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Molecular Docking and ADME-Based Prioritization of 20 Quinazolinone Scaffolds for Anticonvulsant Potential

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ABSTRACT
Quinazolinone derivatives have attracted significant attention for their broad pharmacological potential, particularly in the treatment of central nervous system (CNS) disorders such as epilepsy. In the present study, a series of twenty novel quinazolinone derivatives were designed and evaluated for their potential anticonvulsant activity through molecular docking studies. The compounds were docked into the active site of the GABAAreceptor, a well-established target for antiepileptic drugs, using its crystallographic structure (PDB ID: 4COF). Molecular docking was carried out using AutoDockVina, and binding affinities were compared to standard antiepileptic agents. Several compounds demonstrated high binding affinity toward the receptor, with key hydrogen bonding and hydrophobic interactions involving critical amino acid residues such as TYR157, THR202, and PHE77. The top-performing derivative exhibited a binding energy of –9.3 kcal/mol, suggesting strong interaction and potential modulation of GABAergic signaling. These results support the potential of quinazolinone scaffolds as promising leads for the development of new anticonvulsant agents, and warrant further in vitro and in vivo validation.

I. INTRODUCTION

Eplipsy is a chronic neurological disorder characterized by a predisposition to generate unprovoked, recurrent seizures. These seizures arise from sudden bursts of abnormal electrical activity within clusters of neurons in the brain. Globally, an estimated 50 million individuals are affected by epilepsy, making it one of the most prevalent neurological conditions worldwide. Although epilepsy can be diagnosed at any age, it is most commonly observed in children and the elderly[1].Seizure manifestations in epilepsy vary widely, ranging from momentary lapses in awareness or mild muscle jerks to severe convulsions accompanied by a loss of consciousness. The clinical symptoms depend largely on the region of the brain involved during the seizure episode[2].The etiology of epilepsy is diverse. It can stem from genetic abnormalities, structural damage to the brain, infections of the central nervous system, metabolic imbalances, autoimmune disorders, or, in some cases, unknown origins. For example, brain trauma or cerebrovascular accidents may result in structural epilepsy, while inherited mutations in ion channel genes are often associated with genetic forms[3].Diagnosis typically involves a comprehensive clinical evaluation, including a detailed medical history, seizure description, and diagnostic tools such as electroencephalography (EEG) and neuroimaging techniques like MRI or CT scans[4].The International League Against Epilepsy (ILAE) provides a classification system based on seizure onset (focal, generalized, or unknown) and etiology[5].

Beyond its physical implications, epilepsy significantly affects patients' mental and social well-being. Individuals may experience stigma, anxiety, reduced quality of life, and limitations in education or employment[6].Nevertheless, with appropriate pharmacological intervention, lifestyle modifications, and in selected cases, surgical or neuromodulatory procedures, many patients achieve satisfactory seizure control and lead productive lives[7,8].Advancements in fields such as neuroimaging, genetic testing, and precision medicine have substantially improved the diagnostic accuracy and management of epilepsy, paving the way for more effective and individualized treatment strategies[8,9].

1.1 Quinazolinones as Anticonvulsant

Quinazolinones represent an important class of nitrogen-containing heterocycles widely recognized for their diverse biological activities, including anticancer, anti-inflammatory, antimicrobial, and notably, anticonvulsant

International Journal of Pharmaceutical Research and Applications
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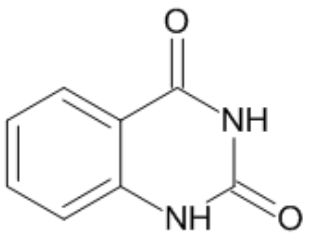
properties[10].Structurally, quinazolinones are bicyclic compounds composed of a benzene ring fused to a pyrimidine ring, with variations at key positions enabling structural modification and pharmacological optimization[11].

The anticonvulsant potential of quinazolinone derivatives has been supported by both in vivo and in silico studies. These compounds often act by modulating neurotransmitter systems involved in seizure activity, such as GABAergic and glutamatergicpathways[12,13]. Several quinazolinone analogues have shown efficacy in standard experimental seizure models like maximal electroshock seizure (MES)and pentylenetetrazole (PTZ)-induced seizures in mice, indicating their utility in suppressing both generalized and partial seizures.Substitution patterns on the quinazolinone scaffold significantly influence anticonvulsant efficacy[14]. Electron-withdrawing groups (e.g., –Cl, $-NO_2$, –F) at certain positions enhance CNS activity, while bulky substitutions may affect blood-brain barrier permeability[15].The presence of aryl or alkyl moieties at position 2 or 3 of the quinazolinone ring often improves binding affinity for CNS receptors, including GABAA, a major inhibitory neurotransmitter receptor targeted by many existing antiepileptic drugs[16,17]. Recent molecular docking studies have provided further insights into the interaction of quinazolinone derivatives with the GABAA receptor, using the crystal structure (PDB ID: 4COF). These studies demonstrate that selected derivatives exhibit strong binding affinities and engage key residues (e.g., TYR157, THR202, PHE77), suggesting their potential to modulate GABAergic signaling effectively.Overall, quinazolinone derivatives offer a promising scaffold for the development of novel anticonvulsant agents[18,19,20]. Their structural versatility, coupled with evidence of favorable interactions at CNS targets, supports ongoing research into their mechanism of action, optimization, and clinical potential for epilepsy treatment[21].



