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Molecular Docking, Drug-likeness and Molecular Properties Study of Some Novel Quinazolinone-1,3,4-OxadiazoleDerivativesAgainst the GABA(A) Receptor Indicates the New Approach to Epilepsy Treatment

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ABSTRACT:
Epilepsy is a prevalent neurological illness that affects about 1% of the world's population. In less than 70% of cases, anticonvulsants are successful in lowering the intensity and frequency of seizures. It has also been linked to a range of negative side effects, ranging from the aesthetic (gingival hyperplasia) to the life-threatening (cardiac arrest). A review of the literature reveals that many quinazolinone derivatives, including quinazolinone with thiazolidine and quinazolinone with oxadiazole have been discovered. The antiepileptic drug was designed using quinazolinone-1,3,4-oxadiazole derivatives and selective GABA activation in this study. By substituting at position-3 of quinazolinone, the potential activity of quinazolinone-1,3,4-oxadiazole derivatives can be boosted. Molecular docking of particular GABA activation was required to predict their antiepileptic activity. The molecular docking of quinazolinone-1,3,4-oxadiazole derivatives was doneusing PyRx and Biovia discovery studiovisualizersoftware. 4cof is the Protein Data Bank (PDB) code for this protein. GABA(A)R-Beta3 was docked with sixteen quinazolinone-1,3,4-oxadiazole molecules. The interaction was assessed using the docking score. Clonazepam was used as the reference standard in this investigation. The docking scores of sixteen quinazolinone-1,3,4-oxadiazole derivatives ranged from ***-8.6 to -9.6 kcal/mol****. When compared to the conventional chemical clonazepam, all sixteenquinazolinone-1,3,4-oxadiazole derivatives have a greater docking score. Because it has the lowest docking score, derivative****5c****has a larger binding energy than other quinazolinone-1,3,4-oxadiazole derivatives. All of the new quinazolinone-1,3,4-oxadiazole derivatives can be synthesised, and they've been tested in vitro.*

KEYWORDS: *Quinazolinone-1,3,4-oxadiazole;Epilepsy; GABA(A)Receptor; Molecular docking; Molecular Properties and Drug-likeness.*

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I. INTRODUCTION:

Epilepsy is a common neurological illness that affects roughly 1% of the global population and is defined by repeated seizure attacks. Antiepileptic medications are used simply to control symptoms and are neither preventative nor curative. They can have a direct effect on ion channels or have an indirect effect on the production, metabolism, or function of neurotransmitters or receptors that modulate channel opening and closure. Antiepileptic medication mechanisms can be divided into numerous categories for the most basic understanding: Sodium channel blockers, calcium current inhibitors, GABA enhancers, and glutamate blockers are the four primary classes.[1,2]

These medications have been shown to reduce seizures, however they have certain unwanted side effects, such as sleepiness, ataxia, gastrointestinal disturbances, gingival hyperplasia, hirsutism, and megaloblastic anaemia, which negate their therapeutic value. Furthermore, roughly 30% of patients are resistant to these medications. Given the foregoing, novel epilepsy drugs with greater selectivity and a lower side effect profile are urgently needed. The construction of heterocycles as scaffolds with a high degree of variation has been a prominent emphasis in modern drug research. Certain heterocyclic ring modifications, such as the insertion of different substituents, may lead to new compounds with improved pharmacological properties. Quinazoline is an important milestone that can be found in a total of nine FDA-approved drugs. Pharmaceuticals

use nitrogen heterocycles as one of their preferred molecular scaffolds [3]. Quinazolinones are one of the most important quinazoline families, as they are the key scaffold components of roughly 150 naturally occurring alkaloids and medications [4]. Quinazolinone analogues have been reported to have anti-inflammatory [5], antibacterial [6], antioxidant [7], anticancer [8], anticonvulsant [9], antiviral [10], and antihypertensive properties [11], according to several investigations.

Antiepileptic drugs must pass through the blood-brain barrier to be effective[12]. Highly lipophilic compounds can easily pass through the brain interstitial. In vitro determination of brain-blood partitioning is complex, time-consuming, expensive, and not always available, making it ineffective for screening a large number of new compounds[12]. To calculate the ClogP values of the newly synthesised compounds to reflect their total lipophilicity, we adopted an alternate method based on computerised models.Although the specific mechanisms of quinazolinone action are unknown, a study in epilepsy shown that quinazolinones can improve GABA action. The major goal of this study was to look at the interactions between quinazolinone-1,3,4-oxadiazole derivatives and GABA, as well as the effects of GABA activation in epilepsy. The residues involved in quinazolinones down regulating action on GABA were also identified using docking analysis.

II. MATERIAL AND METHODS:

The study of molecular docking was carried out on a system with computational specifications (HP Pavilion AMD Ryzen™ 5 Hexa Core 5500 APU @ 2.1GHz with turbo boost up to 4GHz Processor version 5500U and 16.00 GB RAM with 64-bit Windows-11 operating system).

- PubChem webserver
- Protein Data Bank
- Biovia discovery studio visualizer
- PyRx

PubChem Webserver:

PubChem is an open chemistry database at the ***National Institutes of Health*** **(NIH).** Since the launch in 2004, PubChem has become a key chemical information resource for scientists, students and general public. We gather the information SDF(structural data format) of drugs.

Protein Data Bank:

It has archive information about the 3D shapes of proteins, nucleic acids, and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture.

