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EUROLEPTICS TARGETING METABOTROPIC GLUTAMATE RECEPTOR (GRM5): MOLECULAR DOCKING STUDIES OF SUBSTITUTED QUINOLINES

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ABSTRACT

Schizophrenia, a complex neuropsychiatric disorder having significant health challenges like physical, psychological and social issues globally. To reduce those by the management of schizophrenia with novel quinoline derivatives, as it poses various pharmacological properties including potential antipsychotic activity. Quinolines ability to modulate pathways implicated in schizophrenia, such as glutamatergic neurotransmission, highlights their promise as antipsychotic agents. Furthermore, the structural versatility of quinoline scaffolds allows for rational drug design, facilitating the development of potent and selective compounds with improved efficacy and safety profiles. The present study explores the potential of quinoline compounds by performing molecular docking studies against the metabotropic glutamate receptor 5 (GRM5). Using molecular docking techniques, ligands were docked against the GRM5 receptor (PDB ID: 6N51) using iGEMDOCK, comparing their efficacy with standard antischizophrenia agents such as Dipraglutamate and Mavaglurant. The majority of the ligands displayed better binding affinities compared to standard drugs Clozapine (-95.3 K. Cal/mol) and Risperidone (-92.7 K. Cal/mol). Among all, top 2 ligands 3a8b1c (-105.8 K. Cal/mol) and 4a12b1c (-104.5 K. Cal/mol) were chosen for visualization and detailed analysis using Discovery studio. All the ten derivatives 1QN-10QN were orally bioavailable, high gastrointestinal absorption, high blood brain barrier penetration, moderate solubility and metabolised by CYP 2C9 enzyme in liver and intestine. Despite these promising attribute, further preclinical and clinical investigations are warranted to elucidate the full therapeutic potential of quinoline derivatives in the management of schizophrenia could offer an effective and safer alternative.

Keywords: GRM5 receptor, Schizophrenia, Quinoline derivatives, Molecular Docking, iGEMDOCK Software, Discovery Studio Visualizer.

INTRODUCTION

Schizophrenia is a severe mental disorder characterized by profound disruptions in thinking, affecting language, perception and the sense of self [1-2]. It can impair functioning through the loss of an acquired capability to earn a livelihood [3]. Several enzymes are involved in the pathophysiology of schizophrenia like dopamine related enzymes, glutamate related enzymes, serotonin related enzymes, neuroinflammatory enzymes [1-2]. Among those, the metabotropic glutamate receptor 5 (mGluR5) is a G-Protein coupled Receptor encoded by

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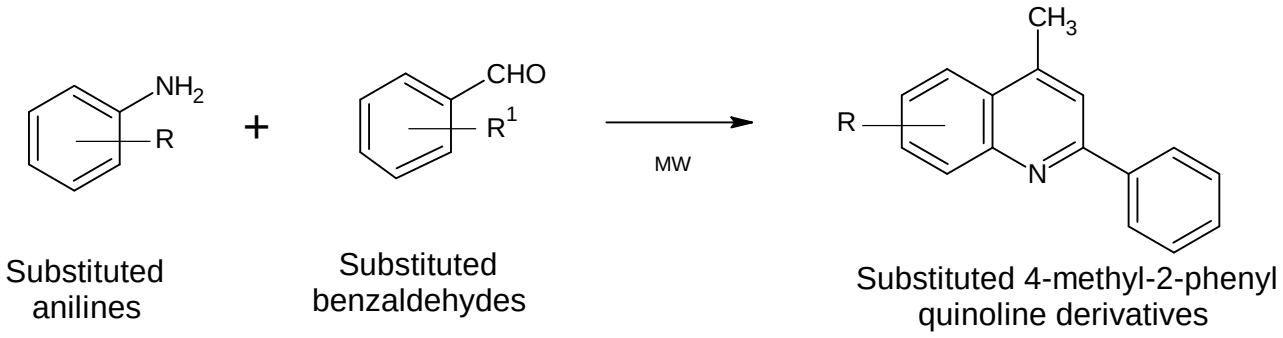
GRM5 gene, plays a key role in glutamatergic neurotransmission and cognition. And its dysregulation has been associated with this disorder particularly by reducing NMDA receptor functions leading to cognitive defects, psychotic symptoms and abnormal brain connectivity [4,5]. Commercially available neuroleptics are MPEP (2-methyl-6-(phenylethynyl)pyridine)[6], MTEP (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine) [6], fenobam [7], basimglurant [7], mavoglurant [7], dipraglurant [7] used as mGluR5 antagonist having various heterocyclic ring in its structure. The core chemical moiety of mavaglurant is indole ring whereas dipragurant is imidazopyridine ring [7]. As quinoline is a bioisostere of imidazopyridine and indole with little structural variance [8], this study focusses on substituted quinolines.