1.2 Computational Studies for design Compound

In recent years, computational approaches have become invaluable in drug discovery, enabling the prediction of drug-receptor interactions prior to experimental validation[22]. For the development of quinazolinone-based anticonvulsant agents, molecular docking and related in silico techniques provide significant insights into their binding affinity, interaction patterns, and structure-activity relationships with central nervous system targets such as the GABAAreceptor[23].

Target Selection and Docking Protocol

The GABAAreceptor, a ligand-gated chloride channel responsible for mediating inhibitory neurotransmission in the brain, is a well-established target for antiepileptic drugs. In this study, the crystal structure of the GABAAreceptor was retrieved from the Protein Data Bank (PDB ID: 4COF). This structure was chosen due to its relevance in benzodiazepine binding and its detailed resolution, making it suitable for docking studies[18,24].

Twenty quinazolinone derivatives were designed and subjected to molecular docking using AutoDockVina. Ligands were energy-minimized and converted into compatible file formats using Open Babe[25]. The receptor was prepared by removing water molecules and adding polar hydrogens, while grid box parameters were adjusted to cover the known active site pocket.

In addition to docking, the pharmacokinetic profile of the top-performing derivatives was evaluated using SwissADMEand pkCSMtools[26]. Most compounds complied with Lipinski's Rule of Five and exhibited high CNS permeability, low predicted toxicity, and good oral bioavailability, making them suitable candidates for further development[27].

1.3 Design of Molecules

In this study, a set of 20 structurally diverse quinazolinone derivatives was designed and subjected to molecular docking analysis against the GABAA receptor (PDB ID: 4COF) to investigate their potential as anticonvulsant agents

International Journal of Pharmaceutical Research and Applications
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3-anilino-2-(4-hydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one	3-anilino-2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one
3-anilino-2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one	3-anilino-2-phenyl-2,3-dihydroquinazolin-4(1H)-one
N-phenyl-1',4'-dihydro-3'H-spiro[cyclohexane-1,2'-quinazolin]-3'-amine	3-anilino-2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2046-2063 www.ijprajournal.com ISSN: 2456-4494

3-anilino-2-(3-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one	10-anilino-9-oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-b]quinazolin-10-ium
3-anilino-2-(2,4-dichlorophenyl)-2,3-dihydroquinazolin-4(1H)-one	3-anilino-2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one
3- anilino-2-(3-methylphenyl)-2,3-dihydroquinazolin-4(1H)-one	3-anilino-2-(2,6-dichlorophenyl)-2,3-dihydroquinazolin-4(1H)-one

International Journal of Pharmaceutical Research and Applications
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2-(3-aminophenyl)-3-anilino-2,3-dihydroquinazolin-4(1H)-one	3-anilino-2-(5-hydroxy-2-methylphenyl)-2,3-dihydroquinazolin-4(1H)-one
3-anilino-2-(3,5-dimethoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one	3-anilino-2-(2-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one
3-anilino-2-(4-bromo-3,5-dihydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one	3-anilino-2-(3-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2046-2063 www.ijprajournal.com ISSN: 2456-4494

3-anilino-2-(3,4-dihydroxy-5-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one	3-anilino-2-[3-(trifluoromethyl)phenyl]-2,3-dihydroquinazolin-4(1H)-one

Table 1: Designed Compounds

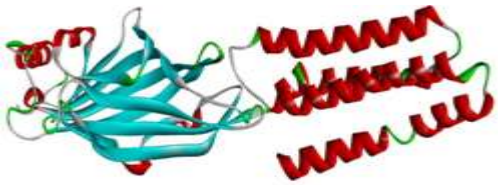
II. MATERIAL AND METHOD

Step 1: Ligand Preparation

A total of 20 quinazolinone derivatives were initially constructed using ChemSketch software. Each molecular structure was refined using the "Clean Structure" function and saved in .mol file format. These files were then imported into Avogadro, where energy minimization and geometry optimization were performed. The optimized ligands were subsequently exported in .pdb format for molecular docking studies[28].

Step2:ReceptorPreparation

Three-dimensional structures of the Human gamma-aminobutyric acid type A receptor (GABAA) were retrieved in .pdb format from the RCSB Protein Data Bank, specifically using the crystal structures with PDB ID**4COF**. Protein structures were prepared using PyRx and UCSF Chimera (version 1.14), where all water molecules were removed, polar hydrogen atoms were added, and partial charges were assigned to stabilize the receptor configuration. Energy minimization was applied to optimize the structural conformation for docking simulations[29]