Biovia discovery studio visualizer:

Discovery studio is a suite of software for simulating small molecules and macromolecule systems. It is developed and distributed by Dassault systems **BIOVIA**

PyRx:

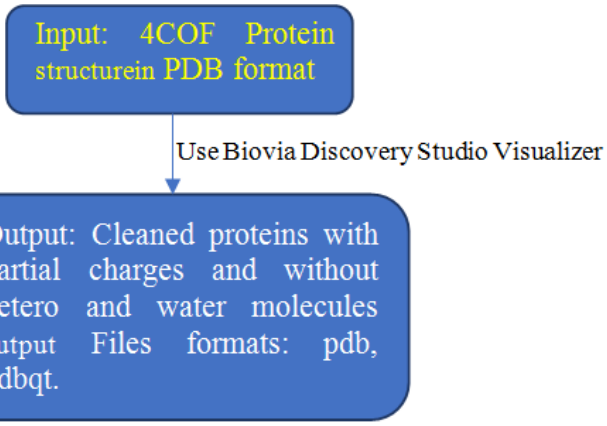
PyRx is a virtual screening software for computational drug discovery that can be used to screen libraries of compounds against potential drugs targets

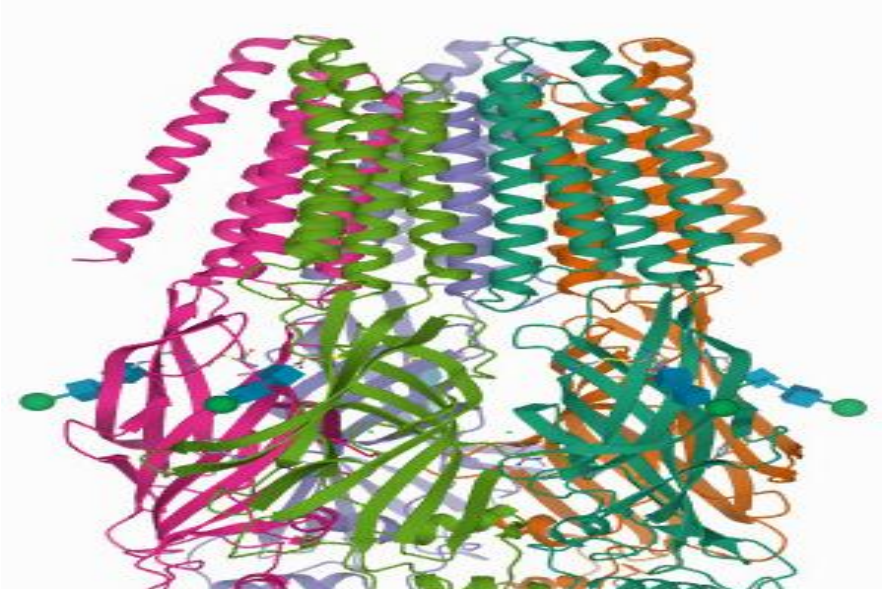
Grid Box Formation:

- Grid box format is used to ensure the ligand and protein are fitted in the grid box.
- Give forward to run the auto dock vina.
- Modify Advanced parameter during the simulations such as number of runs.
- After the successful docking the accuracy of docking is often quantified by root mean square deviation (RMSD) between ligand and protein.

Preparation of Target Protein X-Ray Structure

Upload protein structures from your files or download them from the protein data bank. 4COF (GABA(A)R-beta3 homopentamer) and save as pdb format. Open biovia discovery studio visualizer and prepare a protein.The GABA(A)R-beta3 homopentamer (PDB ID: 4COF) crystal structure of the human gamma-aminobutyric acid receptor was chosen as the protein target and retrieved from http://www.pdb.org / or https://www.rcsb.org/structure/4COF.





PDB ID: 4COF (Fig. 1)

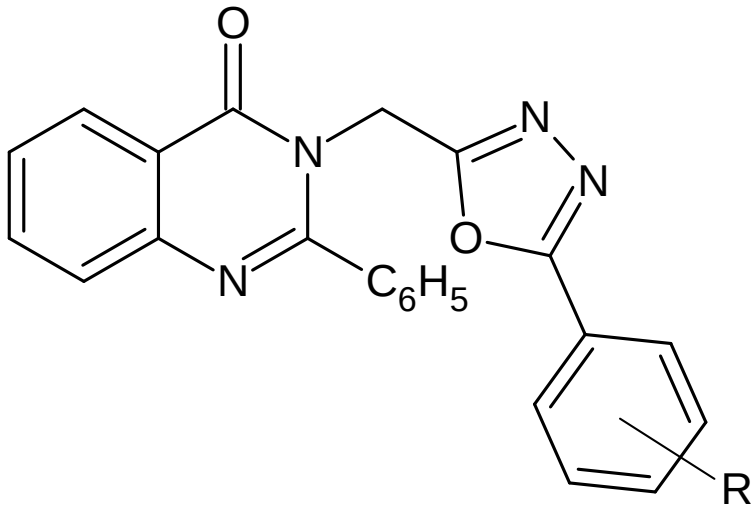
The GABA(A)R-beta3 homopentamer is a human gamma-aminobutyric acid receptor with a crystal structure.