Quinoline is a nitrogen containing heterocyclic compound composed of a fused benzene and pyridine ring, has long been recognized for its diverse pharmacological properties and structural versatility, making it a key scaffold in drug development [9-10]. Quinoline derivatives have been explored for their wide range of biological activities, including, anti-cancer [11-12], neuroprotective [13-14], anti-inflammatory [15-16], anti-hypertensive [17-18], anticonvulsant [17], antioxidant [13,19], antiviral [20-21], antimalarial [22-23], anti-microbial [24] and antibacterial [25] effects. In recent years, attention has turned to the potential of quinoline-based compounds in targeting the GRM5 [26-27], which is implicated in neurological disorders such as schizophrenia. Modifying quinoline derivatives might be a promising mGluR5 antagonist activity for the development of new antipsychotic agents aimed at restoring glutamate balance in the brain, thus offering potential therapeutic benefits for patients with schizophrenia.

EXPERIMENTAL

Based on the outlined Scheme 1, a variety of substituted aromatic aldehydes, aromatic amines, and aromatic phenyl acetylene were selected to develop the substituted Quinolines [28].



Scheme 1: Design of substituted quinolines.

ADMET Prediction:

These compounds were subjected to *in silico* pharmacokinetic properties screening using Swiss ADME tool [29] to assess absorption, distribution, metabolism and excretion properties like gastro intestinal absorption, skin permeability, blood brain barrier penetration, plasma glycoprotein binding, CYP enzymes and Brain Or IntestinaL EstimateD permeation (BOILED-Egg) model. All the 10 ligands Simplified Molecular Input Line Entry System (SMILES) notations were generated using chemsketch, enter those smiles in Swiss ADME tool and run the programme. Then compounds with favourable ADME profiles were then evaluated for their potential targets using Swiss Target Prediction tool [30]. The majority of these

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compounds identified GRM5 receptor as a potential target. Further, docking studies were performed based on these results.

Docking Score Prediction:

The 2D structures of the ligands were initially designed using 'ChemSketch' and saved in '.mol' format. These structures were subsequently converted to '.pdb' format using Avogadro software [31]. Total 98 compounds were docked by standard docking using iGEMDOCK software [32-33] and top 10 ligands (1QN-10QN) were subjected to accurate docking further along with standard drugs such as Mavoglurant and Dipraglurant. The interactions and alignment of the ligands with the receptors active site were visualized using Discovery Studio Visualizer software. The protein structure (fig. 1) retrieved from the Protein Data Bank (PDB ID: 6n51) [34] having resolution $4A^0$, was used to assess the molecular interactions between the designed ligands and standard antagonists of the GRM5 receptor. An accurate docking approach was employed with the software calculating the scoring function by integrating electrostatic energy, hydrogen bonding and Van der Waals interactions. The docking simulations evaluated molecular interactions and binding affinities, and the top two compounds with the highest binding energy were selected for further visualization.

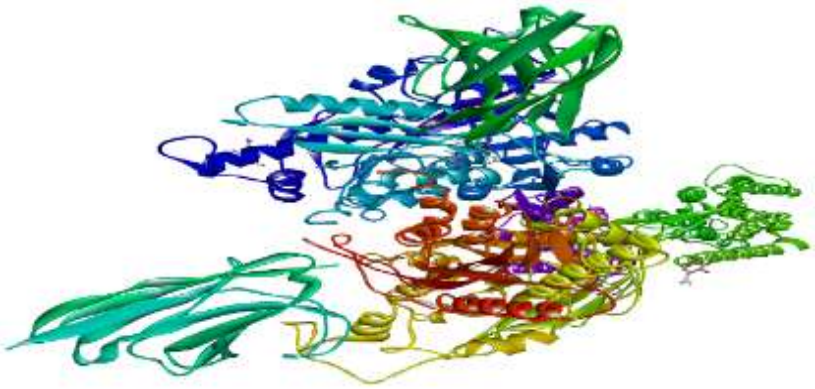

Fig. 1: Structure of cleaned protein (PDB ID: 6N51)

