Synthesis, Biological Evaluation, and Insilico Studies of Novel 4(3H)-Quinazolinone Derivatives as Atypical Antipsychotics

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Abstract

Schizophrenia is a psychiatric illness characterized by a change in mental acceptance of thoughts. Atypical antipsychotics affect serotonin and dopamine levels by acting on the 5HT2A and D2 receptors, respectively. The aim of this study was to create a new sequence of 3[(2-aminopyridin-1(4H)-yl) diazenyl] quinazolin-4(3H)-one derivatives by designing and synthesizing them. Atypical antipsychotics' biological potential was determined by testing the synthesized derivatives for antagonistic action against dopamine D2 and serotonin 5HT2A. Molecules 5b, 5c, 5e, 5f, and 5j were discovered to be significantly active. According to SAR findings, the presence of electron withdrawing groups increased biological activity. Because of its therapeutic index of 15.46, the 5b molecule was chosen as the best molecule. The therapeutic index of 5e, 5f, and 5j compared favorably to the normal. The mechanistic function of the synthesized molecules was validated through docking studies of the 5b molecule and validation with standard Ketanserin. All of the synthesized compounds had strong antagonist activity against the dopamine D2 and serotonin 5HT2A receptors, suggesting atypical antipsychotic activity.

Keywords

Schizophrenia, Quinazolinone, Atypical antipsychotics, Docking, Ketanserin

• Introduction

Mental disorders are the quite common disorders that the twenty first century is experiencing. Schizophrenic disorder could be a psychological state that causes a person' emotions to alter and their ability to differentiate between reality and fiction. Patients have traumatic events that are connected to a sleep design that's disrupted[1]. According to pathophysiology reports, dopamine-related serotonin levels should be elevated. Although it was later established that the response was an extrapyramidal aspect impact, dopamine D2 is essential for neuroleptic medication reactivity[2]. According to research, marketed drugs such as neuroleptic agent and olanzapine have lost their receptor affinity and are more likely to dissociate. The majority of atypical antipsychotics contain 5HT2A antagonistic as well as D2 receptor antagonistic properties[3].While creating new atypical antipsychotic medications, healthy chemists are increasingly resorting to certain targets[4]. Atypical antipsychotics are considered to have less adverse effects than traditional antipsychotics[5]. Mechanistic investigations of atypical antipsychotics can provide information about the pathophysiology of schizophrenia, which might lead to the development of novel bioactive compounds having greater effectiveness with fewer adverse effects than currently available medications[6].

The goal of this research was to create novel amino pyridine derivatives of quinazolinones that could have effective action on D2 and 5HT receptors[7,8] as well as to evaluate pharmacological action for atypical neuroleptic activity. Aminopyridine derivatives with a quinazolin-4(3H)-one moiety was synthesized using a microwave-assisted method[9,10]. Aminopyridine and quinazoline-4 (3H)-one derivative are shown to have D2 and 5HT antagonistic activity [11,12]. New quinazoline-4(3H)-one derivative with low adverse effects and improved pharmacological efficacy were included in the study. Designing of new derivatives with potent antagonistic activity may lead to the development of new series of compounds.

• Experimental

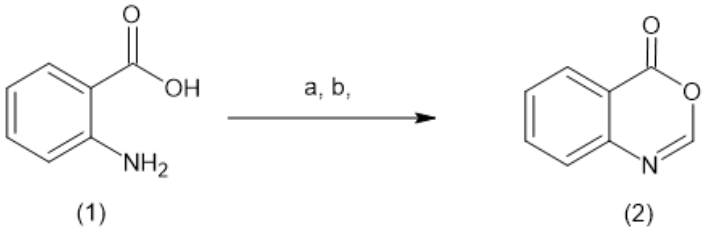
Materials and methods:

The physicochemical properties of compounds were monitored for melting point, retardation factor (Rf value), IR studies using LABHOSP melting point apparatus, Merck Precoated TLC Plates, and SHIMADZU-FTIR IR-Affinity-1 spectrophotometer[14] . The Bruker ACF-300 MHz spectrometer of CDRI, Lucknow was used to analyze the proton NMR spectra of the synthesized compounds. The chemical shift data obtained were reported accordingly. The synthesized derivatives were also analyzed for mass spectra using a SHIMADZU GCMS-2010 mass spectrometer. Pharmacological studies were performed at Priyadarshini J. L. college of Pharmacy, Nagpur, Maharashtra, India using a validated model for antipsychotic model evaluation.

