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In Vivo Antipsychotics: Synthesis, Spectral, Docking and Pharmacokinetic Properties of New 1-(4-(3,4-dihydroquinolin-2(1H)-one-7-yloxy)butyl)-3-methyl-2,7-diphenyl-1,4-diazepan-5-one Analogs of Aripiprazole

Selvarasu Sekar[1], Srinivasan Pazhamalai[1], Ganesan Ariharasivakumar[2], Mannathusamy Gopalakrishnan[1*]

[1]Department of Chemistry, Annamalai University, Chidambaram-608002, Tamil Nadu, India
[2]Department of Pharmacology, KMCH College of Pharmacy, Coimbatore-641048, Tamil Nadu, India

ABSTRACT

A series of new 1-(4-(3,4-dihydroquinolin-2(1H)-one-7-yloxy)butyl)-3-methyl-2,7-diphenyl-1,4-diazepan-5-one analogs of aripiprazole was synthesized by the replacement of 2,3-dichlorophenyl-4-piperazine/diazepane moiety with 3-methyl-2,7-diphenyl-1,4-diazepan-5-one to explore the influence of structural features. All the synthesized compounds are characterized by elemental analysis, Fourier Transform Infrared (FTIR), Proton Nuclear Magnetic Resonance (^{1}H-NMR), Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR), Heteronuclear Single Quantum Coherence (HSQC) (2D NMR) and mass spectrometry of compound 4a. All the multi target ligands have been docked against, human A_2A adenosine receptor and human β_2-adrenergic G-protein-coupled Receptors (GPCRs), both receptor and ligand interaction shows an excellent dock score. Absorption Distribution, Metabolism and Excretion (ADME), properties were also evaluated in the desirable range, finally these compounds have orally drug-likeness property. In this event was done to screening the neuroleptic activity of the synthesized compounds with different anti-psychotic animal models.

Keywords: ADME properties, Antipsychotic, Aripiprazole, *In vivo*, Molecular docking

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. 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 [1]. Antipsychotics are occasionally referred to as neuroleptic drugs and some antipsychotics are recognized major tranquilizers. Atypical antipsychotics are safer than typical antipsychotics [2], they still have rigorous side effects, together with tardive dyskinesia, neuroleptic malignant syndrome, augmented risk of stroke, unexpected cardiac death, blood clots and diabetes [3].

Schizophrenia is a composite neuropsychiatric disorder characterized by the progress of three different kinds of symptoms: positive, negative and cognitive. For the behavior of this disorder, the first generation of antipsychotic drugs was discovered about 50 years ago (e.g., Chlorpromazine, haloperidol), described as selective D_2 dopamine antagonists, today they are known as typical antipsychotics [4]. In a development of CNS active agents, several recently launched antidepressant/antipsychotic drugs e.g. amisulpride and aripiprazole, or compounds investigated in clinical trials (Vortioxetine) [5] display mixed Serotonin (5-HT) and dopamine (D) receptor profile. It was freshly found, that these drugs perform as 5-HT_7 receptor antagonists and this mechanism is dependable for their antidepressant properties [6] Moreover, the multimodal receptor profile of aripiprazole and its functional profile-partial agonist of D_2, 5-HT_1A receptors, antagonist of 5-HT_2A and 5-HT_7 sites, might under line its board efficacy antipsychotic, antidepressant and anxiolytic effects. The D receptor partial agonist's aripiprazole and cariprazine stand for promising options for the treatment of schizophrenia [7-9] 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 antipsychotics that have no Extra Pyramidal Symptoms (EPS) at the doses frequently used in therapy and are effective also against the negative symptoms [10-12]. 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, 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.

MATERIALS AND METHODS

All the reported melting points were taken in open capillaries. An IR spectrum was recorded in a Agilent Cary 650 FTIR spectrophotometer by KBr pellet technique and only noteworthy absorption levels are listed in reciprocal centimeters. ^{1}H and ^{13}C-NMR spectra were recorded respectively at 400 and 100.6 MHz, on a Bruker AMX 400 spectrometer using Deuterated Chloroform ($CDCl_3$) as solvent and Tetramethylsilane (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.