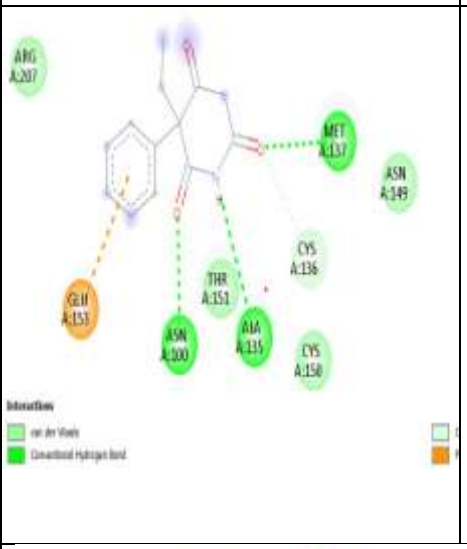
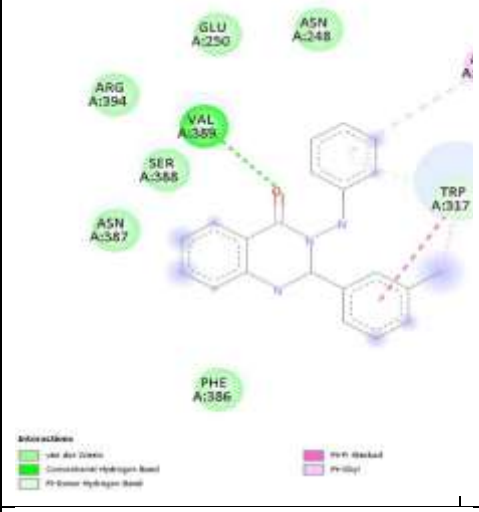
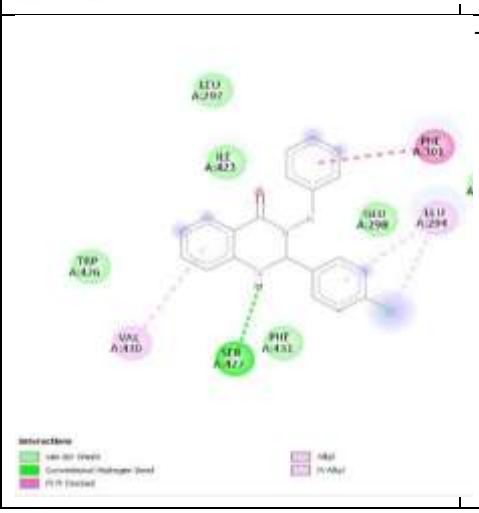
Step 3: Receptor–Ligand Docking Simulation

Molecular docking studies were conducted using PyRxandUCSF Chimera 1.14 to predict the optimal binding orientation of the ligands within the receptor's active site. Multiple ligand conformations were generated by allowing rotational and positional flexibility[30]. The docking grid was precisely centered over the active site of the receptor to ensure accurate interaction modeling. The dimensions of the grid box were optimized to cover the entire ligand-binding pocket, ensuring comprehensive interaction analysis[31].

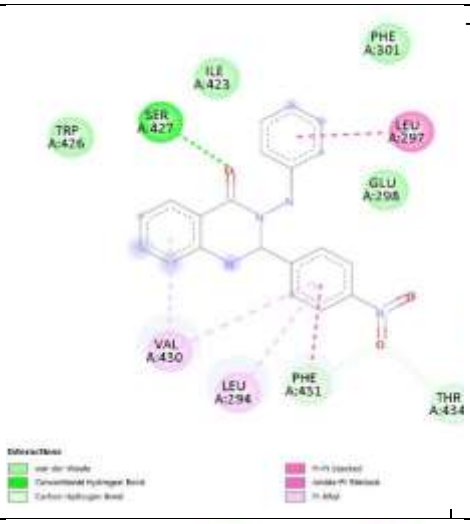
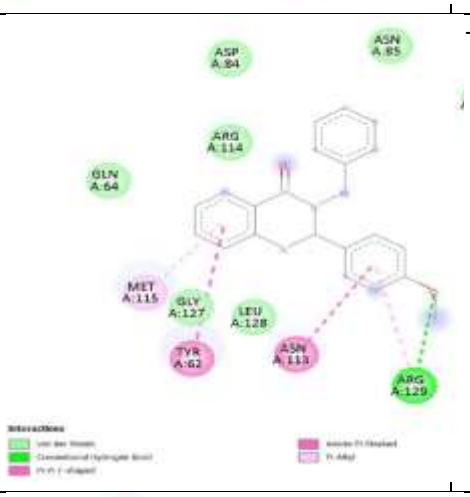
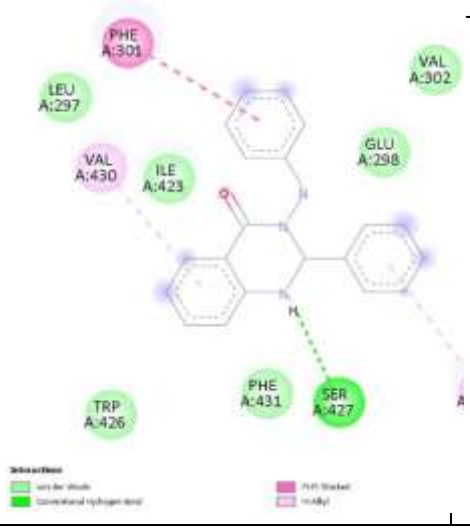
Step 4: Interaction Visualization

Post-docking visualization of receptor–ligand complexes was performed using Discovery Studio Visualizer[32].Both2D interaction maps and3D molecular renderingswere generated to illustrate key binding features, such as hydrogen bonds, hydrophobic contacts, and π-π interactions between the ligands and critical amino acid residues within the receptor binding site[33].