Design of novelquinazolinone-1,3,4-oxadiazolederivatives

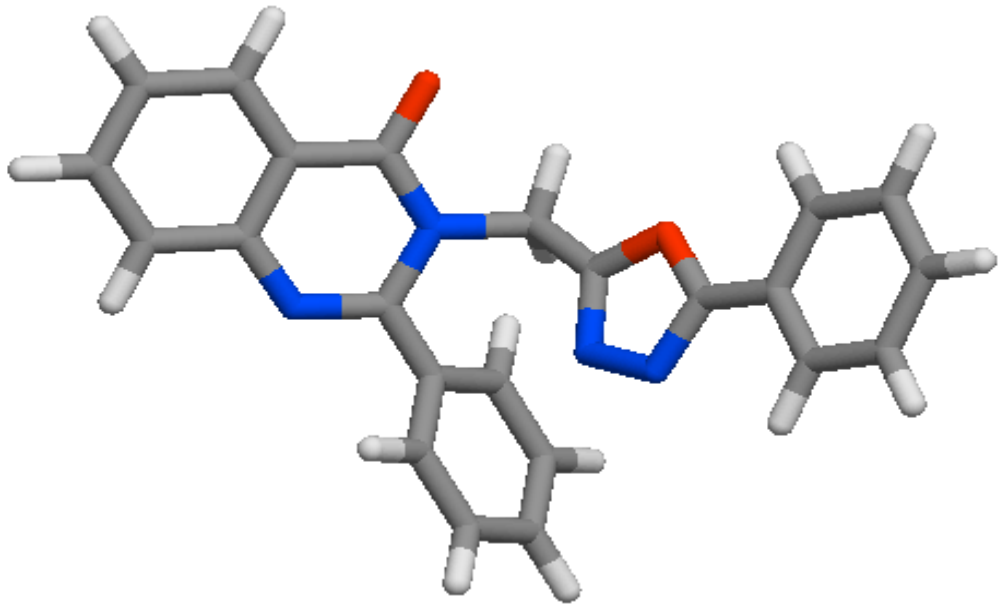
Novel drug development entails (i) identifying the lead compound, (ii) manipulating the lead compound's substituent, and (iii) identifying a list of new substituents. In this study, the antiepileptic medication quinazolinone-1,3,4-oxadiazole is a new lead chemical [13]. To make novel compounds, the substituents are chosen. Some of the substituents are -H, -CH3, -OCH3, -Cl, -NO2, and -OH. They are substituted for the benzylidene group connected to the methyl-1,3,4-oxadiazol side chain.

Ligands Preparation of Ligands

Chem Sketch Ultra 8.0 was used to draw the structures of quinazolinone-1,3,4-oxadiazole derivatives in fig.2 and 3. (Cambridge Soft). Chem 3D Ultra 8.0 was used to convert the 2D structures (fig.2) of chemicals into 3D structures (Fig.3). MMFF 94 techniques were used to optimise molecules and minimise the shape of the ligands, which were then saved as PBD files that could be read by PyRx and Biovia discovery studiovisualizerapplication. Load the ligand in the open babel in the pyrx software and minimize the energy of the ligand (energy minimizes).



2D Structure (Fig.2)



3D Structure (Fig.3)

Prediction of drug-likeness and molecular properties

The drug-likeness of a chemical substance is defined as a balance between its molecular properties, which has a direct impact on a drug's biological activity, pharmacodynamics, and pharmacokinetics in the human body [14]. The "drug-likeness" test was conducted using Lipinski's "Rule of Five," ro5 (Lipinski et al., 1997). The distributions of compound molecular weights (MW), calculated lipophilicity (logP), number of hydrogen bond acceptors (HBA), and number of hydrogen bond donors (HBD) were used to assess the "drug-likeness" of compounds [15]. Based on these four chemical descriptors, the technique provides a watchful approach to apparent absorption problems; the rule stipulates that most "druglike" molecules must have log P 5, molecular weight 500, number of hydrogen bond acceptors 10, and number of hydrogen bond donors 5. Molecules that violate more than one of these criteria may impair oral bioavailability [16].

Molecular Docking Study of usingPyRx and Biovia discovery studiovisualizer Software

Molecular docking is a computer simulation of a ligand binding to a receptor that helps anticipate the binding molecule's affinity and activity to the protein target. Molecular docking techniques on PyRx and Biovia discovery studiovisualizersoftware werewerewas used to investigate the interaction of quinazoline derivatives with GABA. As a protein target, we used the crystal structure of human GABAa (code 4COF, http://www.pdb.org/or https://www.rcsb.org/structure/4COF). Before screening the ligands, the docking process was validated by re-docking the 4COF ligand into its binding pocket within the GABAa crystal to obtain the docked posture and root-mean-square distance (RMSD).

Thesixteen new derivatives of 3-{[5-(4-Substitutedphenyl)-1,3,4-oxadiazol-2-yl]methyl}-2-phenylquinazolin-4(3*H*)-one (5a-5p)were synthesized by condensation between2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetohydrazideand aromatic aldehyde in presence of acetic acid and ethanol via2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)-N'-[(E)-phenylmethylidene]acetohydrazide.