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, 60 ml) in 5 ml con H_2SO_4 in ice cold conditions, (0.65 g, 0.01 mol) of sodium azide was added for 30 min with constant stirring [14-16]. 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 washed with water and filtered to gives the pure title 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(1H)-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-(1H)-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; FTIR (KBr) (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 (d, J=6.8 Hz, 3H, CH_3), 2.68 (d, J=20 Hz, 1H, 6ax), 3.15 (dd, J=2.8, 11.2 Hz, 1H, 6eq), 3.71 (d, J=7.6 Hz, 1H, H_2), 4.13 (d, J=10.4, Hz, 1H, H_7), 3.84 (m, 1H, H_3), 3.48 (t, J=6.8 Hz, 2H, –N-CH_2), 3.96 (t, J=6 Hz, 2H, quinolione attached O-CH_2), 2.05 (m, 2H, CH_2), 1.93 (m, 2H, CH_2), 2.61 (t, J=7.2 Hz, 2H, O=C-CH_2 quinolinone), 2.89 (t, J=7.6 Hz, 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: $C_{31}H_{35}N_3O_3$), elemental analysis, Calc. for: C-74.82; H-7.09; N-8.44, Expe: C-74.37; H-6.87; N-8.30, yield 96%.

1-(4-(3,4-dihydroquinolin-2(1H)-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; FTIR (KBr) (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, J=7.6 Hz, 3H, CH_3), 1.12 (m, 2H, CH_2), 3.16 (s, 1H, H_6ax), 2.66 (d, J=14.0 Hz, 1H, H_6eq), 3.65 (s, 1H, H_2), 4.14 (d, J=10.4 Hz, 1H, H_7), 3.78 (m, 1H, H_3), 3.47 (t, J=6.4 Hz, 2H, –N-CH_2), 3.95 (t, J=6 Hz, 2H, quinolione attached O-CH_2), 2.04 (m, 2H, CH_2), 1.91 (m, 2H, CH_2), 2.59 (t, J=7.6 Hz, 2H, O=C-CH_2 quinolinone), 2.87 (t, J=7.6 Hz, 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): (M.F: $C_{32}H_{37}N_3O_3$), elemental analysis, Calc. for: C-75.12; H-7.29; N-8.21, Expe: C-74.89; H-7.05; N-8.07, yield 95%.

1-(4-(3,4-dihydroquinolin-2(1H)-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; FTIR (KBr) (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, J=7.2 Hz, 3H, CH_3), 0.99, (m, 2H, CH_2), 1.11 (m, 2H, CH_2), 3.15 (dd, J=3.6, 10.4 Hz, 1H, H_6ax), 2.66 (s, 1H, H_6eq), 3.77 (d, J=7.6 Hz, 1H, H_2), 4.14 (d, J=10.4 Hz, 1H, H_7), 3.76 (m, 1H, H_3), 3.48 (t, J=6.4 Hz, 2H, –N-CH_2), 3.96 (t, J=6 Hz, 2H, quinolione attached O-CH_2), 2.05 (m, 2H, CH_2), 1.92 (m, 2H, CH_2), 2.61 (t, J=7.2 Hz, 2H, O=C-CH_2 quinolinone), 2.89 (t, J=8 Hz, 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): (M.F: $C_{33}H_{39}N_3O_3$), elemental analysis, Calc. for: C-75.40; H-7.48; N-7.99, Expe: C-75.14; H-7.27; N-7.83, yield 97%.

1-(4-(3,4-dihydroquinolin-2(1H)-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; FTIR (KBr) (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, J=7 Hz, 3H, CH_3), 1.06-1.25, (m, 6H, CH_2, CH_2, CH_2), 2.63 (s, 1H, H_6ax), 3.16 (d, J=11.5 Hz, 1H, H_6eq), 3.75 (d, J=10.2 Hz, 1H, H_2), 4.14 (d, J=10.4 Hz, 1H, H_7), 3.94 (m, 1H, H_3), 3.48 (t, J=6.4 Hz, 2H, –N-CH_2), 3.96 (t, J=6 Hz, 2H, quinolione attached O-CH_2), 2.05 (m, 2H, CH_2), 1.93 (m, 2H, CH_2), 2.61(t, J=7.2 Hz, 2H, O=C-CH_2 quinolinone), 2.89 (t, J=7.6 Hz, 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), (M.F: $C_{34}H_{41}N_3O_3$), elemental analysis, Calc. for: C-75.66; H-7.66; N-7.79, Expe: C-75.48; H-7.48; N-8.68, yield 98.5%.