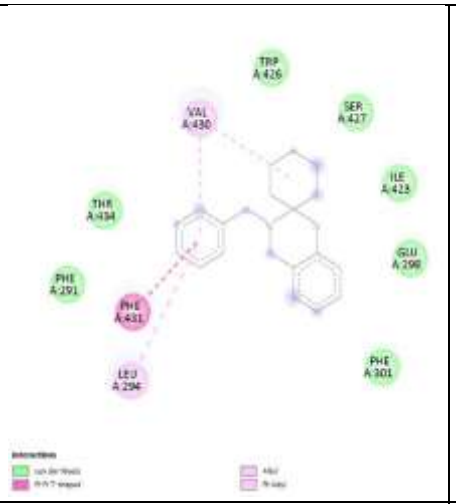
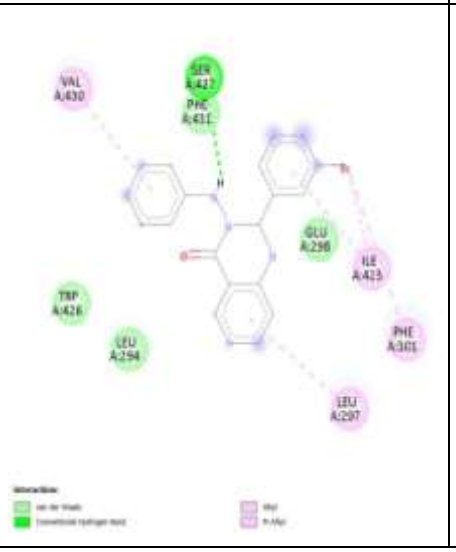
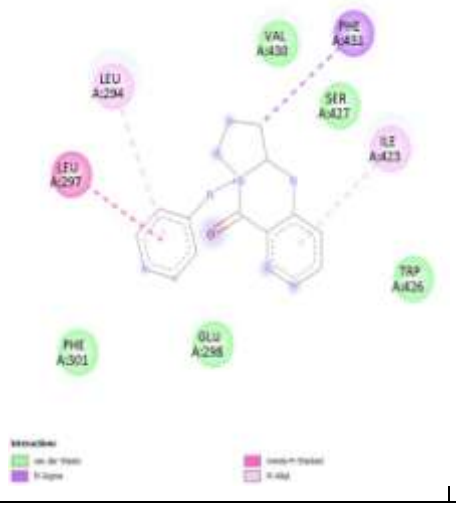
International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2046-2063 www.ijprajournal.com ISSN: 2456-4494

Sr.no	Structure	IUPAC Name	2D Structure	Binding Score
Std		5-ethyl-5-phenyl-1,3-diazinane-2,4,6-trione		6.1
D-1		3-anilino-2-(4-hydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one		-7.2
D-2		3-anilino-2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one		-7.8

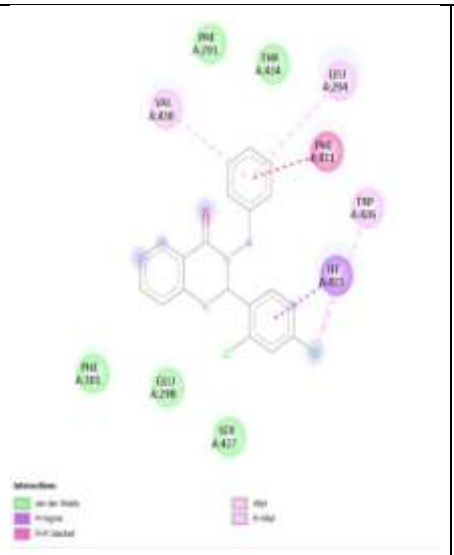
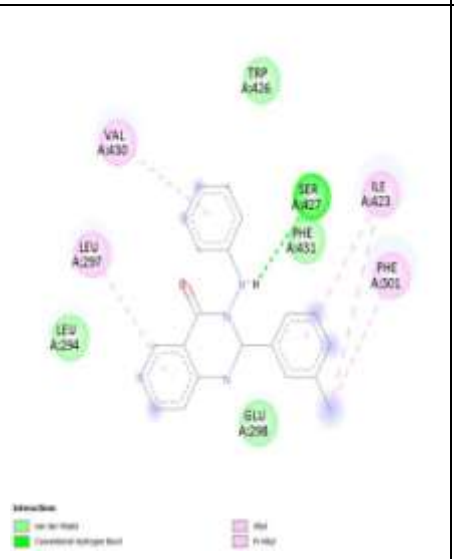
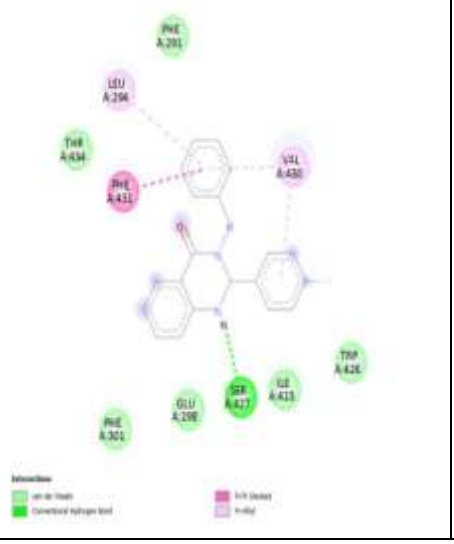
International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2046-2063 www.ijprajournal.com ISSN: 2456-4494