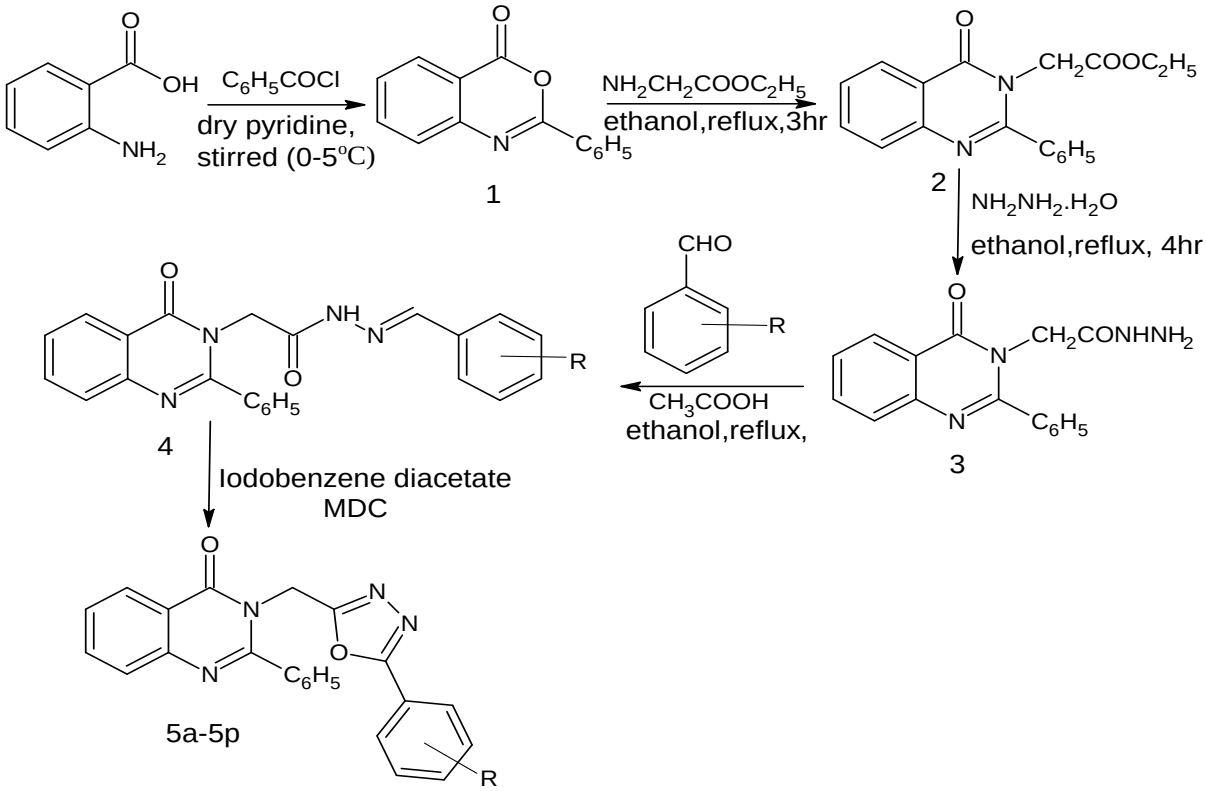


Fig.4: Scheme of synthesis.

III. RESULTS AND DISCUSSION:

Virtual screening trials by performing docking using an ensemble of static receptor conformations, virtual screening trials are the most viable way for involving protein in the docking process. Modern drug design use molecular docking to better understand the interactions between ligands and receptors. Based on the drug-receptor interaction mechanism, these tactics contribute in the development of innovative medicines with distinctive activity. Computer-aided drug design (CAAD) is used to find small compounds by orienting and scoring them in the active binding area of a protein. The docking simulation technique was used with quinazolinone-1,3,4-oxadiazole derivatives and GABAa as the protein target, and it was done withPyRx and Biovia discovery studiovisualizersoftware. Two criteria were used to select the best docked proteins: ligand binding position and fitness function score comparison. The RMSD was used to find the best position for ligand binding.

A docking score, which predicts pharmacological activity, reflects the binding energy required to build a connection between the ligand and the receptor. It also aids in the strengthening of the ligand-receptor connection. **Table no.1** shows the binding energy value of sixteen quinazolinone-1,3,4-oxadiazole derivatives. The approximate docking score of sixteen quinazolinone-1,3,4-oxadiazole ranged from **-8.6 to -9.6 kcal/mol**. When compared to the reference compound clonazepam, all sixteenquinazolinone-1,3,4-oxadiazole derivatives had a higher docking score. Because it has the lowest docking score (-9.6 kcal/mol), derivative compound 5c has a larger binding energy than otherquinazolinone-1,3,4-oxadiazole derivatives, the docking simulation technique was employed, and Molecular docking of specific GABA activation was required to predict their antiepileptic efficacy, which was done with PyRx Software. The best docked proteins were chosen using two criteria: ligand binding position and fitness function score comparison. The binding energy required to form a connection between the ligand and the receptor is reflected in a docking score that predicts pharmacological activity. It also helps to strengthen the ligand-receptor relationship. The compound 5cgreatest binding affinity for quinazolinone-1,3,4-oxadiazole analogues was anticipated to be -9.6kcal/mol, as shown in Table No.1.

Table no:1. The docking score of quinazolinone-1,3,4-oxadiazolederivatives with GABA(A)R (5a-5p)

Compound Code	Molecular Formula	R-Derivatives	Ligand	rmsd/ub	rmsd/lb	Docking Score
5a	$C_{23}H_{16}N4O_2$	-H	4cof_-H_uff_E=536.70	0	0	-9.4
5b	$C_{24}H_{18}N_4O_2$	2-CH_3	4cof_2-CH3_uff_E=617.02	0	0	-9.2
5c	$C_{24}H_{18}N_4O_2$	**3-CH_3**	**4cof_3-CH3_uff_E=601.55**	**0**	**0**	**-9.6**
5d	$C_{24}H_{18}N_4O_2$	4-CH_3	4cof_4-CH3_uff_E=605.61	0	0	-9.4
5e	$C_{24}H_{18}N_4O_3$	2-OCH_3	4cof_2-OCH3_uff_E=583.80	0	0	-8.7
5f	$C_{24}H_{18}N_4O_3$	3-OCH_3	4cof_3-OCH3_uff_E=558.79	0	0	-9.0
5g	$C_{24}H_{18}N_4O_3$	4-OCH_3	4cof_4-OCH3_uff_E=555.06	0	0	-9.5
5h	$C_{23}H_{15}ClN_4O_2$	2-Cl	4cof_2-Cl_uff_E=564.69	0	0	-8.9
5i	$C_{23}H_{15}ClN_4O_2$	3-Cl	4cof_3-Cl_uff_E=543.46	0	0	-8.6
5j	$C_{23}H_{15}ClN_4O_2$	4-Cl	4cof_4-Cl_uff_E=536.30	0	0	-9.2
5k	$C_{23}H_{15}N_5O_4$	2-NO_2	4cof_2-NO_2_uff_E=653.13	0	0	-9.1
5l	$C_{23}H_{15}N_5O_4$	3-NO_2	4cof_3-NO_2_uff_E=606.27	0	0	-9.0
5m	$C_{23}H_{15}N_5O_4$	4-NO_2	4cof_4-NO2_uff_E=580.08	0	0	-9.5
5n	$C_{23}H_{16}N_4O_3$	2-OH	4cof_2-OH_uff_E=555.24	0	0	-9.4
5o	$C_{23}H_{16}N_4O_3$	3-OH	4cof_3-OH_uff_E=542.01	0	0	-9.0
5p	$C_{23}H_{16}N_4O_3$	4-OH	4cof_4-OH_uff_E=536.74	0	0	-9.5
Clonazepam	$C_{15}H_{10}ClN_3O_3$	Std.	4cof_2802_uff_E=452.08	0	0	-7.4