1-(4-(3,4-dihydroquinolin-2(1H)-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; FTIR (KBr) (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, (t, J=6.8 Hz, 3H CH_3), 1.00-1.25, (m, 1H, 3-pentyl), 2.66 (d, J=1.2 Hz, 1H, H_6ax), 3.15 (dd, J=3.2, 10.4 Hz, 1H, H_6eq), 3.76 (d, J=7.6 Hz, 1H, H_2), 4.14 (d, J=10.4 Hz, 1H, H_7), 3.77(m, 1H, H_3), 3.48 (t, J=6.8 Hz, 2H, –N-CH_2), 3.96 (t, J=6 Hz, 2H quinolione attached O-CH_2), 2.05 (m, 2H, CH_2), 1.93 (m, 2H, CH_2), 2.63 (t, J=7.2 Hz, 2H, O=C-CH_2 quinolinone), 2.89 (t, J=7.6 Hz, 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): (M.F: $C_{35}H_{43}N_3O_3$), elemental analysis, Calc. for: C-75.92; H-7.83; N-7.59, Expe: C-75.83; H-7.69; N-7.41, yield 96.8%.

1-(4-(3,4-dihydroquinolin-2(1H)-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; FTIR (KBr) (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, (t, J=7.2 Hz, 3H, CH_3), 1.04-1.25 (m, 13H, 3-hexyl), 2.67 (s, 1H, H_6ax), 3.15 (dd, J=3.2, 10.8 Hz, 1H, H_6eq), 3.71 (t, J=8, Hz, 1H, H_2), 4.15 (d, J=10.4 Hz, 1H, H_7), 3.75 (m, 1H, H_3), 3.61 (t, J=6 Hz, 2H, –N-CH_2), 3.97 (t, J=6 Hz, 2H, quinolione attached O-CH_2), 2.05 (m, 2H, CH_2), 1.92 (m, 2H, CH_2), 2.62 (t, J=7.6 Hz, 2H, O=C-CH_2 quinolinone), 2.88 (t, J=7.6 Hz, 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), (M.F: $C_{36}H_{45}N_3O_3$), elemental analysis, Calc. for: C-76.16; H-7.99; N-7.40, Expe: C-76.02; H-7.84; N-7.14, yield 98.3%.

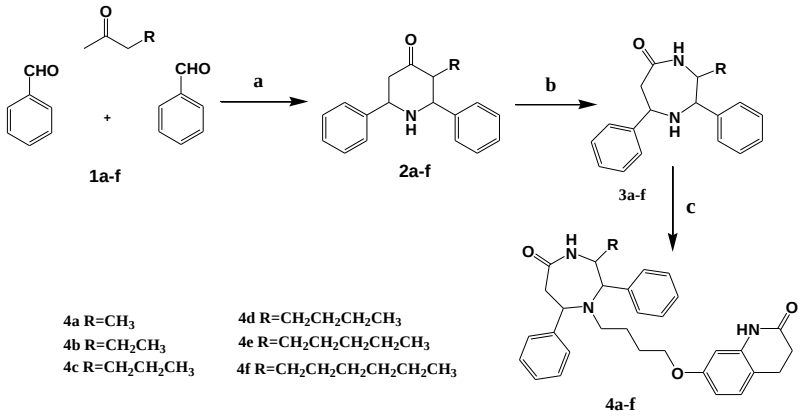
HSQC spectral analysis of synthesized compound 1-(4-(3,4-dihydroquinolin-2(1H)-one-7-yloxy)butyl)-3-methyl-2,7-diphenyl-1,4-diazepan-5-one (4a)

The synthesized compound 4a was further analyzed by HSQC spectral analysis for confirmation of its structure. In the HSQC spectrum (supplementary) 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

Chemistry

The synthesis of all drug compounds is outlined in scheme-1. A three-step synthetic strategy was adopted for the synthesis of substituted 1-(4-(3,4-Dihydroquinolin-2(1H)-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].



Scheme 1: Reagents and conditions: (a) EtOH, NH_4OAc warm, (b) Con H_2SO_4, NaN_3, NaOH solution (20%), (c) Dichloromethane, 7-(4-bromobutoxy)-3, 4-dihydroquinolin-2(1H)-one, N-ethyldiisopropylamine, reflux 2hr, 96%

Schmidt reactions [14-16] of azide with ketone when treated with Bronsted or Lewis acids at 0-5°C were converted in to diazepane (3a-f) in good to excellent yields in the second step. The debromination reactions of 7-(4-bromobutoxy)-3,4-dihydro-2-(1H)-quinolinone with 3-alkyl-2,7-diphenyl-1,4-diazepan-5-one in aqueous medium to produced target compounds (4a-f).