RESULTS AND DISCUSSION

Evaluation of Physicochemical characteristics:

All the derivatives 1QN-10QN, obeys lipinski's rule of five which implies that their molecular features is similar to that of oral medicine. All the quinoline derivatives are within the ranges of molecular weight, number of hydrogen bond acceptors (HBA), number of hydrogen bond donars (HBD) and lipophilicity about ≤ 500, ≤10, ≤5 and ≤5 respectively (Table 1). The partition of the 1QN-10QN derivatives into the aqueous compartment is presented with log Po/w values is about 3.18-4.39. Aqueous solubility indicated with log S with the range of -4.04 to -4.84 and all the derivatives are moderately soluble as its values are less than specific range -4 to 0.5 log mol/L [35]. The bioavailabilty (BA) scores of quinoline derivatives was 0.55-0.85 and molar refractivity (MR) values ranges from 74.17-86.35 cm^3/mol. It indicates that the high structural stability due to resonance, moderate bioavailability due to less aqueous solubility and high activity towards lipophilic receptors [36].

Table 1: Physicochemical properties of substituted Quinolines (1QN-10QN) by SwissADME

Code	Mol. Wt	Wlog P	HBA	HBD	TPSA	Log P	Log S	Solubility criteria	MR	BA

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1QN	253.73	4.86	1	0	12.89	4.39	-4.84	Moderate	77.16	0.55
2QN	261.32	4.41	2	0	29.96	3.8	-4.23	Moderate	82.34	0.55
3QN	263.29	3.91	3	1	50.19	3.38	-4.49	Moderate	79.1	0.85
4QN	235.28	3.92	2	1	33.12	3.48	-4.25	Moderate	74.17	0.55
5QN	235.28	3.92	2	1	33.12	3.41	-4.25	Moderate	74.17	0.55
6QN	261.32	4.41	2	0	29.96	3.83	-4.23	Moderate	82.34	0.55
7QN	249.31	4.22	2	0	22.12	3.82	-4.36	Moderate	78.64	0.55
8QN	262.35	4.28	1	0	16.13	3.83	-4.39	Moderate	86.35	0.55
9QN	219.28	4.21	1	0	12.89	3.86	-4.24	Moderate	72.15	0.55
10QN	234.3	3.8	1	1	38.91	3.29	-4.04	Moderate	76.55	0.55
DPG	265.28	3.35	3	0	30.19	3.18	-3.79	Soluble	74.98	0.55
MVG	327.42	2.81	3	1	49.77	3.2	-3.94	Soluble	97.68	0.55

Mol. Wt- Molecular weight, Wlog P- partition coeffiecient by Wildman and Crippen's method, HBA- number of hydrogen bond acceptors, HBD- number of hydrogen bond Donors, TPSA- topological polar surface area, Log P- consensus partition co-efficient (average log P value of approaches ILOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT), Log S- solubility, MR- molar refractivity, BA- bioavailability.

Pharmacokinetic characteristics:

Pharmacokinetics plays a crucial role in drug discovery and development by optimizing absorption, distribution, metabolism and excretion (ADME) properties to get the pharmacological outcome of drug candidate. All the derivatives demonstrated higher GI absorption, implies that 1QN-10QN suitable for intestinal absorption and high blood brain barrier penetration (BBB) suggests that they can cross BBB. Derivatives 1QN-10QN are not plasma glycoprotein (p-gp) substrates reveals that quinoline derivatives remains in the plasma and not expelled out by binding with p-gp protein (Table 2). All the derivatives having low skin permeability ranging from -4.41 to -5.25, indicating they are less active for transdermal route of administration. Quinoline derivatives 1QN-10QN acts as a CYP1A2 and CYP2C19 inhibitors, CYP2C9 substrates. 1QN, 2QN, 3QN, 6QN derivatives acts as a CYP3A4 and CYP2D6 substrates indicating undergoes liver and intestinal metabolism [37] (Table 2).