Synthesis of 3[(2-aminopyridin-1(4H)-yl) diazenyl] quinazolin-4(3H)-one derivatives

Synthesis of 4H-3,1-benzoxazin-4-one (2)

Formyl chloride (0.01 mol) was added dropwise after dissolving anthranilic acid (1 mmol) in pyridine (15 mL). The reaction mixture was refluxed for 2 hours. The hot reaction mixture was initially allowed to cool and then neutralized with a saturated sodium bicarbonate solution[15].The pale-yellow solid of 4H-3,1-benzoxazin-4-one was separated, purified, washed with cold water, and recrystallized from ethanol. The synthetic scheme is shown schematically in Figure 1.

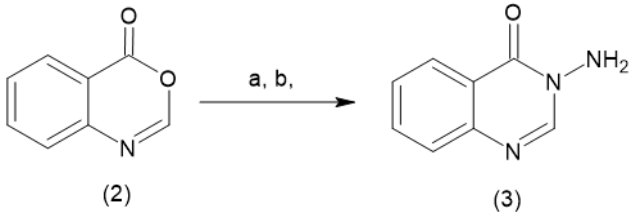


(1) Anthranilic Acid (2) 4H-3,1- benzoxazine-4-one

Fig. 1: Synthesis of 4H-3,1-benzoxazin-4-one (2), a. Pyridine, b. Formyl Chloride

Synthesis of 3-amino-quinazolin-4(3H) ones (3)

The synthesized 4H-3,1-benzoxazin-4-one (2) (0.01 mol) was dissolved in pyridine (15 mL), and then 80% hydrazine hydrate (0.15 mol) was added. The reaction mixture was microwaved for 10 minutes at 180 watts. White product of 3-amino-quinazolin-4(3H)-one (3) was recryallized using ethanol(95%).[16]. A schematic illustration of the synthesis is shown in Figure 2.

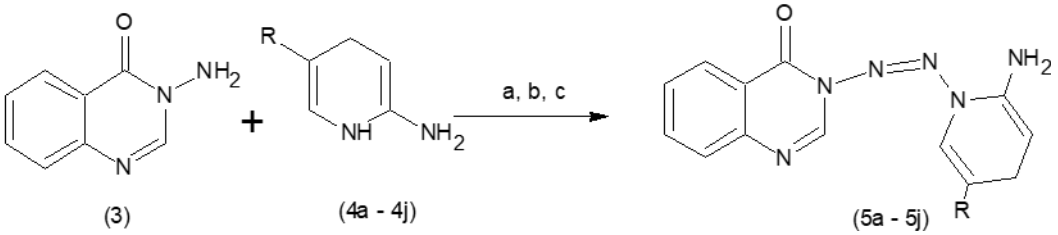


4H-3,1-benzoxazin-4-one 3-aminoquinazolin-4(3H)-one

Fig. 2: Synthesis of 3-amino-quinazolin-4(3H) ones (3), a. Pyridine, b. 80% Hydrazine Hydrate

Synthesis of 3[(2-aminopyridin-1(4H)-yl) diazenyl] quinazolin-4(3H)-one derivatives (5a-5j)

In acetic acid, the 3-amino-quinazolin-4(3H) ones (3) (1 mmol) is dissolved (6 ml). Side by side, concentrated sulphuric acid (2 mL) and sodium nitrite solution (76 mg, 1.1 mmol) (3 mL) were applied to the reaction mixture. At temperatures ranging from 0 to 5 ^{0}C, the mixture was stirred. A methanolic solution of 2-amino-1,4-dihydropyridine derivatives (1 mmol) was applied to this cold solution, and the mixture was stirred at 0 to 5^{o}C. The solution was kept aside overnight. The resulting precipitate was filtered and ethanol recrystallized. Figure 3 depicts a graphical representation of the synthesis. Table 1 shows the physiochemical characterization of synthesized molecules (5a–5j).