FTIR spectrum of compound 3a showed a sharp and intense absorption band in the region of 1670 and 1629 cm^{-1} while is due the presence of C=O groups, the region 3085 and 2932 cm^{-1} is due to aromatic and aliphatic C-H stretching frequency. An absorption band around 3428 cm^{-1} is assigned to N-H stretching. In the ^{1}H-NMR spectrum of compound 3a, a doublet at 0.83 ppm (d, J=6.08 Hz, 3H, CH_3) is due to methyl proton diazepam-5-one ring and a singlet for N-H proton appeared at 6.04 and 8.49 ppm is assigned for diazepan-5-one and quinolinone moiety. The appearance of doublet of doublet at δ 2.68 (J=20 Hz) and δ=3.15 (J=8 Hz) may be due to the H6ax and H6eq protons of the diazepane ring. The H_2 and H_7 protons appears as a doublet at δ=3.71 (d, J=7.06 Hz, 1H, H_2) and 4.13 (d, J=10.04 Hz, 1H, H_7), whereas the H_3 proton appears as a multiplet at δ 3.48 ppm. The aryl protons are appear as a multiplet in the range δ=6.35-7.42 ppm. The diazepane ring attached N-CH_2- and quinolinone attached O-CH_2- protons are appeared at 3.48 (t, J=13.02 Hz) and 3.96 (t, J=12 Hz) ppm. Two set of multiplet are appear in the range of 2.05 (CH_2) and 1.93 (CH_2) ppm, while due to the presence of linker chain. The two set of triblet is due to methylene protons quinolinone ring 2.61 (t, J=7.06 Hz, 2H, O=C-CH_2) and 2.89 (t, J=14.08 Hz, CH_2).

The formation of 1-(4-(3,4-dihydroquinolin-2(1H)-one-7-yloxy)butyl)-3-methyl-2,7-diphenyl-1,4-diazepan-5-one was confirmed by its ^{13}C-NMR spectrum. The carbon signals from 102.23-158.50 ppm are assigned to aromatic carbons. The signals at 172.03 ppm (quinolinone) and 175.96 ppm (diazepan-5-one) are due to amide carbonyl carbon respectively. The methyl and methylene carbons are followed by 19.82, 24.61, 27.86, 29.44, 31.10, 33.48, 47.52, 54.83, 59.64, 67.03 and 71.12 ppm. The mass spectrum of compound (4a) shows the molecular ion peak at m/z 498.3 (M+1) by the addition of one proton which is consistent with the proposed molecular mass (497.6) of compound 4a (Supporting information).

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 (Figure 1). 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 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 (1.622Å), 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 (2.083Å).

Table 1: Molecular docking studies of 2RH1 protein with synthesized compounds

Entry	Glide score	Glide energy	Number 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

The quinolinone amide group was strongly interacted with oxygen atom of the Tyr 271 residue with the bond distance (2.408Å) 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 (Figure 2). The observed docking Glide score presented in Table 2.

Table 2: Molecular docking studies of 3EML protein with synthesized compounds

Entry	Glide score	Glide energy	Number 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

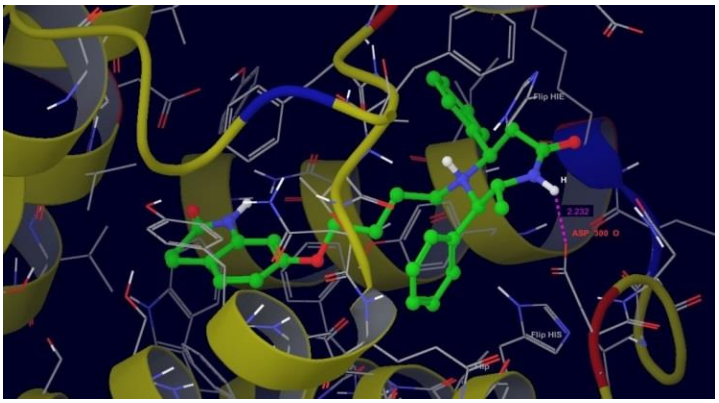


Figure 1: Binding pocket of compound 4a with human A2A Adenosine receptor

ADME property

Lipinski's rule of five also known as the Pfizer's rule of five, based on the observation that most orally administered drugs are relatively small and moderately lipophilic 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]. The synthesized compounds were subjected to a computational program using QIKPROP 3.7 [20] module of Schrödinger software for the in combo determination of pharmacokinetic.