D-3		3-anilino-2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one		-6.7
D-4		3-anilino-2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-7.4
D-5		3-anilino-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one		-7.2

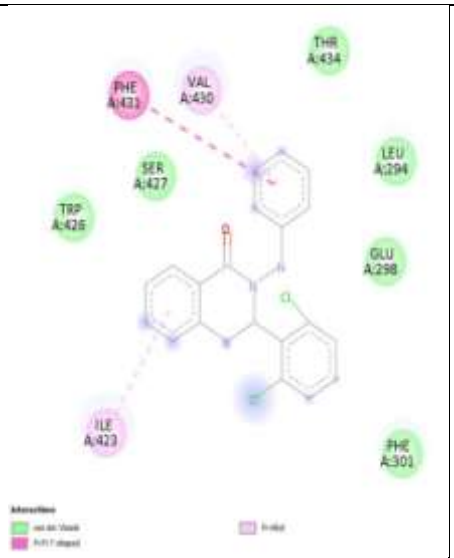
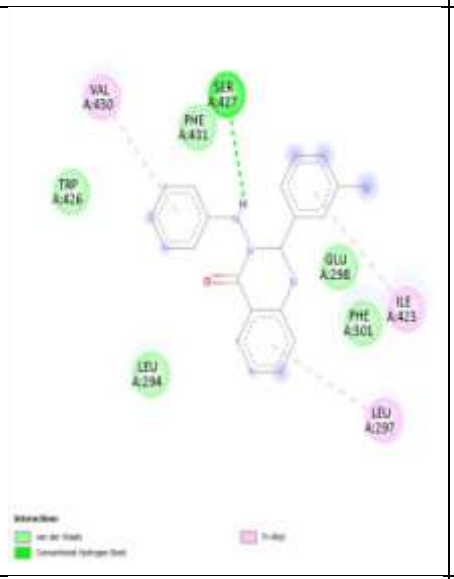
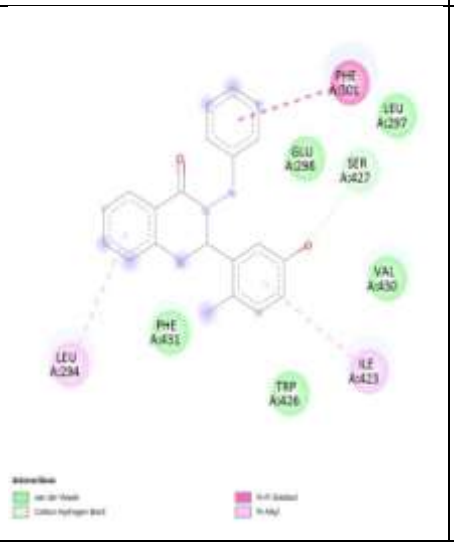
International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2046-2063 www.ijprajournal.com ISSN: 2456-4494

D-6		N-phenyl-1',4'-dihydro-3'H-spiro[cyclohexane-1,2'-quinazolin]-3'-amine		-7.3
D-7		3-anilino-2-(3-bromophenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-7.4
D-8		10-anilino-9-oxo-1,2,3,3a,4,9-hexahydropyrrolo[2,1-*b*]quinazolin-10-ium		-7