3-aminoquinazolin-4(3H)-one 2-amino-1,4-dihydro pyridine 3[(2-aminopyridin-1(4H)-yl) diazenyl]quinazolin-4(3H)-one derivatives

Fig. 3: Synthesis of 3[(2-aminopyridin-1(4H)-yl) diazenyl] quinazolin-4(3H)-one derivatives (5a – 5j) a. Acetic Acid, b. Sodium Nitrite c. Sulphuric acid

Pharmacological evaluation of atypical antipsychotic activity[(7)]

The synthesized compounds had been examined for atypical antipsychotic operation using

biological models like apomorphine-induced climbing behavior [17] and 5-hydroxytryptophan (5HTP)-induced head twitches model for D2 receptor inhibitory activity [18]. Acute toxicity (LD50) tests were carried out on male Wistar rats. The powerful dose (ED50) become determined the use of the Probit log scale method and the LD50 was computed using the Organization for Economic Co-operation and Development (OECD) guidelines TG 423 (up and down form) [19,20].

Experimental animals

For preliminary screening of all synthesized compounds, 20-25 g Albino Swiss male mice were used. The animals were held in normal conditions with a 12:12 light: dark period and 23° C (±3°C) and relative humidity of 30–70% was maintained. The animals were chosen at random and labelled to allow for individual identification. Five days prior to dosing, they were locked in the cage. There were six animals in each group [21].

Apomorphine-induced climbing behavior:

The synthesized compounds were tested on the apomorphine-induced climbing model to test the climbing behavior in mice[21]. Animals were split into six groups at random, each with six animals. Saline was administered to the control group (5ml/Kg) and the regular groups received test/saline (5 ml/kg). The standard group received olanzapine (1 mg/kg).

Climbing instances in which all four paws were hanging in the air were recorded. The scores of each animal were summed together. The results were expressed as a percentage of climbing obstruction as compared to apomorphine-treated control mice.

5HTP-induced head twitches

Monitoring of Head twitches was done using the 5HTP-induced head twitches technique[23]. 5mg/Kg of the compounds were administered using oral gavage. Mice were administered with test chemicals (5 mg/kg). Saline and olanzapine (1 mg/kg) was given to the control and normal groups, respectively. Mice's head twitches were counted at 5-min. intervals for 1 hour after 20 min. of 5HTP (100 mg/kg) treatment. The findings are summarized in Table 2.

Acute oral toxicity study (Up and Down method, OECD Guidelines 423):

The LD50 was calculated using the up-and-down approach [24]. The animals are dosed separately

and were followed for at least 48 hours in this test, which involves a single, sequential dose progression. The first animal is given a dosage one step lower than the goal level. This judgment is based on all of the animals' previous 48-hour survival trends. The experiment was finished with only four animals after an early turnaround in animal results. The findings are summarized in Table 2.

Effective dose (ED50) determination:

The ED_{50} of compounds was measured using the probit log scale method of statistical analysis [(25)]. 5HTP-induced head twitches activity was used to assess the ED50. Before being used, the rats were fasted, and each dose group consisted of ten rats. Animals were examined for 2 hours after receiving the drugs to see which group had the most activity. The calculation was done using the Miller and Tainter statistical analysis method. Probit values were plotted against log doses, with the ED50 value corresponding to probit 5. Table 2 includes the results.

Molecular Docking Studies:

On a Dell Vostro 1550 with an Intel™ Core CPU and Windows-10 64-bit operating system, the molecular docking technique was carried out[(26)]. Three-dimensional receptor structures can be obtained on the Protein Data Bank website (http://www.rscb.org). Ketanserin was chosen as the study's standard because it has been demonstrated to bind to 5-HT2A and D2 receptors. Out of a total of ten compounds, the 5b molecule was chosen as the ligand for the docking study. In animal experiments, 5b is the enzyme that has showed the highest activity.

Preparation of Receptor

The 3D crystalline structure of receptors with the PDB id 4oaj was chosen from the protein database. The receptor we chose must be able to bind to both 5-HT2A and D2 according to our methodology. The receptor 4oaj had all of the necessary properties. After the co-crystallizing the receptor with the ligand, it was successfully downloaded. The structure of the downloaded receptor was visualized using Discovery Studio Visualizer. After the co-crystallization ligand was extracted and the protein was stored in.pdb format.