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 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 (QPlog Po/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.

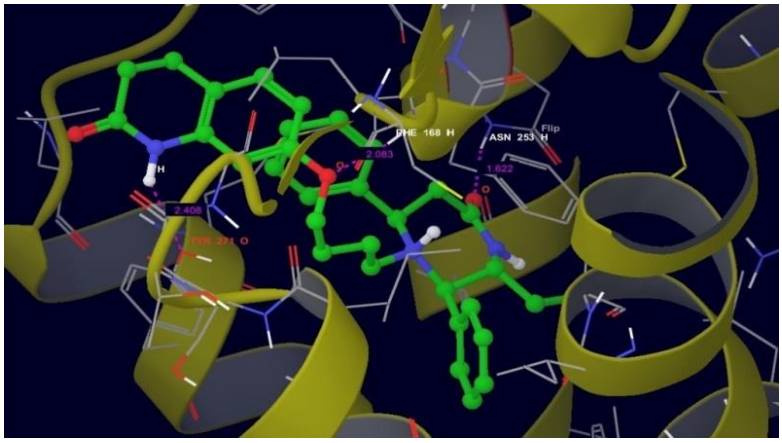


Figure 2: Binding pocket of compound 4a with human β2-Adrenergic G-protein-coupled Receptors (GPCR)

Table 3: ADME properties of synthesized compounds

Entry	Molecular weight	HBD	HBA	QPlogPo/w	QPlogPBB	QPPCaco2	QPlogHERG	QPlogS
1	497.63	2.00	7.75	4.189	-1.096	39	-6.555	-5.416
2	511.66	2.00	7.75	4.497	-1.034	48	-6.474	-5.127
3	525.69	2.00	7.75	4.869	-1.134	48	-6.637	-5.535
4	539.72	2.00	7.75	5.244	-1.236	48	-6.794	-5.949
5	553.74	2.00	7.75	5.621	-1.338	48	-6.552	-6.373
6	567.77	2.00	7.75	6.000	-1.439	48	-7.089	-6.798

The predicted ADME properties have been calculated in particular; eight descriptors were determined and analyzed such as molecular weight, HBD, HBA, QPlogPo/w, QPlogPBB, QPPCaco2, QPlogHERG and QPlogS 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 obeys the Lipinski's rule of five with one violation, therefore molecular weight having more than 500. The predicted octanol/water partition coefficient (QPLogPo/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. 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 Madin-Darby Canine Kidney Epithelial Cells (MDCK) 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 (QPlogS) parameter with respect to lead compound 4a-f assessed and all the compounds were predicted to have QPlogS values in the permissible range. Furthermore, the QPlogHERG descriptor for the prediction about the IC50 value of HERG K+ channel blockage was predicted for the test compounds.

***In vivo* antipsychotic activity**

Inhibition of amphetamine induced stereotype

Results from this study shows that all the stereotypic activities like sniffing, rearing and licking [23] 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 among 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.

Table 4: Inhibition of amphetamine induced stereotype in rats

Groups	Sniffing	Rearing	Licking
Control	17 ± 0.730297	7 ± 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	$4.66667 \pm 0.210819^{ns}$
Amphetamine+4b	$10.6739 \pm 0.760117^{**}$	5.3677 ± 0.36518	$4.33333 \pm 0.210819^{ns}$
Amphetamine+3c	11.1893 ± 0.78476^{ns}	5.8737 ± 0.8958	$3.33333 \pm 0.210819^{*}$
Amphetamine+4d	$11.2873 \pm 1.83773^{**}$	6 ± 0.12333	3.66667 ± 0.210819
Amphetamine+4e	$12.4576 \pm 0.87654^{*}$	6.3578 ± 0.918937	2.3337 ± 0.210819
Amphetamine+4f	$12.6667 \pm 0.760117^{ns}$	6.6673 ± 1.11555	$2.66667 \pm 0.421637^{ns}$

Values are expressed as mean ED_{50} ± SEM statistical significance (p) calculated by one way ANOVA followed by Dunnett's (n=6); $^{ns}p > 0.05$, $*p < 0.05$, $**p <$

0.01, ***p < 0.001, calculated by comparing treated groups with control group

Aripiprazole and synthesized compounds 4a-f showed decrease in amphetamine-induced stereotype compared to the control (Figure 3). 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.