Table 2: Pharmacokinetic properties of substituted Quinolines (1QN-10QN) by SwissADME

Code	GIA	BBB	P gp	log Kp (cm/sec)	Cytochrome P enzymes inhibitors (CYP)				
					1A2	2C19	2C9	2D6	3A4
1QN	High	Yes	No	-4.41	Yes	Yes	No	No	No
2QN	High	Yes	No	-5.13	Yes	Yes	No	No	No
3QN	High	Yes	No	-5.25	Yes	Yes	No	No	No
4QN	High	Yes	No	-4.99	Yes	Yes	No	Yes	Yes
5QN	High	Yes	No	-4.99	Yes	Yes	No	Yes	Yes
6QN	High	Yes	No	-5.13	Yes	Yes	No	No	No
7QN	High	Yes	No	-4.85	Yes	Yes	No	Yes	Yes
8QN	High	Yes	No	-4.82	Yes	Yes	No	Yes	Yes
9QN	High	Yes	No	-4.61	Yes	Yes	No	Yes	No
10QN	High	Yes	Yes	-5.22	Yes	Yes	No	Yes	Yes
DPG	High	Yes	No	-5.45	Yes	Yes	Yes	Yes	No

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MVG	High	Yes	No	-6.01	No	No	Yes	Yes	No

GIA- gastro intestinal absorption, BBB- blood brain barrier, P gp- plasma glycoprotein, log Kp- skin permebility.

Drug-likeness:

A molecule is said to have drug-like properties by fulfilling the five approaches Lipinski (Rule of five), Muegge, Ghose, Veber and Egan Rule. All the derivatives, 1QN-10QN possess drug-like properties as it satisfies all those rules and synthetic possibility scores (Table 3). Brain Or IntestinaL EstimateD permeation (Boiled Egg) model used to predict the GI absorption and brain penetration of small molecules by taking Wlog P on y-axis and TPSA on x-axis respectively (fig. 2). All the ten ligands along with standard drugs correctly lies inside the boiled Eggs yolk. It indicates that they cross BBB [38].

Table 3: Drug-likeness rules violation and synthetic possibility scores of substituted Quinolines (1QN-10QN)

Code	Drug-likeness Rules violations					Lead likeness	Synthetic posibililty
	Lipinski	Ghosh	Veber	Egen	Muegge		
1QN	0	0	0	0	1	1	1.97
2QN	0	0	0	0	0	1	2.02
3QN	0	0	0	0	0	1	2.03
4QN	0	0	0	0	0	2	1.99
5QN	0	0	0	0	0	2	1.88
6QN	0	0	0	0	0	1	2.03
7QN	0	0	0	0	0	2	2.02
8QN	0	0	0	0	0	1	2.18
9QN	0	0	0	0	1	2	1.89
10QN	0	0	0	0	0	2	2
DPG	0	0	0	0	0	0	3.04
MVG	0	0	0	0	0	0	4.34

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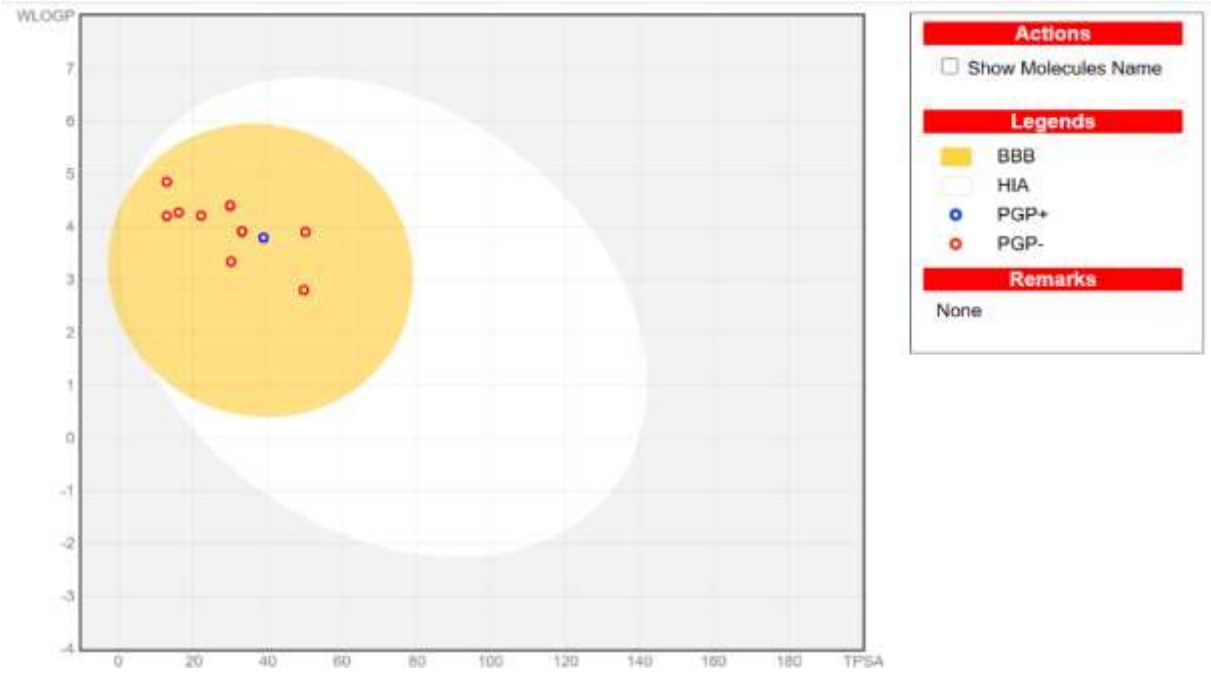