Preparation of Ligand

Because it exhibited the strongest antipsychotic effect, 3-[(2-amino-5-chloropyridin-1(4H)-yl] quinazolin-4(3H)-one (5b) was chosen as the ligand. The ligand's 2D structure was drawn in ChemSketch and then converted to .pdb format using Open Babel. The Mol file of the ligand is converted to PDB format by the Open Babel application, which is required by the PyRx software.

Docking Studies

PyRx software, which executed on the Autodock Vina interface, was used to do the analysis [(27)]. The ligand was generated by identifying the torsion root, rectifying the torsion angles, applying needed charges, optimizing using UFF (Universal force field) with default value of 4. To carry out all of the aforementioned protocols, the PyRx software employed the OpenBabel interface. On a receptor that had been produced with ligand and ketanserin, a molecular docking study was performed. All of the ligands' chemical structures are shown in Figure 1.

Docking Validation

To validate the docking method, the ligand and standard molecule output files were extracted and visualized using Pymol software. We may view all of the best conformers identified by the vina program using the application. The interaction of both ligand and standard conformers with the target structure was examined, and the conformer with the strongest link was chosen. Figure 6 shows the binding relationship of the best-chosen conformer.

Results and discussion:

Results of synthetic studies

The physicochemical data are summarized in Table 1 and spectral analysis were summarized as follows. The spectral studies of 5b molecule is represented in Fig 4.

3-[(2-aminopyridin-1(4H)-yl) diazenyl] quinazolin-4(3H)-one (5a)

% yield: 45 %, M.P.: 180-181° FTIR: 3500 (O-H str), 3062 (Ar-C-H str), 1665 (C=O, str), 1601, 1566 and 1452 (Ar-C=C, str) MS (m/z): 267(M^+), and MW 267 g/mol.

3-[(2-amino-5-chloropyridin-1(4H)-yl)diazenyl]quinazolin-4(3H)-one (5b)

% yield: 58 %, M.P.: 172-174° FTIR: 3064.3 (Ar-C-H str), 1671 (C=O, str), 1692 (C=N),1452 (Ar-C=C, str), and 850 (C-X) MS (m/z): 303(M^+), and MW 303 g/mol.

3-[(2-amino-5-nitropyridin-1(4H)-yl)diazenyl]quinazolin-4(3H)-one (5c)

% yield: 57 %, M.P.: 170-172° FTIR: 3068 (Ar-C-H str), 1680 (C=O, str), 1666 (C=N), 1340-1345 (NO_2) and 1452 (Ar-C=C) MS (m/z): 312(M^+), and MW 312 g/mol.

3-[(2-amino-5-methoxypyridin-1(4H)-yl)diazenyl]quinazolin-4(3H)-one (5d)

% yield: 65 %, M.P.: 164-167° FTIR: 3068 (Ar-C-H str), 1683 (C=O, str), 1672 (C=N), 1319 (C-O), 1452 (Ar-C=C), MS (m/z): 297(M^+), and MW 297 g/mol.

3-[(2-amino-5-nitropyridin-1(4H)-yl)diazenyl]quinazolin-4(3H)-one (5e)

% yield: 68 %, M.P.: 162-164° FTIR: 3061 (Ar-C-H str), 1661 (C=O, str), 1698 (C=N), 977 (C-X) and 1457 (Ar-C=C, str), MS (m/z): 347(M^+), and MW 347 g/mol.

3-[(2-amino-5-nitropyridin-1(4H)-yl)diazenyl]quinazolin-4(3H)-one (5f)

% yield: 48 %, M.P.: 160-162° FTIR: 3052.5 (Ar-C-H str), 1645 (C=O, str), 1694 (C=N), 967 (C-X) and 1550 (Ar-C=C, str), 3114 (NH_2) MS (m/z): 285.5(M^+), and MW 285.5 g/mol.

3-[(2-amino-5-nitropyridin-1(4H)-yl)diazenyl]quinazolin-4(3H)-one (5g)

% yield: 49 %, M.P.: 157-159° FTIR: 3111.3 (Ar-C-H str), 1642 (C=O, str), 1692 (C=N), 1546 (NH_2) and 1462 (Ar-C=C, str), 3440 (NH_2) MS (m/z): 282 (M^+), and MW 282 g/mol.