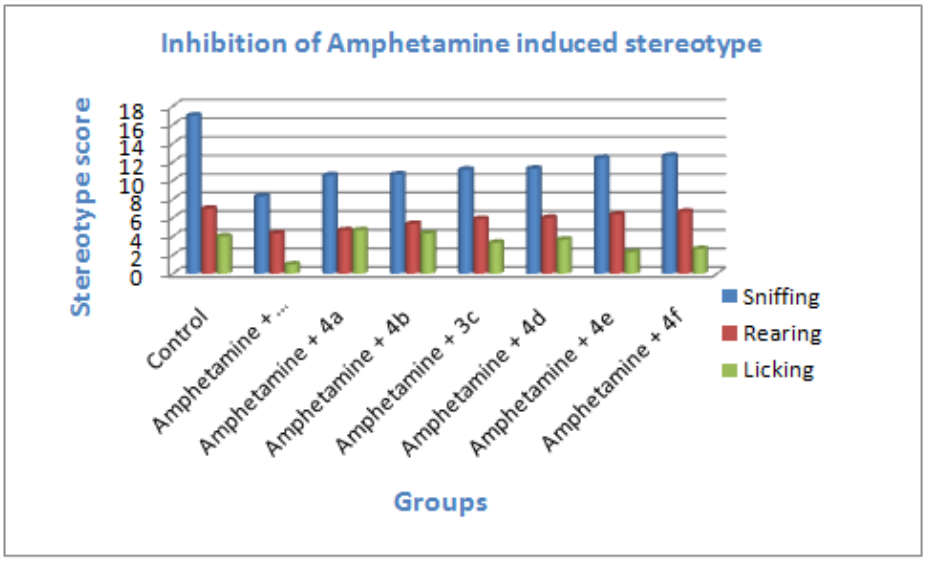


Figure 3: Amphetamine induced stereotype activity of synthesized compounds

Phencyclidine induced Bizarre pattern of locomotor activity

The central nervous system locomotor activity [24,25] of the synthesized compounds 4a-f ware tested by using act photometer and the results are shown in Table 5. The locomotor activity noticed that most of the compounds were shows excellent of reducing locomotor activities against control group were observed at 10 mg/kg concentrations.

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 ± 2.39444***
Phencyclidine+4b	279.333 ± 0.918937^{ns}
Phencyclidine+4c	284.333 ± 3.47051***
Phencyclidine+4d	287.637 ± 4.69515***
Phencyclidine+4e	290 ± 2.38544**
Phencyclidine+4f	295.333 ± 1.17379^{ns}

The most of the quinoline compounds produce significant depressant activity at all the tested compounds in 10mg/kg concentrations. In this experiment, all the synthesized drug candidates 4a-f was expressed higher depressant activity when compared to standard CNS depressant drug Aripiprazole are shows in Figure 4.

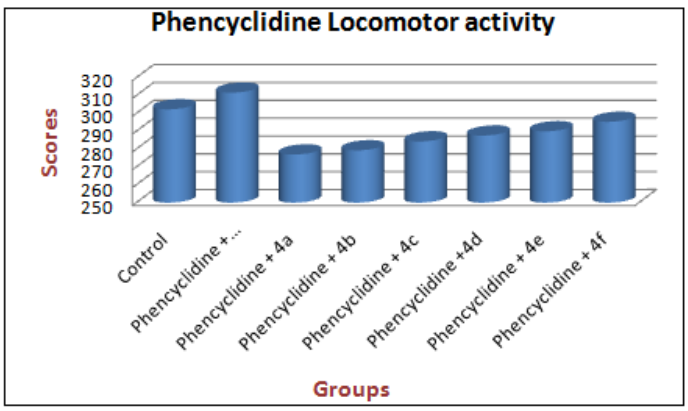


Figure 4: Locomotor activity of synthesized compounds against control and reference drug

Phencyclidine induced social withdrawal 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).

Table 6: Phencyclidine induced social withdrawal test

Groups	Social exploration	Anogenital inspection
Control	7.345 ± 0.558	4 ± 0.632
Phencyclidine + Aripiprazole	5.677 ± 0.557*	3 ± 0.365*
Phencyclidine + 4a	6.09 ± 0.365	3.29 ± 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	3.79 ± 0.558
Phencyclidine + 4f	8.87 ± 0.365	4 ± 0.365

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 (Figure 5).