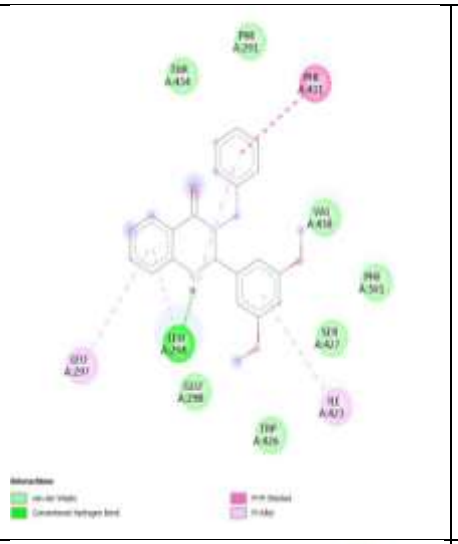
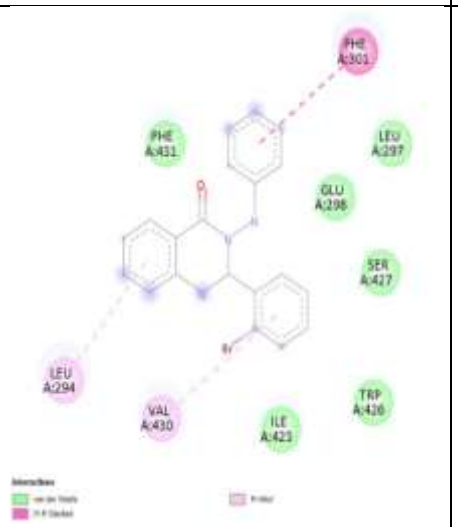
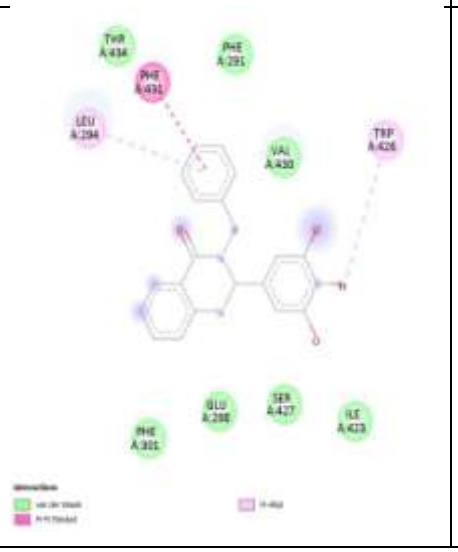
International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2046-2063 www.ijprajournal.com ISSN: 2456-4494

D-9		3-anilino-2-(2,4-dichlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-8
D-10		3-anilino-2-(3-methylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-7.6
D-11		3-anilino-2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-7.6

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2046-2063 www.ijprajournal.com ISSN: 2456-4494

D-12		3-anilino-2-(2,6-dichlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-7.1
D-13		2-(3-aminophenyl)-3-anilino-2,3-dihydroquinazolin-4(1*H*)-one		-7.1
D-14		3-anilino-2-(5-hydroxy-2-methylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-7.9

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2046-2063 www.ijprajournal.com ISSN: 2456-4494

D-15		3-anilino-2-(3,5-dimethoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-7.5
D-16		3-anilino-2-(2-bromophenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-7.9
D-17		3-anilino-2-(4-bromo-3,5-dihydroxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-7.2

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 2046-2063 www.ijprajournal.com ISSN: 2456-4494

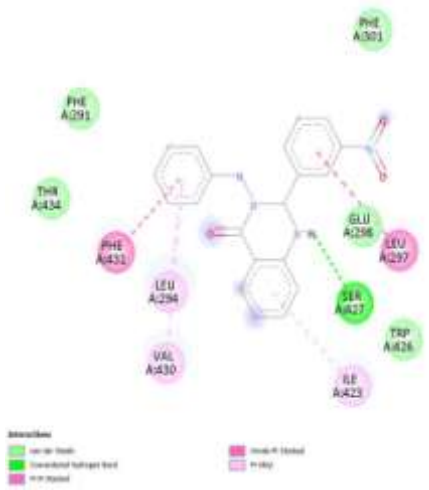
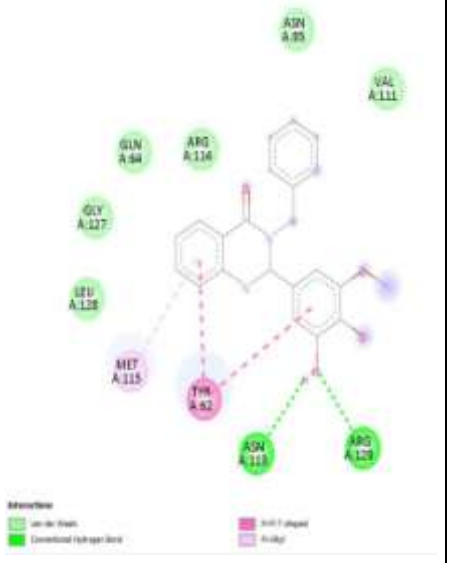
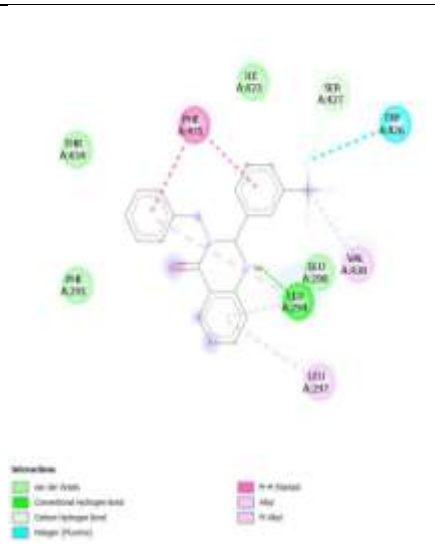
D-18		3-anilino-2-(3-nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-8.6
D-19		3-anilino-2-(3,4-dihydroxy-5-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one		-7.3
D-20		3-anilino-2-[3-(trifluoromethyl)phenyl]-2,3-dihydroquinazolin-4(1*H*)-one		-8.3

Table 2: Docking results of all Compounds

International Journal of Pharmaceutical Research and Applications
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2.2 Docking results

The binding affinities of the quinazolinone derivatives ranged from –6.5 to –9.3 kcal/mol, with several compounds exhibiting superior interactions compared to standard antiepileptic drugs. Notably, the most active compound demonstrated strong hydrogen bonding and hydrophobic interactions with key amino acid residues, including TYR157, PHE77, THR202, and GLY200. These residues are known to participate in ligand binding within the GABAAbenzodiazepine site, suggesting that the quinazolinone scaffold may exert anticonvulsant effects by enhancing GABAergic transmission.