3-[(2-amino-5-methoxypyridin-1(4H)-yl)diazenyl]quinazolin-4(3H)-one (5h)

% yield: 65 %, M.P.: 164-167° FTIR: 3065 (Ar-C-H str), 1695 (C=O, str), 1660 (C=N), 1319 (C-O), 1451 (Ar-C=C), MS (m/z): 283 (M^+), and MW 283 g/mol.

3-[(2-amino-5-methoxypyridin-1(4H)-yl)diazenyl]quinazolin-4(3H)-one (5i)

% yield: 45 %, M.P.: 169-171° FTIR: 3061 (Ar-C-H str), 1690 (C=O, str), 1661 (C=N), 1452 (Ar-C=C), 972 (C-X) MS (m/z): 348(M^+), and MW 348 g/mol.

3-[(2-amino-5-methoxypyridin-1(4H)-yl)diazenyl]quinazolin-4(3H)-one (5j)

% yield: 55 %, M.P.: 171-173° FTIR: 3059 (Ar-C-H str), 1695 (C=O, str), 1659 (C=N), 1319 (C-O), 1442 (Ar-C=C), 971 (C-X) MS (m/z): 393 (M^+), and MW 394 g/mol.

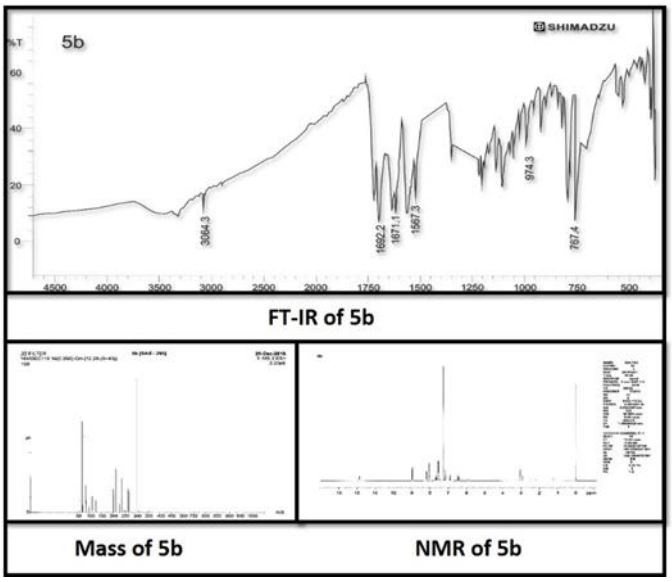
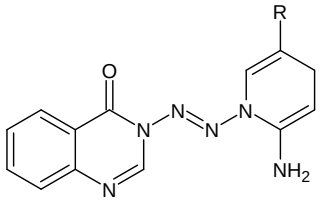


Fig 4: Spectral data of 3-[(2-amino-5-chloropyridin-1(4H)-yl) diazenyl] quinazolin-4(3H)-one (5b)

Table 1: Physicochemical data of (5a-5j)



Compound Code	**R Substitution**	**Molecular formula**	**Molecular Weight**	**Yield (%)**	**Melting Point (°C) ***	**Rf Value ****
5a	-H	$C_{13}H_{12}N_6O$	268	45	180-181	0.64
5b	-Cl	$C_{13}H_{11}ClN_6O$	303	58	172-174	0.55
5c	-NO_2	$C_{13}H_{11}N_7O_3$	313	57	170-172	0.51
5d	-OCH_3	$C_{14}H_{14}N_6O_2$	298	65	164-167	0.64
5e	-Br	$C_{13}H_{11}BrN_6O$	347	68	162-164	0.68
5f	-F	$C_{13}H_{11}FN_6O$	286	48	160-162	0.58
5g	-NH_2	$C_{13}H_{13}N_7O$	283	49	157-159	0.57

5h	-OH	$C_{13}H_{12}N_6O_2$	284	57	145-147	0.56
5i	$-SO_3H$	$C_{13}H_{12}N_6O_4S$	348	45	169-171	0.59
5j	-I	$C_{13}H_{11}IN_6O$	394	55	171-173	0.68

