Section: Research Paper

DOCKING STUDIES OF PIRACETAM DERIVATIVES (N-(N-ACYL-3-OXOMORPHOLINO) ACETAMIDE WITH GABA-ERGICRECEPTORS

[*]Aadesh Kumar[1], Ganesh Prasad Mishra[1], Nidhi Dhama[1]

[1] Department of Pharmaceutical chemistry, Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University Meerut, Uttar Pradesh, India

*Corresponding author: E-mail: adesh.adi.choudhary@gmail.com

ABSTRACT

The ability of in silico methodologies to provide epochal benefits to both regulatory requirements and the pharmaceutical sector to analyses the safety profile has been made possible by advancements in computational research. Piracetam is the first nootropic drug to be widely used in medicine, and its success can be linked to cyclic gamma-aminobutyric acid derivatives. Schrodinger Maestro (v11.1) software was used to conduct a molecular docking investigation of suggested derivatives with protein obtained from protein data bank. A possible route for the creation of brand-new neuroprotective medications is the manufacture of piracetam compounds with significant nootropic action. The purpose of the study is to carry out molecular docking studies to predict the GABA-ergic and glutamatergic activities of N-acyl derivatives of 2-(2-oxopyrolidin-1-yl)-acetamide by analyzing the energy of interactions between modelled structures and GABAA and AMPA receptors, followed by targeted synthesis. Out of total 40 only20 derivatives were found to active because of suitable interaction with the receptor and are the potential candidates for peripheral neuropathy.

Keywords Neuroprotective, Glycoprotein, Docking, GABAergic

INTRODUCTION

A systematic search for effective therapeutic drugs that target human Brain diseases linked to emotional problems has become necessary in recent years. Currently utilized medications in clinical settings include those having neuroprotective effects on the maintenance of brain function and advantages for the resilience of neurons to aggressive endogenous and external stimuli. Particularly, it has been suggested that a fascinating class of drugs known as "nootropics" can enhance cognition, memory, and other CNS activities. It has been demonstrated that nootropics improve nerve cells' resistance to the effects of hypoxia, drunkenness, and post-traumatic brain injury[1,7,12].

Low toxicity, compatibility with other CNS medications from different pharmacological categories, and virtually complete lack of negative side effects are all significant benefits of nootropics. Nootropics help neurons function more effectively, exchange proteins and nucleic acids within cells, produce adenosine triphosphate, transfer glucose across the blood-brain barrier (BBB), and use it further in brain tissues.

It is advisable to integrate several molecular modelling techniques while looking for new biologically active substances (BACs) that affect the glutamatergic and/or GABAergic systems. By combining molecular logical descriptors with a structure-based analysis of molecular databases containing ligands with known activities, for instance, it is possible to identify structural motifs or common structural fragments (referred to as "pharmacophores") that are responsible for a particular class of activity[8]. It is feasible to determine the ideal ligand locations at protein binding sites and to discover correlations with the potency of the desired pharmacological effect by combining conformational analysis with molecular docking approaches.

The purpose of the work is to use molecular docking to predict the GABA-ergic activities of derivatives of piracetam by analyzing the energy of interactions between modeled structures and GABAA receptors, followed by targeted synthesis. Particularly, it has been suggested that a fascinating class of drugs known as "nootropics" can enhance cognition, memory, and other CNS processes[13]. It has been demonstrated that nootropic medications improve nerve cells' resistance to the effects of hypoxia, drunkenness, and post-traumatic brain injury[3].

The low toxicity, compatibility with other CNS medications from different pharmacological classes that affect the central nervous system, and nearly complete lack of negative side effects of nootropic medicines are key benefits[4].Nootropics play a role in enhancing neuronal processes, exchanging nucleic acids and proteins inside cells, producing adenosine triphosphate, transporting glucose across the blood-brain barrier (BBB), and using it further in brain tissues[5].

It is advisable to integrate several molecular modelling techniques while looking for new biologically active substances (BACs) that affect the glutamatergic and/or GABAergic systems. By combining molecular logical descriptors with a structure-based study of molecular databases containing ligands with known activities, for instance, it is possible to identify structural motifs or common structural fragments (referred to as "pharmacophores") that are responsible for a certain class of activity[9].It is feasible to determine the ideal ligand locations at protein binding sites and to discover correlations with the potency of the desired pharmacological effect by combining conformational analysis with molecular docking approaches[6].