2D and 3D interaction maps generated through Discovery Studio Visualizer further confirmed the orientation and depth of binding within the receptor pocket. π–π stacking with aromatic residues and halogen bonding also contributed to improved receptor affinity in halogenated derivatives.

A molecular docking study was conducted on a series of twenty quinazolinone derivatives (D1–D20) to evaluate their binding affinity towards the target receptor implicated in anticonvulsant activity. The binding affinities of these compounds were compared with the standard drug Phenobarbitone, which exhibited a binding affinity of −6.1 kcal/mol.

Among the tested compounds, most showed higher binding affinities than the standard, indicating stronger interactions with the receptor. The binding affinity values ranged from **−6.7** to −8.6 kcal/mol, with compound D18 showing the highest binding affinity at −8.6 kcal/mol, followed by D20 (−8.3 kcal/mol) and D9 (−8.0 kcal/mol). Several other compounds such as D14 and D16 also displayed strong binding affinities of −7.9 kcal/mol, suggesting potent interaction potential.

III. PHYSICOCHEMICAL PROPERTIES

Sr. no	Molecules	Log P	Molecular Weight	Lipinski Rules	Violations	HBD	TPSA (Å²)	HBA	Rotatable Bonds
Std-1.	Phenobarbitone	1.06	232.23	Yes	0	2	75.27	3	2
Std-2.	Diazepam	2.68	284.7	Yes	0	0	32.67	2	1
1.	D-1	1.86	331.37	Yes	0	3	64.60	2	3
2.	D-2	2.42	349.81	Yes	0	2	44.37	1	3
3.	D-3	1.82	360.37	Yes	0	2	90.19	3	4
4.	D-4	2.20	321.37	Yes	0	2	61.44	1	3
5.	D-5	3.03	345.39	Yes	0	2	53.60	1	2
6.	D-6	2.43	293.41	Yes	0	2	27.30	2	4
7.	D-7	2.89	300.21	Yes	0	2	44.37	1	3
8.	D-8	1.15	336.15	Yes	0	2	41.13	2	2
9.	D-9	2.84	298.13	Yes	0	2	44.37	1	3
10.	D-10	2.44	330.52	Yes	0	2	44.37	1	3
11	D-11	2.25	389.52	Yes	0	2	44.37	2	3
12	D-12	2.59	378.31	Yes	0	2	44.37	1	3
13	D-13	1.79	344.12	Yes	0	3	70.39	1	3
14	D-14	2.36	362.74	Yes	0	3	64.60	2	3

International Journal of Pharmaceutical Research and Applications
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15	D-15	2.97	336.55	Yes	0	2	62.83	3	5
16	D-16	2.83	321.21	Yes	0	2	44.37	1	3
17	D-17	2.10	347.26	Yes	0	4	84.83	3	3
18	D-18	2.18	350.78	Yes	0	2	90.19	3	4
19	D-19	2.16	312.49	Yes	0	4	94.06	4	4
20	D-20	2.39	328.62	No	0	2	86.32	4	4

Table 3: Physicochemical properties of all designed compounds

All 20 quinazolinone derivatives demonstrate favorable physicochemical and drug-likeness properties, with no Lipinski rule violations, suitable lipophilicity, and acceptable TPSA values for CNS activity. These features collectively suggest that the designed molecules are promising candidates for further pharmacological evaluation as potential anticonvulsant agents.

2. ADME Studies

Code	**Absorption (intestinal human absorption) %absorbed**	**Distribution**			**Metabolism**	**Excretion**	
		PPB (%)	**VD L/kg**	**BBB**	**CYP1A2 inhibitor**	**CL mL/min/kg**	**T1/2 (hr)**
D-1	92.889	97.6	0.391	Yes	Yes	3.37	0.699
D-2	100	98.8	0.443	Yes	Yes	2.019	0.808
D-3	92.376	96.9	0.913	Yes	Yes	1.775	0.811
D-4	92.189	98.1	0.695	No	Yes	3.586	0.576
D-5	91.635	96.6	0.539	Yes	Yes	2.103	0.829
D-6	90.345	95.9	2.985	No	Yes	5.888	0.21
D-7	91.426	92.55	0.363	No	Yes	4.678	0.745
D-8	90.629	89.23	1.405	Yes	Yes	5.739	0.933
D-9	89.232	100	0.186	Yes	Yes	3.706	0.045
D-10	92.584	99.78	0.195	Yes	Yes	3.588	0.131
D-11	91.854	99.23	0.569	No	Yes	3.560	0.049
D-12	88.821	100.4	0.556	Yes	Yes	3.651	0.048
D-13	93.406	98.63	0.693	Yes	Yes	4.707	0.114
D-14	93.026	99.36	0.305	No	Yes	5.098	0.377
D-15	93.754	99.98	0.649	Yes	Yes	5.901	0.211
D-16	90.461	99.91	0.460	Yes	Yes	1.952	0.092
D-17	94.825	100.1	0.281	Yes	Yes	1.954	0.328
D-18	92.753	100	0.424	Yes	Yes	2.642	0.111
D-19	80.834	99.64	0.323	Yes	Yes	5.893	0.791
D-20	91.145	99.83	0.786	No	Yes	4.210	0.038