Fig. 2: Boiled egg model of quinoline derivatives (1QN-10QN);
Blue coloured dot- PGP substrate (10QN), Red Dot-PGP inhibitors, area under white eclipsed portion- human intestinal absorption, area under yellow circle- Blood Brain Barrier permeation.

Docking:

All the 10 ligands showed good docking score relative to the standard drugs of GRM5 receptor including Dipraglurant and Mavoglurant. The top two compounds with the highest binding energies 10QN (-66. 2171K.Cal/mol) and 2QN (-63.9603 K.Cal/mol) were selected for further visualization. The top 10 compounds displayed highest binding affinity with least energy compared to the standard GRM5 receptor. The top two ligands 10QN and 2QN (fig. 3) showed binding energies of -66.2171 K.Cal/mol and -63.9603 K.Cal/mol respectively, both surpassing that of the standard drug Dipraglurant (-65.8736 K.Cal/mol, Table 4). In 3D interactions, multiple conventional hydrogen bonds were observed while 2D interactions provided a clearer understanding of the interacting amino acid residues (Table 5). Notably, compound 10QN formed two conventional hydrogen bonds with the GRM5 receptor, whereas 2QN did not form any such bonds. Both Dipraglurant and Mavoglurant formed one conventional hydrogen bond each with the receptor. Two amino acid residues, ARG:208 and TYR:209 were shared between Dipraglurant and 10QN, while ARG:208, TYR:209, ARG:508, TRP:211 and ASP:496 were common between Dipraglurant and 2QN (Table 4). Additionally, TRP:211 and ARG:508 were common between Mavoglurant and 2QN. By combining the molecular properties and binding energy results, substituted quinoline derivatives are allosteric modulators of mGluR receptor, as its transmembrane domain has hydrophobic site [39].

10QN **2QN**

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Fig. 3: Chemical structures of the ligands 10QN and 2QN

Table 4: The interacting amino acid residues and the binding energies of ten ligands GRM5 receptor complex.

Ligand code	Binding Energy (K. Cal/mol)	Interacting active site amino acid residues
MAVAGLURANT (3QN)	-67.9689	PRO:514, ARG:508, TRP:211
10QN	-66.2171	ARG:208, TYR:209, ASN:210
DIPRAGLURANT (8QN)	-65.8736	ARG:208, TYR:209, ARG:508, TRP:211, ASP:496
2QN	-63.9603	ARG:208, TYR:209, ASN:210, ASP:496, TRP:211, ARG:508
3QN	-63.7031	ARG:208, TRP:211, ASN:210, ARG:508, ASP:496, TYR:209
5QN	-63.0735	ASP:496, TYR:209, TRP:211, ARG:208, ASN:210, ARG:508
8QN	-63.0711	ARG:208, TRP:211, ASN:210, ARG:508, TYR:209, ASP:496
4QN	-62.5558	ARG:508, ASN:210, TYR:209, ARG:208 ASP:496
6QN	-61.9538	ASP:496, TYR:209, TRP:211, ARG:508, ASN:210, ARG:208
7QN	-61.9483	ASP:496, TYR:209, TRP:211, ARG:508, ASN:210, ARG:208
1QN	-59.0052	:208, ARG:508, ASN:210 ARG, TRP :211, ASP:496, TYR:209
9QN	-56.76	ARG:208, TRP:211, ASN:210, ARG:508, TYR:209, ASP:496
2-ACETAMIDO-2-DEOXY-BETA-D-GLUCOPYRANOSE	-52.9418	LYS:207, ASN:210, TRP:211, ARG:208, THR:212

Table 5: 2D and 3D image visualization of the top Two Ligands 10QN, 2QN and standard antagonists of mGluR- Dipraglurant, Mavoglurant