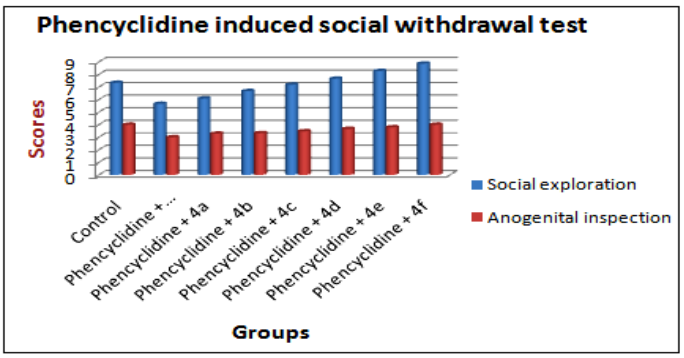


Figure 5: Social exploration and anogenital inspection activity of synthesized compounds

Conditioned avoidance response in rats

All the groups significantly decreased the escape response compared to the control group [25] (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 (Figure 6). However, there was no dose-dependent reduction of escape response for the synthesized compounds. In this study the no of escaping time increases is depended upon substitution because, the alkyl chains increase from methyl to hexyl. 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	No of times escaped
Group-I Control	15 ± 0.730297
Group-II Aripiprazole	8 ± 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*

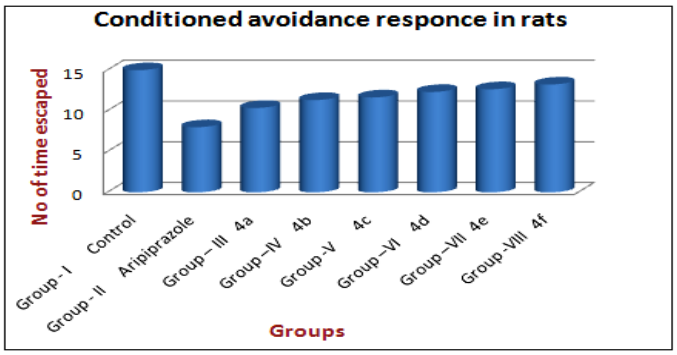


Figure 6: Effect of aripiprazole alone and synthesized compounds in Albino rats dose response

Induction of catalepsy in rats

All the treatment groups increased the mean cataleptic scores significantly [24,25] ($P < 0.05$) compared with the control group (Figure 7). 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.

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	2.679 ± 0.0735149***
Group-IV 4b	2.333 ± 0.0545283***
Group-V 4c	2.034 ± 0.0877117***
Group-VI 4d	1.986 ± 0.169286***
Group-VII 4e	1.536 ± 0.0345***
Group-VIII 4f	1.045 ± 0.105262***

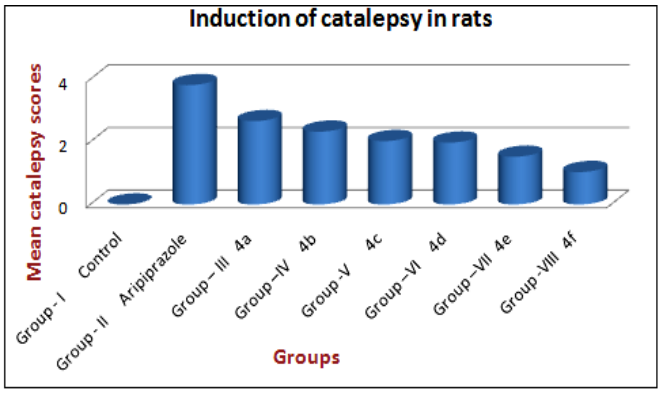


Figure 7: Effect of mean cataleptic activity on synthesized compounds against aripiprazole

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).

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. The synthesized compound 1-(4-(3,4-dihydroquinolin-2(1H)-one-7-yloxy)butyl)-3-methyl-2,7-diphenyl-1,4-diazepan-5-one (4a) showed an excellent effect with lower ED_{50} value which is lower than that of Aripiprazole. Quinoline-5-one derivatives have shown potential effects in reducing the positive symptoms of schizophrenia by reducing the dopamine level in brain.

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