (Table-7).

TABLE-7
CONDITION AVOIDANCE RESPONSE IN RATS

Groups	Number of times escaped
Group-I Control	15.0000 ± 0.730297
Group-II Aripiprazole	8.0000 ± 0.365148***
Group-III **4a**	10.367 ± 0.760117^{ns}
Group-IV **4b**	11.3333 ± 0.760117***
Group-V **4c**	11.6667 ± 0.918937***
Group-VI **4d**	12.3333 ± 0.918937***
Group-VII **4e**	12.6667 ± 0.760117^{ns}
Group-VIII **4f**	13.2467 ± 1.11555*

Induction of catalepsy in rats: All the treatment groups increased the mean cataleptic scores significantly ($P < 0.05$) compared with the control group (Fig. 5). However, the increase in mean cataleptic score was increased by almost 100 % in case of the test compounds, whereas 300 % in case of the standard drug aripiprazole. However, most the animals of the compounds **4a-f** treated groups corrected their stretched limb position within 10 seconds, but they needed a touch or some kind of push for their movement to start. There was no significant difference in cataleptic score among the same dose of the test groups. The induction of catalepsy once again pointed out the fact that all the compounds like the standard drug could be acting on the dopaminergic neurons of the brain. Aripiprazole is known to decrease the dopamine levels on various dopaminergic pathways of the brain, which is the reason for extra pyramidal motor disorders. Further analysis of the data showed that there were no significant dose-dependent effects for synthesized compounds in decreasing the dopamine levels (Table-8).

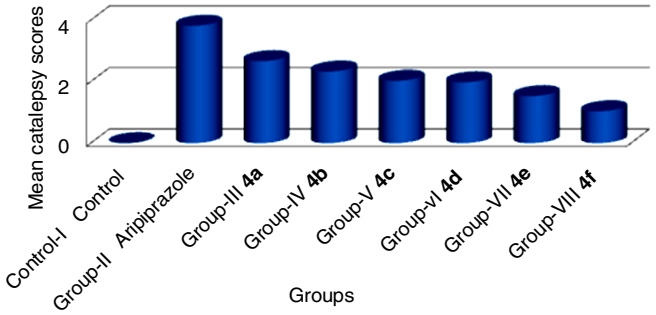


Fig. 5. Effect of mean cataleptic activity on synthesized compounds against aripiprazole

TABLE-8
INDUCTION OF CATALEPSY ACTIVITY IN RATS

Groups	Mean cataleptic scores
Group-I Control	0 ± 0
Group-II Aripiprazole	3.8234 ± 0.141248***
Group-III **4a**	2.6790 ± 0.0735149***
Group-IV **4b**	2.3330 ± 0.0545283***
Group-V **4c**	2.0340 ± 0.0877117***
Group-VI **4d**	1.9860 ± 0.169286***
Group-VII **4e**	1.5360 ± 0.0345***
Group-VIII **4f**	1.0450 ± 0.105262***

Conclusion

In the present study, our attention was focused on synthesis, molecular docking, ADME properties and *in vivo* antipsychotic activities of quinoline-5-one derivatives. The docking results revealed that compound **4a** showed minimum binding energy and ADME properties of all these compounds have orally drug-likeness property. In this experiment, all the synthesized drug candidates **4a-f** were expressed higher depressant activity when compared to standard CNS depressant drug aripiprazole.

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