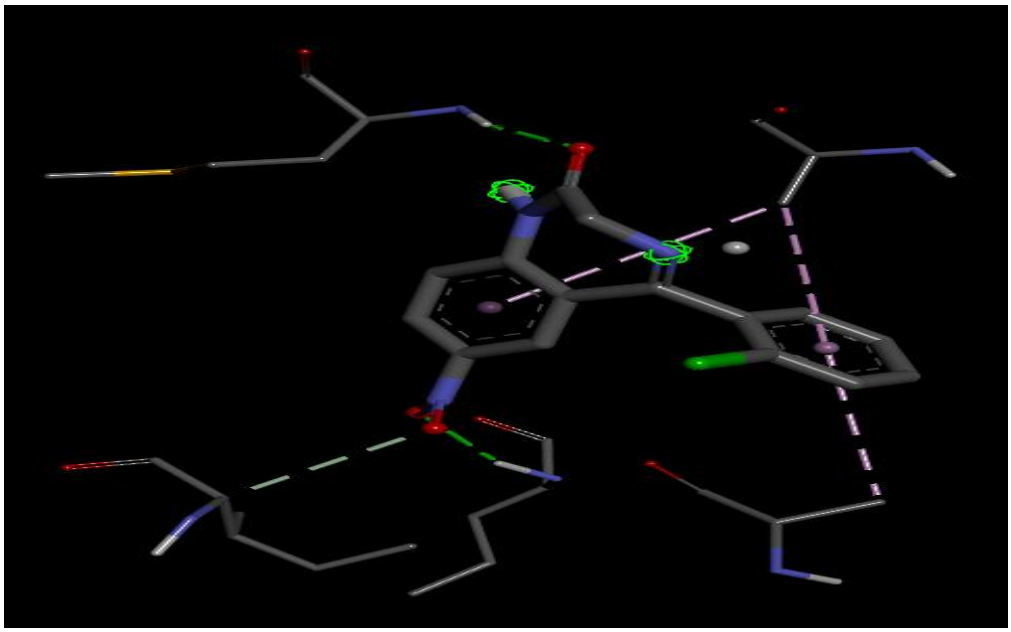


Fig.5: 3D structure of clonazepaminteracts with GABA(A)R

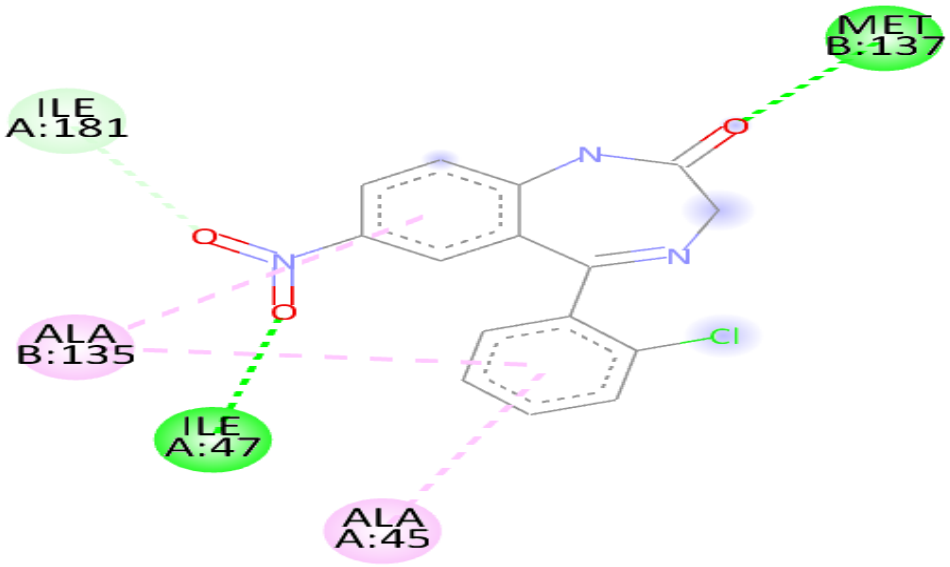


Fig.6: 2D structure of clonazepam interacts with GABA(A)R

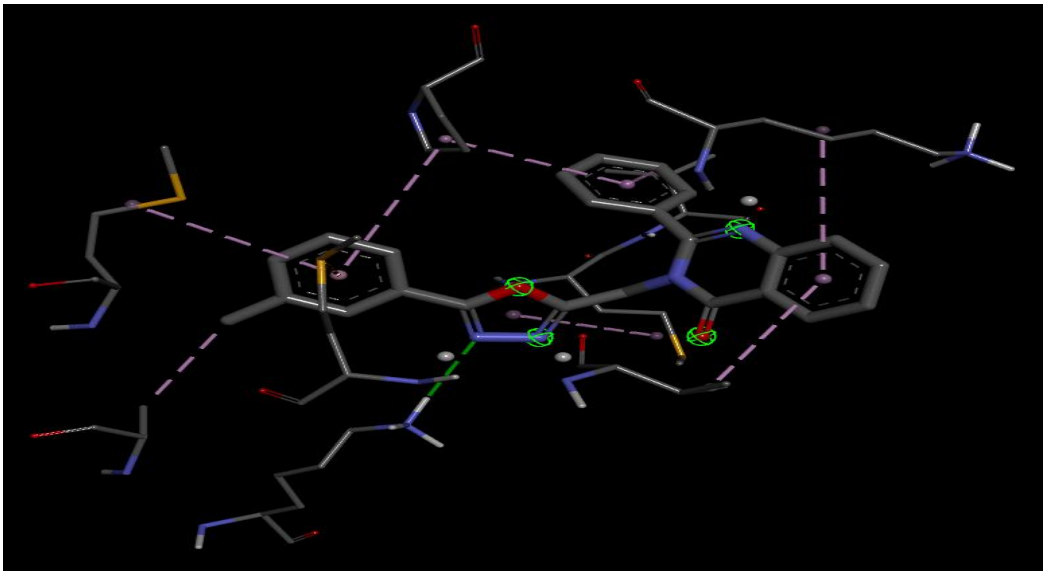


Fig.7: 3D structure of 3-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]methyl}-2-phenylquinazolin-4(3*H*)-one interact with GABA(A)R