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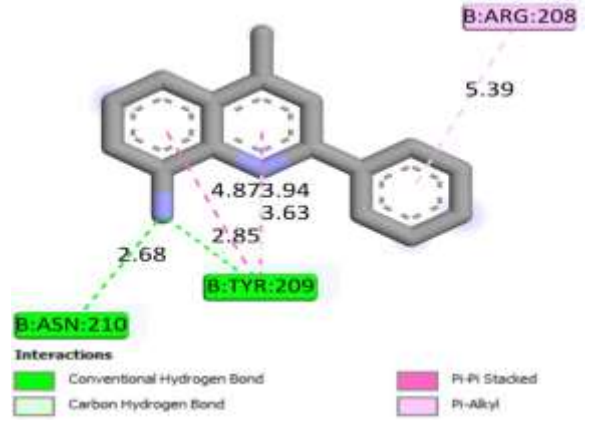
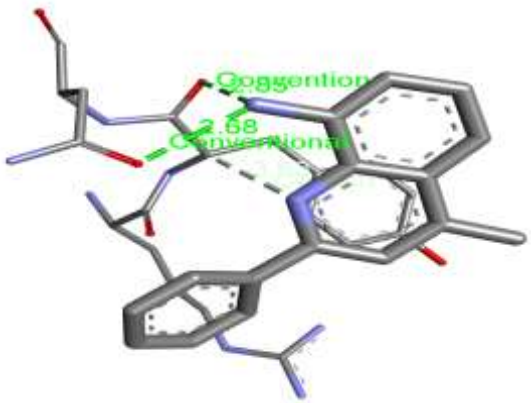
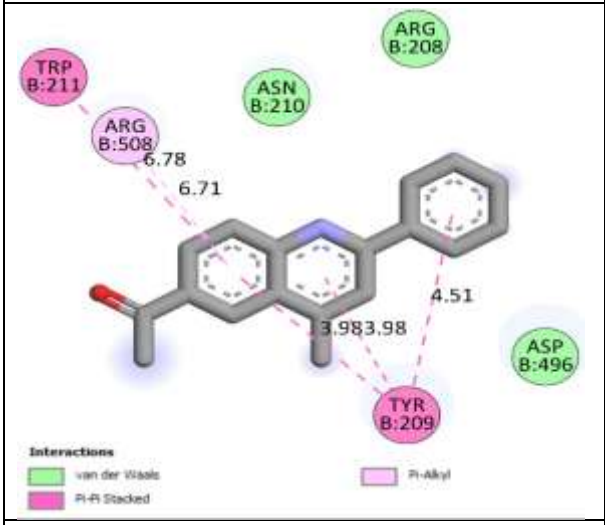
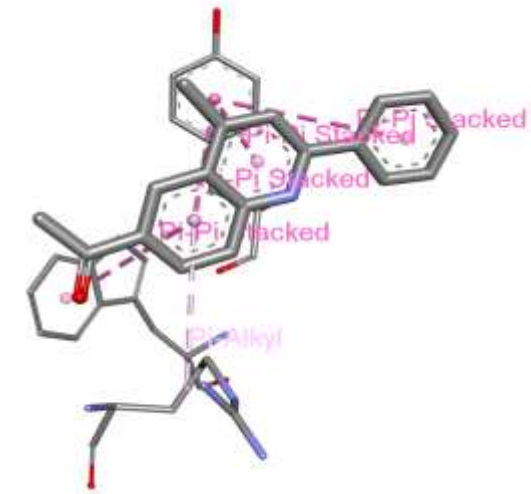
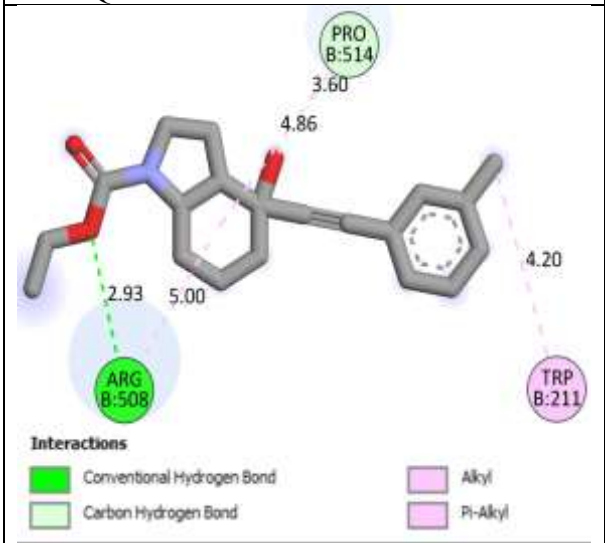
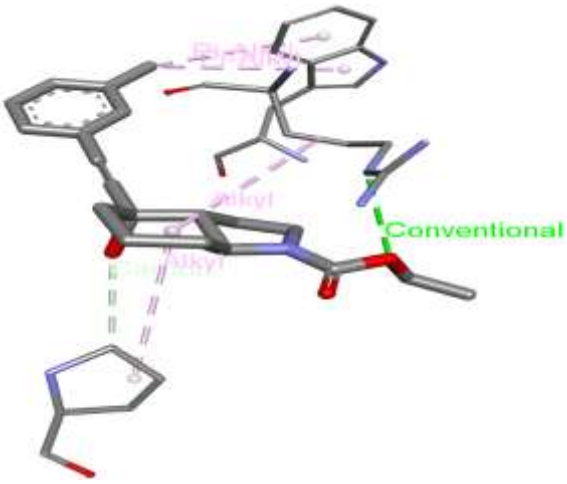
	