**Mobile phase for (5a-5j) was n-hexane: ethyl acetate (7:3)

Results of antipsychotic activity screening

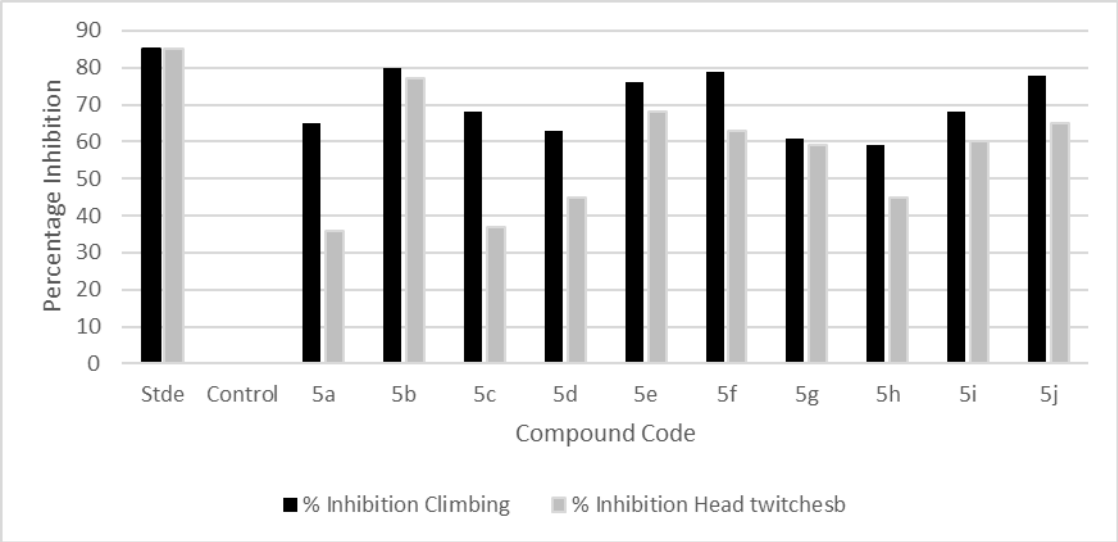
An apomorphine-induced climbing behavior paradigm and a 5HTP-induced head twitches model were used to investigate the antipsychotic efficacy of the synthesized compounds in mice. The findings are summarized in Table 2.

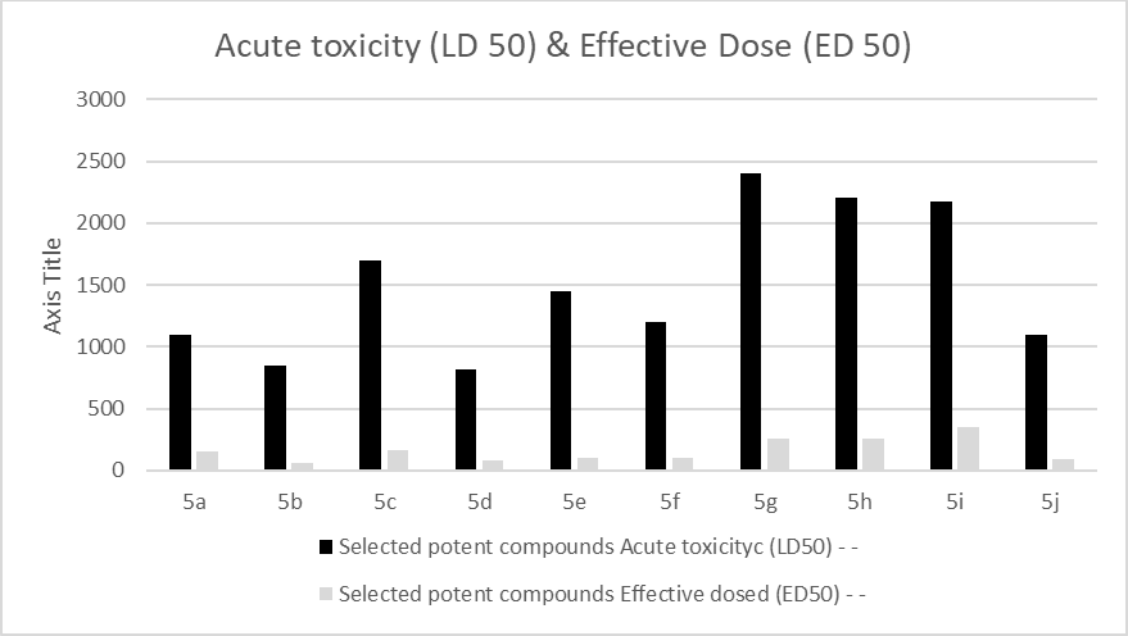
The table also includes the data for the acute toxicity analysis and successful dosage determination. The therapeutic index was calculated for each molecule that was synthesized. The data were statistically analyzed using ANOVA, and all of the outcomes were deemed significant. Molecules 5b, 5c, 5e, 5f, and 5j were shown to have greater activity levels. According to SAR findings, the presence of electron withdrawing groups boosted biological activity. The 5b molecule was discovered to have the most potent action, with a therapeutic index of 15.46, which was much higher than the average. The therapeutic indexes of 5e, 5f, and 5j were all higher than the average.