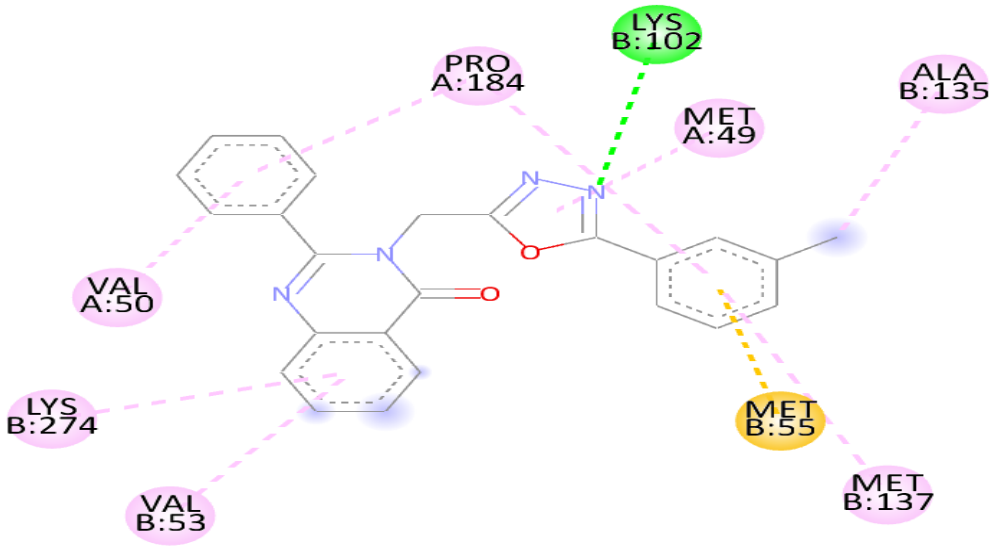


Fig.8: 2D structure of 3-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]methyl}-2-phenylquinazolin-4(3*H*)-one interact with GABA(A)R

Every quinazolinone-1,3,4-oxadiazole derivative formsa linkage withprotein residue by hydrogen bonding. The compounds 5g, 5m and 5p interact with clonazepam in a hydrogen bond with protein residues in a similar way(ALA B:135). Compound5c is one of the showed best docked complex scores with binding energy -9.6 kcal/mol and it interacts with MET B:137, PRO A:184, VAL A:50, ALA B:135, MET A:49, LYS B:274, VAL B:53 and LYS B:102 amino acid resides in the active site of target protein.At C-2, a phenyl moiety was substituted, and at N-3position linked to a 2-methyl-5-(4-nitrophenyl)-1,3,4-oxadiazole. It has a larger binding energy to connect with the target receptor because of this. In Fig.6and 8 the interaction compound clonazepam and hydrogen bonds are depicted, while compound5cis depicted in fig.8.