10QN LIGAND 2D INTERACTION	10QN LIGAND 3D INTERACTION
	
2QN LIGAND 2D INTERACTION	2QN LIGAND 3D INTERACTION
	
MAVAGLURANT LIGAND 2D INTERACTION	MAVAGLURANT LIGAND 3D INTERACTION

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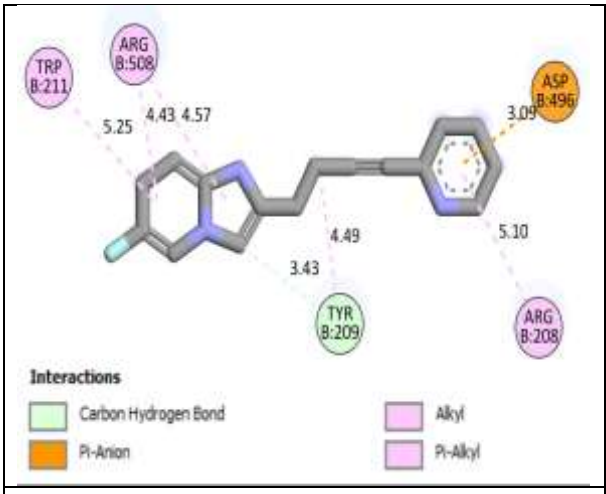
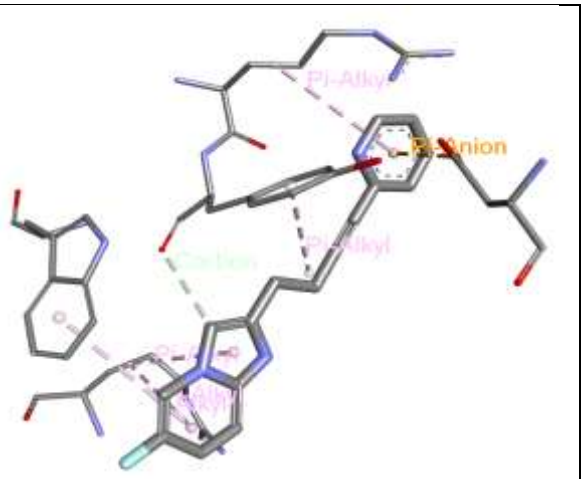
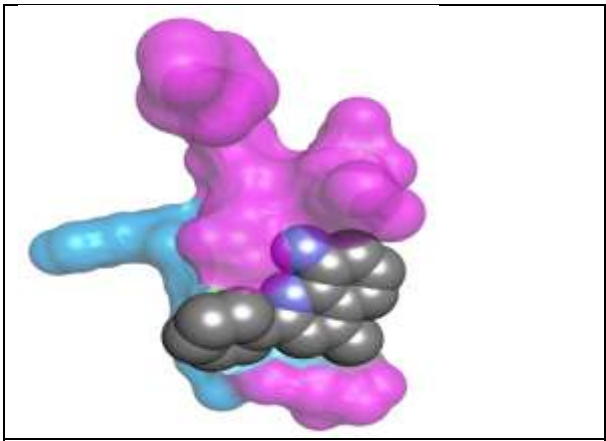
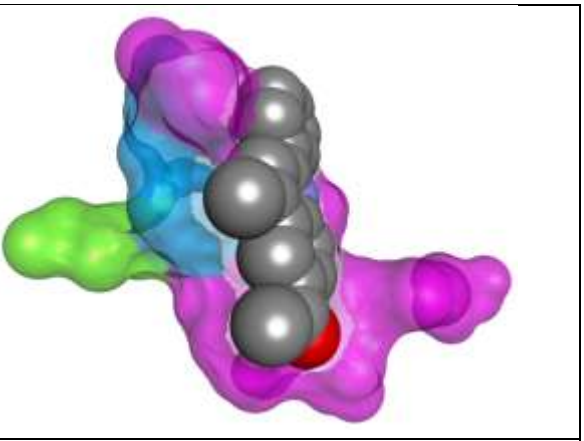
	