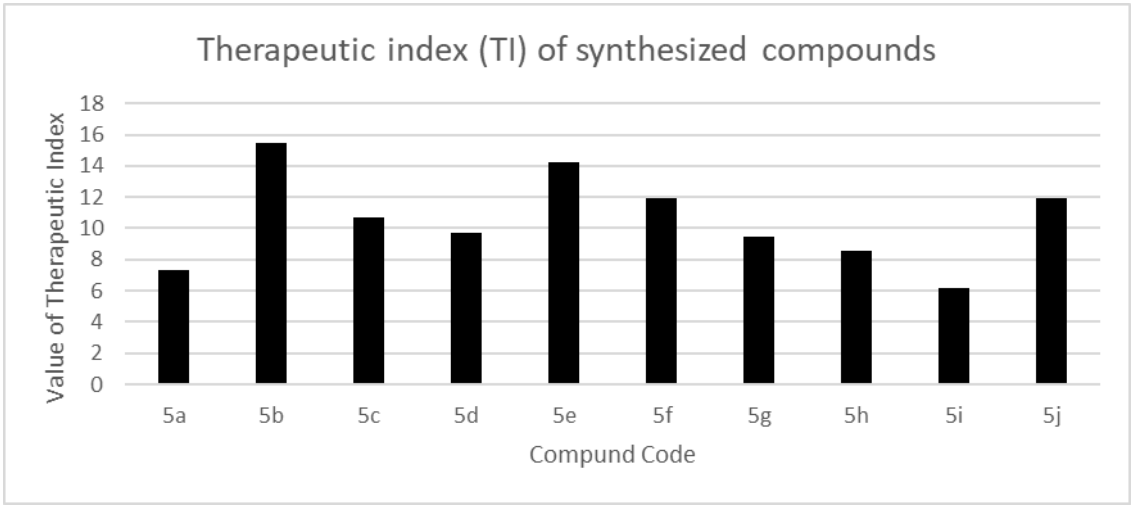
Table 2: Pharmacological evaluation of the synthesized compounds

Compounds	**% Inhibition Study**		**Dose Studies**		**Therapeutic Study**
	Climbing Study[a]	**Study of Head Twitches[b]**	**Dose Determination (LD50)**	**Calculation of Effective dose[d] (ED50)**	**Therapeutic index (TI)**
Std (Olanzapine)	87	87	-	-	12.54
Control	0	0	-	-	-
5a	65	36	1100	150	7.33
5b	80	77	847	54.8	15.46

5c	68	37	1700	158.9	10.69
5d	63	45	815	83.9	9.71
5e	76	68	1450	101.8	14.24
5f	79	63	1200	100.6	11.93
5g	61	59	2400	254	9.45
5h	59	45	2200	258	8.53
5i	68	60	2178	354	6.15
5j	78	65	1100	92	11.96







Results of Docking Studies

The results of docking testing are shown in Figure 5. The ligand attached to major amino acids at the active site is shown in Figure 4a. 4b, 4c, and 4d represent the ligand's docked conformation with the target at the active site. Docking validation verifies that the ligand is bound at the same pharmacophoric active location as normal boundaries, as illustrated in Figure 6. This backs up that the molecule was designed and produced with biological activity in mind. The binding affinity of the normal molecule was determined to be -7.4 Kcal/mol, whereas that of the ligand (5b) was found to be -9.5 Kcal/mol. The greater binding affinity might explain the powerful biological action. These findings back up the mechanism of the synthesized molecule.