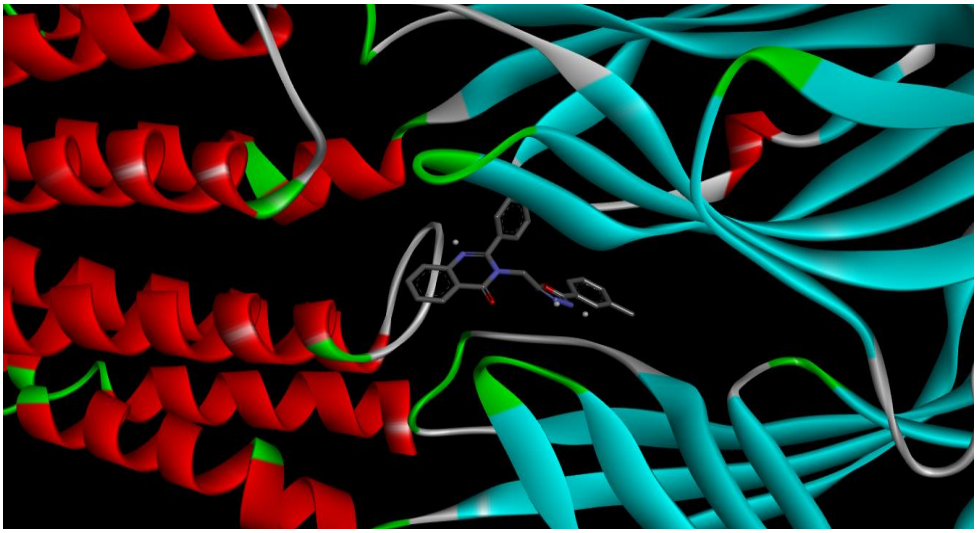
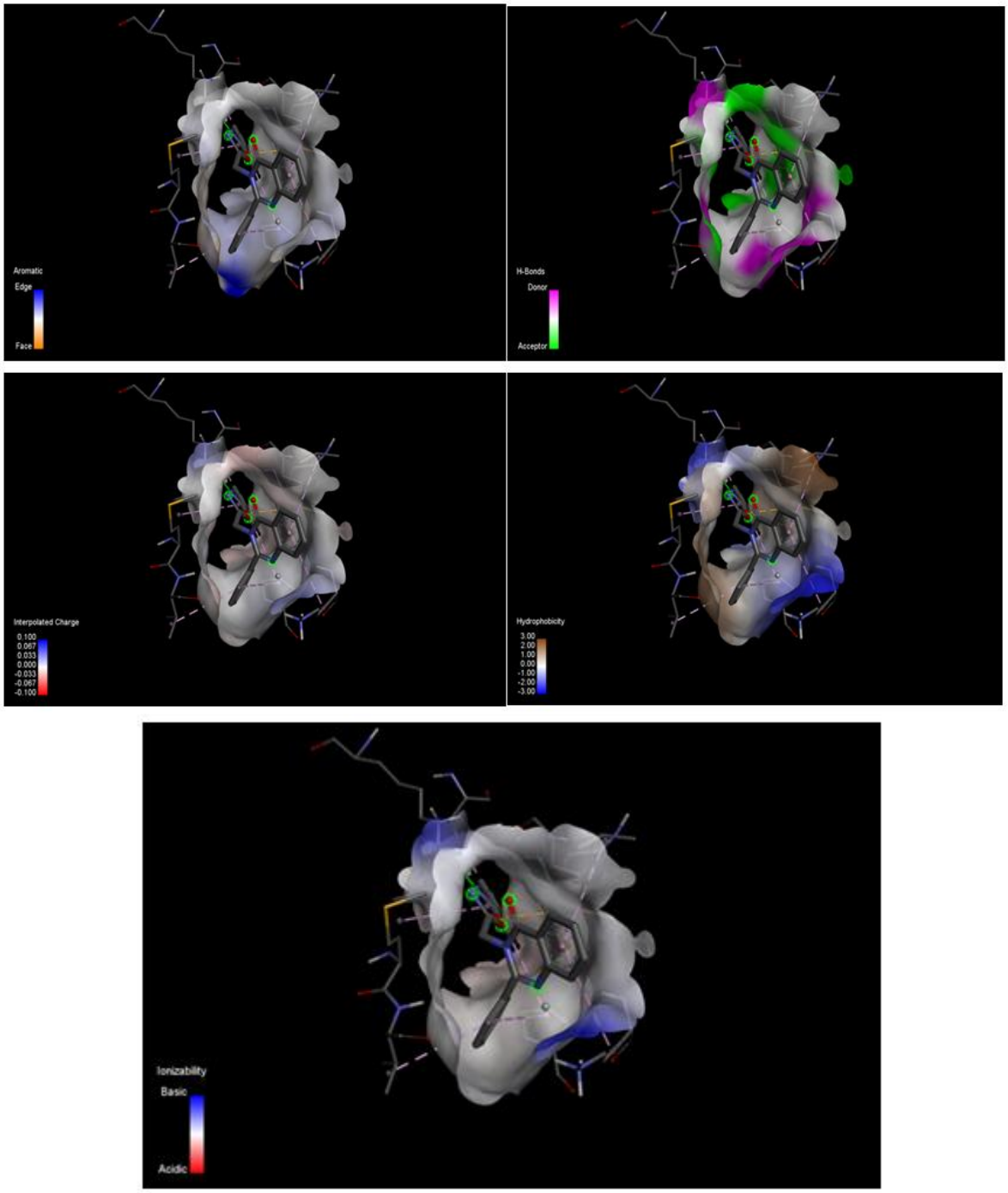


Fig.9: 3D structure of quinazolinone-1,3,4-oxadiazole derivatives (5c)interact with GABA(A)R (PDB ID:4COF)



Molecular Properties Calculations and Drug-likeness

The molsoftsoftware was used to forecast the quinazolinone-1,3,4-oxadiazol derivativesscore, molecular characteristics and drug similarity. 3-[5-(Substitutedphenyl)-1,3,4-oxadiazol-2-yl]methyl-2-phenylquinazolin-4(3H)-one molecular structure (5a-5p) Table 2 was created with the help of the molsoft software (**https://www.molsoft.com**) for calculating molecular characteristics (MolLogP, Molecular polar surface area, number of hydrogen bond donors and acceptors, molecular weight) and drug likeness, Blood brain barriers (BBB).

The presence of numerous pharmacophoric traits, such as hydrophobicity, molecular size, flexibility, and the presence of other pharmacokinetic and pharmacodynamic features, influence the pharmacokinetic and pharmacodynamic behaviour of molecules in the living organism, including bioavailability. To obtain good bioavailability, we subjected series of quinazolinone derivatives (5a-5p) to Lipinski's "Rule of Five" for the prediction of some basic pharmacokinetic features. To filter the medications for biological screening, all of the compounds were subjected to a computer investigation.

Lipinski's criterion or rule was followed by 3-[5-(4-Substitutedphenyl)-1,3,4-oxadiazol-2-yl]methyl-2-phenylquinazolin-4(3H)-one derivatives (5a-5p), which exhibited good drug molecular characteristics score (Table no. 2). The majority of the compounds had molLogP values of less than 5, while the chloroand methyl counterparts had larger values, indicating that they had good permeability. All of the derivatives had MolPSA values ranging from 55.53 to 88.91 (far below 160), and their molecular weights were less than 500.The number of hydrogen bond donors 2 and acceptors 7 was determined to be less than 5 and 10, respectively, as defined by Lipinski's limit. All of the following compounds had blood brain barriers (BBB) ranging from 1.72 to 3.55 normal range (6-High, 0-Low) and a drug likeness model score ranging from -0.06 to 0.99, indicating that they followed Lipinski's criterion or rule and had strong drug molecular characteristics is shown in **Table no. 2**.