Table 4: ADME determination of Compounds

The absorption, distribution, metabolism, and excretion (ADME) characteristics of twenty synthesized quinazolinone derivatives (D-1 to D-20) were evaluated to assess their pharmacokinetic behavior.Most compounds exhibited excellent intestinal absorption, with values exceeding 90%, indicating good potential for oral bioavailability. Notably, compound D-2 showed complete absorption (100%), while D-19 presented the lowest absorption among the series at 80.83%, though still within acceptable range.Plasma protein binding (PPB) values were generally high, ranging from 89.23% to 100.4%, suggesting strong binding affinity in systemic circulation. The volume of

International Journal of Pharmaceutical Research and Applications
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distribution (VD) values varied from 0.186 to 2.985 L/kg, indicating a moderate tissue distribution profile. Compounds such as D-6 and D-8 showed higher VD, reflecting broader tissue permeability.Most derivatives (15 out of 20) demonstrated the ability to cross the blood-brain barrier (BBB), a desirable feature for CNS-targeted agents. However, D-4, D-6, D-7, D-11, D-14, and D-20 lacked BBB permeability, potentially reducing central nervous system exposure for non-CNS therapies.All compounds were identified as potential inhibitors of the CYP1A2 enzyme, suggesting possible drug-drug interaction risks during metabolism.

Regarding elimination, the compounds showed variable clearance (CL) ranging from 1.775 to 5.901 mL/min/kg. The elimination half-life ($T_{1/2}$) was generally short, with D-8 (0.933 hr) and D-5 (0.829 hr) displaying longer retention, whereas D-9 (0.045 hr) and D-11 (0.049 hr) were rapidly eliminated.

Overall, derivatives such as D-2, D-13, D-15, and D-17 demonstrated balanced pharmacokinetic profiles—marked by high absorption, favorable distribution, manageable clearance, and moderate half-life—indicating their potential as lead candidates for further drug development.

IV. CONCLUSION

Sr.no	Compounds	Docking score
Std	**Phenobarbitone**	**-6.1**
1	**D-1**	**-7.2**
2	**D-2**	**-7.8**
3	**D-3**	**-6.7**
4	**D-4**	**-7.4**
5	**D-5**	**-7.2**
6	**D-6**	**-7.3**
7	**D-7**	**-7.4**
8	**D-8**	**-7**
9	**D-9**	**-8**
10	**D-10**	**-7.6**
11	**D-11**	**-7.6**
12	**D-12**	**-7.1**
13	**D-13**	**-7.1**
14	**D-14**	**-7.9**
15	**D-15**	**-7.5**
16	**D-16**	**-7.9**
17	**D-17**	**-7.2**
18	**D-18**	**-8.6**
19	**D-19**	**7.3**
20	**D-20**	**-8.3**

Table 5: Docking Score

This research focused on the design and evaluation of twenty novel quinazolinone derivatives for their potential as anticonvulsant agents. Molecular docking studies were conducted using the GABAAreceptor (PDB ID: 4COF) as the biological target. The docking results indicated that several compounds displayed stronger binding affinities than the standard drug phenobarbitone (–6.1 kcal/mol). Among them, derivatives such as D-18 (–8.6 kcal/mol), D-20 (–8.3 kcal/mol), and D-9 (–8.0 kcal/mol) showed exceptional interaction energies, suggesting effective binding with crucial receptor residues like TYR157, PHE77, and THR202, which are known to influence GABAergic activity.

Further analysis through ADME (absorption, distribution, metabolism, and excretion) profiling demonstrated that most compounds had high gastrointestinal absorption rates, favorable plasma protein binding percentages, and suitable volume of distribution values. Notably, compounds D-2, D-13, and D-17 showed near-complete intestinal absorption and effective blood-brain barrier permeability, making them strong candidates for CNS-targeted therapies.

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All derivatives were found to comply with Lipinski's criteria for drug-likeness, suggesting good oral bioavailability. Additionally, the compounds showed low predicted toxicity and were within acceptable ranges for topological polar surface area (TPSA), molecular weight, and lipophilicity (Log P). Metabolic profiling indicated CYP1A2 inhibitory activity for all molecules, pointing to a potential for metabolic interaction that must be carefully considered during further development. Clearance and half-life values varied across the series, with compounds like D-5 and D-8 exhibiting longer systemic retention.In summary, the findings highlight D-2, D-13, D-15, and D-17 as the most promising drug-like candidates due to their favorable docking scores, pharmacokinetic profiles, and physicochemical properties. These derivatives hold potential for development into effective anticonvulsant therapies and merit further investigation through biological assays and clinical modeling.

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