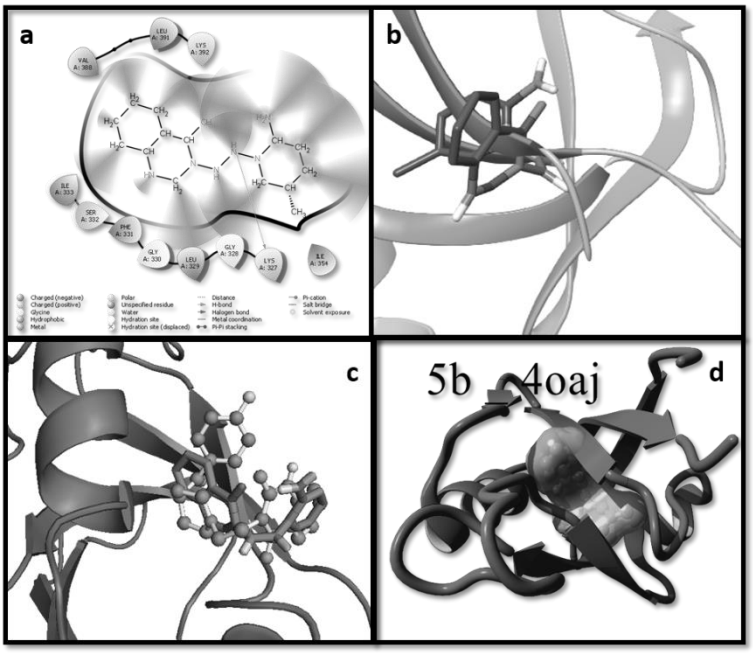


Fig 5: Binding interactions of 5b with target

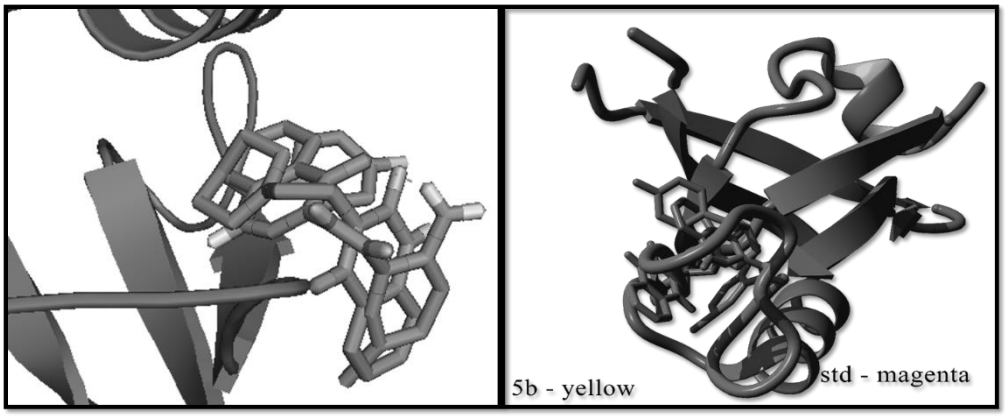


Fig 6: Results of docking validation

CONCLUSION:

The proposed series of compounds 5a-5j were synthesized effectively, and physicochemical characterization confirmed the structures of the synthesized compounds. The synthesized compounds were tested for antipsychotic action, and synthesized molecules 5b, 5c, 5e, 5f, and 5j exhibited the significant bioactivity, with 5b exhibiting the greatest activity. The chloro substituted 5b molecule was discovered to have the greatest therapeutic index (15.46). The molecular docking experiments of 5b were performed using the PDB code 4oaj as a reference. The binding affinity of the standard molecule was found to be -7.4 Kcal/mol, whereas the binding

affinity of ligand (5b) was determined to be -9.5 Kcal/mol with RMSD value zero. Docking validation tests aided us in validating the mechanism responsible for the therapeutic effect of the synthesized drugs. As a result, we believe the compound we synthesized is more effective than currently available atypical antipsychotics.

• Acknowledgements

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• Conflict of Interest (COI)

The authors declare no conflicts of interest.

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Graphical Abstract