Tableno: 2. Prediction Score of Drug-likeness and Molecular Properties. (5a-5p)

Comp. Code	Molecular Formula	mol. wt. (g/mol)	noHBA	noHBD	mol. Log *P*	MolVol (A^3)	MolPSA (A^2)	BBB Score (6-High, 0-Low)	Drug-likeness model score
5a	$C_{23}H_{16}N4O_2$	380.13	5	0	3.60	363.49	55.53	3.53	0.15
5b	$C_{24}H_{18}N_4O_2$	394.14	5	0	3.90	383.09	55.53	3.52	0.49
5c	$C_{24}H_{18}N_4O_2$	394.14	5	0	4.01	384.50	55.53	3.52	0.38
5d	$C_{24}H_{18}N_4O_2$	394.14	5	0	4.17	384.43	55.53	3.52	0.63
5e	$C_{24}H_{18}N_4O_3$	410.14	6	0	3.40	394.59	63.16	3.15	0.17
5f	$C_{24}H_{18}N_4O_3$	410.14	6	0	3.72	395.41	63.07	3.15	0.22
5g	$C_{24}H_{18}N_4O_3$	410.14	6	0	3.68	395.34	63.07	3.15	0.59
5h	$C_{23}H_{15}ClN_4O_2$	414.09	5	0	4.05	378.73	55.53	3.55	0.43
5i	$C_{23}H_{15}ClN_4O_2$	414.09	5	0	4.28	380.76	55.53	3.55	0.39
5j	$C_{23}H_{15}ClN_4O_2$	414.09	5	0	4.32	380.68	55.53	3.55	0.99
5k	$C_{23}H_{15}N_5O_4$	425.11	7	0	3.23	388.51	88.61	1.72	-0.02
5l	$C_{23}H_{15}N_5O_4$	425.11	7	0	3.58	388.55	88.91	1.72	-0.06
5m	$C_{23}H_{15}N_5O_4$	425.11	7	0	3.65	388.48	88.91	1.72	0.18
5n	$C_{23}H_{16}N_4O_3$	396.12	6	1	3.78	374.59	72.08	2.74	0.52
5o	$C_{23}H_{16}N_4O_3$	396.12	6	1	3.29	374.11	73.15	2.72	0.54
5p	$C_{23}H_{16}N_4O_3$	396.12	6	1	3.15	374.04	73.15	2.72	0.87
$C_{15}H_{10}ClN_3O_3$ (Clonazepam)		315.04	4	1	2.38	282.22	66.76	3.05	-0.08

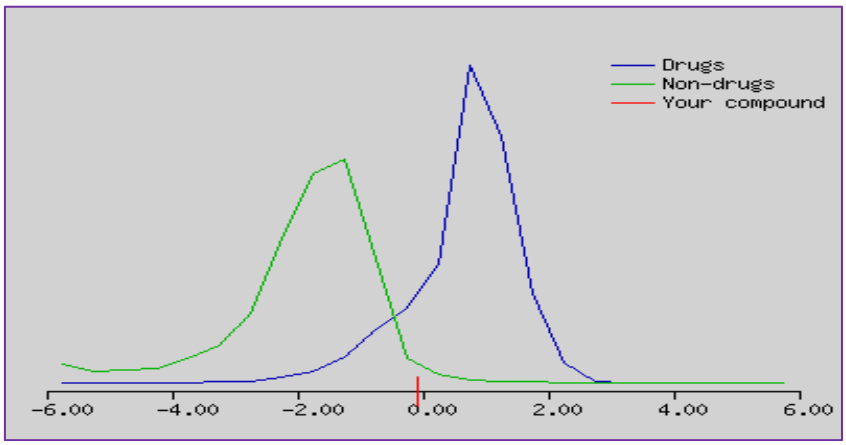


Fig.10: Clonazepam drug-likeness score: -0.08

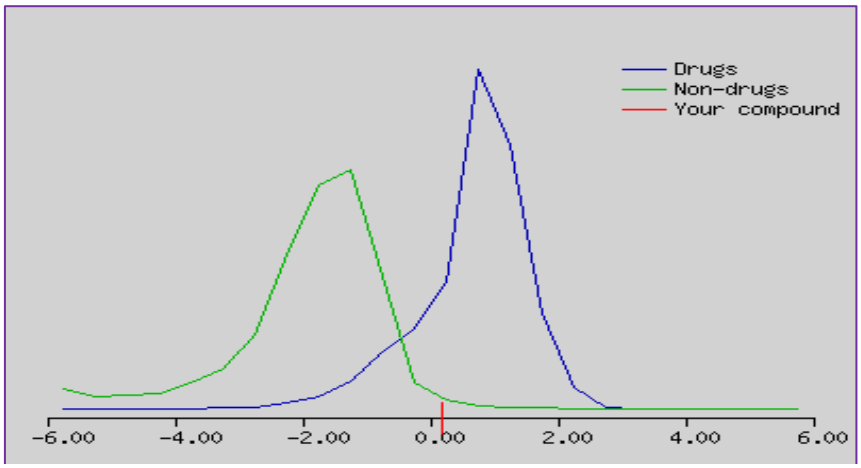


Fig.11: Compound(**5m)**Drug-likenessscore: 0.18

IV. CONCLUSION:

Sixteen molecular structures ofdisubstituted-quinazolin-(3*H*)-4-one with phenyl moiety bound in position-2 and substituted benzylidene linked to 2-methyl-1,3,4-oxadiazole bound in position-3 were docked and a score was calculated to determine the ligands that bind to GABAa protein structure. All derivatives had a higher docking score than clonazepam, according to the results. They have a higher binding energy interaction with the target receptor, which means they have a higher binding energy connection with the target receptor. As a result, these substances could be classified as GABAergic agonists. Synthesis and in vitro testing are required for future exploration in order to obtain antiepileptic activity. All of the derivatives had MolPSA values ranging from 55.53 to 88.91 (far below 160), and their molecular weights were less than 500. The number of hydrogen bond donors 2 and acceptors 7 was determined to be less than 5 and 10, respectively, as defined by Lipinski's limit.

CONFLICT OF INTERESTS:

The authors declare that there were no commercial or financial relationships that may be considered as a potential conflict of interest during the research.

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