MATERIALS AND METHODS

Using Schrodinger software, the ligand-receptor interactions at the GABAA receptor's gamma-aminobutyric acid binding site were computed. Proteins X-ray crystallographic structures were obtained using the protein databank (https://www.rcsb.org/). Specific mistakes, such as missing hydrogen atoms in the protein during X-ray crystallography, were corrected using the protein preparation wizard of the Glide software (Schrödinger Suite 2018-1). The PBD structure's potential hydrogen atoms that were lacking were added, and the bond ordering were allocated. Other alternatives were left to default, and disulphide bonds were formed between two nearby sulphur atoms. Utilizing the OPLS3 force field, full energetic optimization was carried out in the final refinement step. The co-crystallized ligand at the protein's active site was selected in the receptor grid generation panel to automatically expose the x, y, and z coordinates Glide

determines a default center and a default size for the region for which grids will be calculated using the position and size of the ligand.

Molecular docking to the GABAA receptor-binding site: The GABAA receptor is the biological target of docking; it belongs to the family of Cys-loop receptors and has disulfide links between two cysteine residues. The structure of each and every GABA receptor mentioned is a polymorphic protein creation, and it greatly depends on where it is found in the body's tissues. Modern taxonomy divides GABA receptors into two categories: metabotropic GABAB receptors and ionoform receptors of the GABAA/GABAC type[1].The GABAA receptor is a heteropentameric glycoprotein complex, which makes up its supramolecular structure. Seven different subunit kinds can be found in the ionotropic receptor's structure: α, β, γ, δ, ε, π and θ. In contrast, the α subunit is represented by 6 isoforms, the β and γ subunits each have 3 isoforms, and the other types of GABA4 receptor subunits each have one isoform. The GABAA receptor is a pentamer made up of two α-and β-subunits and one γ-subunit[2](Fig. 1).

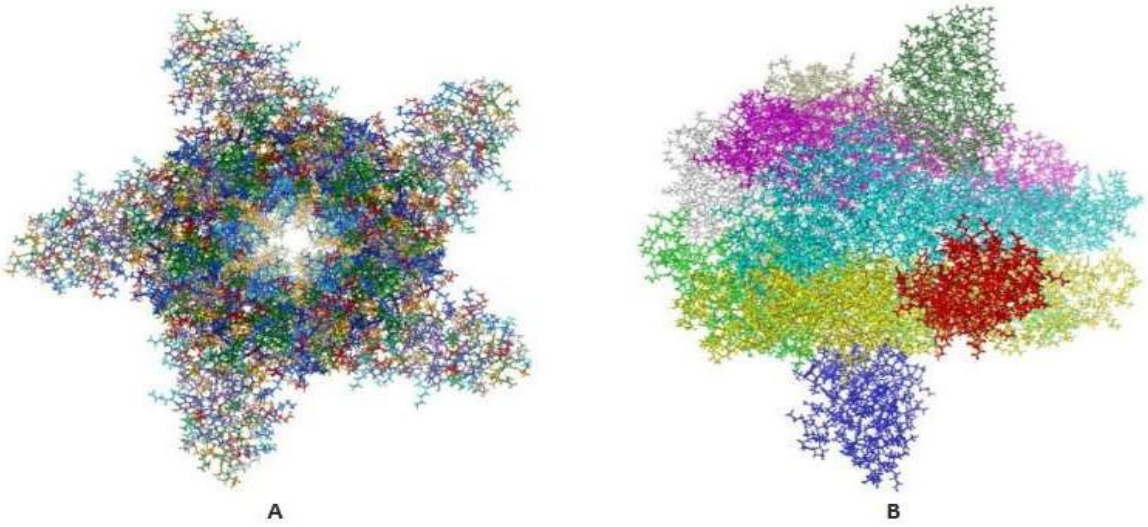


Figure 1 –Molecular structure of the GABAA receptor

Note: A is a horizontal position of the GABAA receptor in the plane; B is a vertical one

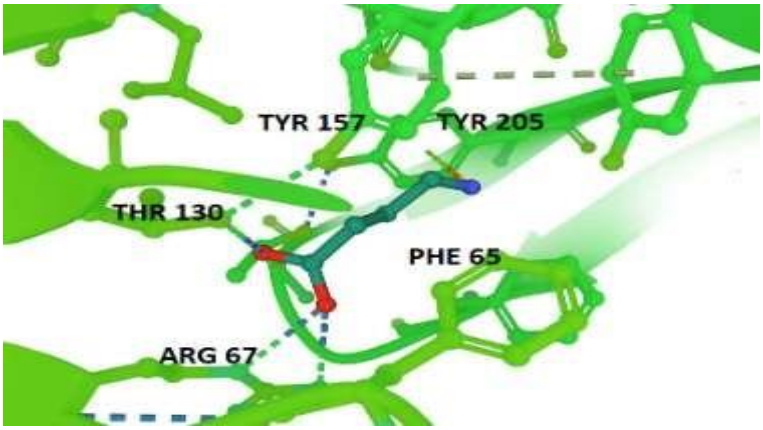


Figure 2 –Location of the gamma-amino butyric acid molecule in the active center of the GABAA receptor

The tertiary structure of each ionotropic channel subunit is represented by an order of 400 amino acid residues. The N-terminal extracellular domain of the subunit is joined to four transmembrane domains, designated M1, M2, M3, and M4, which are structurally organised as α-helices. Gamma-aminobutyric acid, benzodiazepines, barbiturates, and neuronal hormones are examples of different ligands that can be bound by the N-terminal domain of proteins[10]. It is believed that ligand binding and ion channel regulation are carried out via the transmembrane domains M2 and M3[11].