DIPRAGLURANT LIGAND 2D INTERACTION	DIPRAGLURANT LIGAND 3D INTERACTION

Binding pocket analysis:

The pocket analysis of the top compounds 10QN, 2QN, and the standard ligands Dipraglurant and Mavoglurant reveals that all bind to the center of the binding pocket Table 5. The higher binding energy of 2QN may be attributed to the electron-withdrawing group, such as CH_3CO, on the quinoline ring. In contrast, the higher binding energy of 10QN could be due to the presence of electron-donating groups, including NH2 and CH3, on its quinoline ring. These functional groups, along with the shared amino acid residues between these ligands and the GRM5 receptor, likely contribute to the stronger binding affinity of 10QN and 2QN compared to the standard inhibitors Dipraglurant and Mavoglurant.

Table 6: Surface pocket analysis of top 2 compounds 10QN, 2QN and standard GRM5 antagonists Dipraglurant, Mavoglurant.

	
10QN	**2QN**

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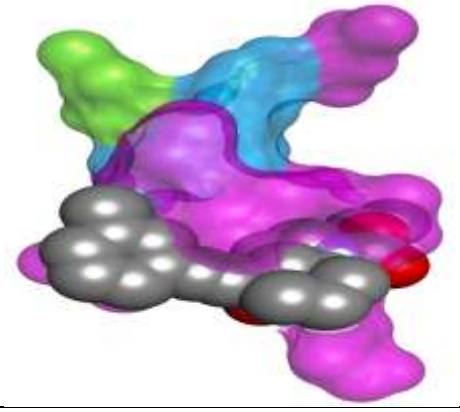	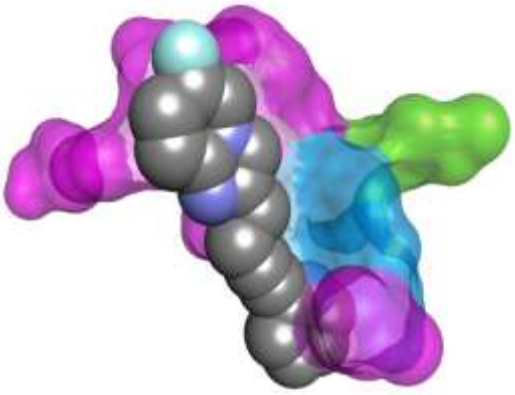
MAVAGLURANT	**DIPRAGLURANT**

CONCLUSION

In the current study, 98 substituted 4-methyl-2-phenyl quinoline derivatives were designed from substituted anilines and substituted benzaldehydes. Top 10 ligands were screened by standard docking methodology using iGemdock. Top 10 ligands (1QN-10QN) were further screened by accurate docking methodology against the same mGluR receptor. These derivatives evaluated for its pharmacokinetic, physicochemical properties and drug-likeness by using online computational tool SwissADME. Among ten derivatives, the top 2 ligands with 8-amino (10QN) and 6-acetyl (2QN) substitution exhibited superior ADME, physicochemical properties and show better binding affinities than standard mGluR receptor antagonists due to the hydrophobic interactions. Along with 2QN and 10QN shared amino acid residue interactions similar to standard GRM5 inhibitors, and ligands exactly fitted at the binding pockets of enzyme. Due to its high lipophilic nature, they can either noncompetitively or allosterically inhibit the mGluR enzyme responses. These results represent strong potential of 10QN and 2QN as neuroleptics and possibility to go for further synthesis, could be utilized for *in vitro* and *in vivo* research.

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CONFLICTS OF INTEREST

No authors declare conflicts of interest.

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