Ligand sketching: The structures were created as ".cdx" files in Chemdraw® Ultra 8.0 software before being converted to ".sdf" files.

Ligand Preparation: The LigPrep module was used to prepare small molecules for molecular docking studies. The module also establishes the conformation with the lowest energy of the ligands. A two-dimensional structure was changed into a three-dimensional one by it. The structures with the lowest energy were used for Qikprop analysis or molecular docking. For each input structure, the LigPrep module produced a variety of output structures using stereochemistry, protonation states, ring conformations, and tautomers. Depending on the ligands being treated, different structures were produced; nevertheless, the quantity of changed structures was constant. The input ligands' stereochemistry, degree of ionisation, and tautomericity were the main factors influencing the number of structures. The stereoisomerism created the possible conformers cis, trans, R, and S. By changing the pH (from 2.0 to 7.0), different structures were formed in the ionisation process. The method generated all possible tautomeric structures simultaneously.

Protein Preparation: The protein structure frequently has an impact on the quality of docking findings. Therefore, it is strongly recommended to select a receptor structure based on resolution. From the PDB, an unusual protein structure file (4EIY) containing heavy atoms, fluids, co-factors, and metal ions was obtained. When building protein structures, the terms "ionisation states" and "tautomeric states" were frequently used. Additionally, multiple bonds, formal charges, and covalent bonds between metal ions and proteins were correctly assigned. When creating the protein files, consideration was given to the direction of the water molecules.

Conflicts involving hydrogen bonds and steric interactions were also resolved during preparation. The Vander Waals scale factor was set to 1.0, and the charge cutoff was set at 0.25. Induced-fit docking (IFD) was used on each ligand, and the posture with the lowest score was validated.

The 3D structure of the protein was prepared using Schrödinger Maestro (v11.1)'s protein creation wizard. This management involved the assignment of bond orders, the use of the CCD database, the addition of hydrogens, the formation of zero-order bonds to metals and disulfide bonds, the conversion of selenomethionines into methionines, the removal of water molecules from heated groups that were higher than 5°A, and the use of Epik to maintain the heated state's pH at its default value of 7.02.0. The OPLS3 force field was used to execute restrained minimization, which converges heavy atoms to an RMSD of 0.30.

Grid Generation: Grid Generation is used to specify the location on the receptor where the ligands should bind. The grid is created by taking into account the binding site's geometry. If the crystal structure is known based on the ligand location, the grid can be identified. A review of the literature led to the identification of the precise binding site [126 A° 126 A° 126 A° (x, y, and z, correspondingly)]. Grid points were separated by 0.375 degrees.

Extra Precision Docking: The IFD was created using a structure-based drug design strategy, which calls for the creation of precise geometry ligands to dock with a biological target's specified structure. The hard state receptor's active site, enzyme, tube, and other parts are docked with the free-state ligands to determine a projected binding mode and gauge the strength of the fit.In receptor-based computational techniques, the attachment of a low-molecular-weight ligand to a macromolecular protein is relevant because the optimal connection with low energy values and likely steric conflicts is identified. Extra-precision (XP) docking mode is a sophisticated sampling mechanism that enhances the relationship between good poses and scores and removes false-positive outcomes from docking investigations.

The system will generate a variety of stances and, using the proprietary scoring method, identify the best ligand poses in terms of energy. Based on the idea that only active molecules would effectively interact with the protein.

The modified growth plan and anchor are the foundation of the XP sampling strategy. The typical procedure is to select the anchor components of a docked ligand (such as rings) and grow the molecule bond by bond from these anchor sites. Following that, scoring and minimizations are done in accordance with the scoring penalties.

The mutation rate was set at 0.02 and the crossover rate to 0.8. The maximum number of energy assessments, generations, and top survivors was one, with a total of 500000 allowable energy assessments, 1000 generations, and a maximum of 1000 top survivors per generation. Translations had a step size of 0.2, quaternions had a step size of 5.0°, and torsions had a step size of 5.0°. The external grid energy was set to 1000.0, the maximum binding energy was set to 0.0, the maximum number of retries was set to 10000, and 10 runs were carried out. The cluster tolerance was set to 0.5. The best postures were selected based on the Glide score obtained from the docking experiments.

Glide Score: After molecular docking, the Glide score or Gscore may be used to determine the best position. When determining G-score, the algorithm rewards favorable hydrophobic, hydrogen-bonding, and metal-ligation interactions while penalising steric conflicts. Normally, the following equation is used to determine G score:

Gscore is calculated as follows: 0.05*vdW + 0.15*Coul + Lipo + H-bond + Metal + Rewards + RotB + Site

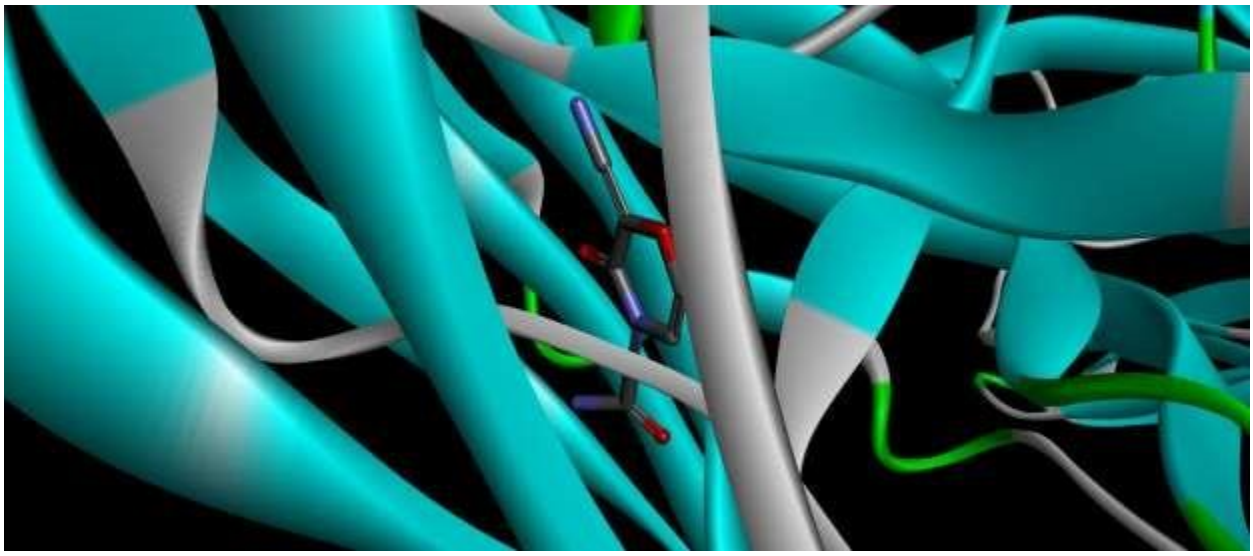


Figure 3: 3D structure of 2-(2-isopropyl-3-oxomorpholino)acetamide

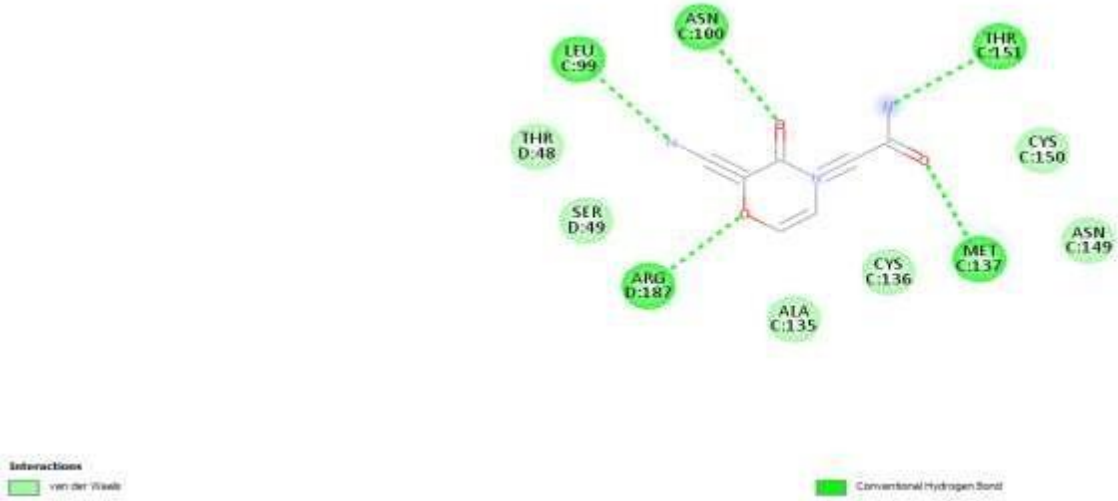


Figure 4: 2D structure of 2-(2-isopropyl-3-oxomorpholino)acetamide

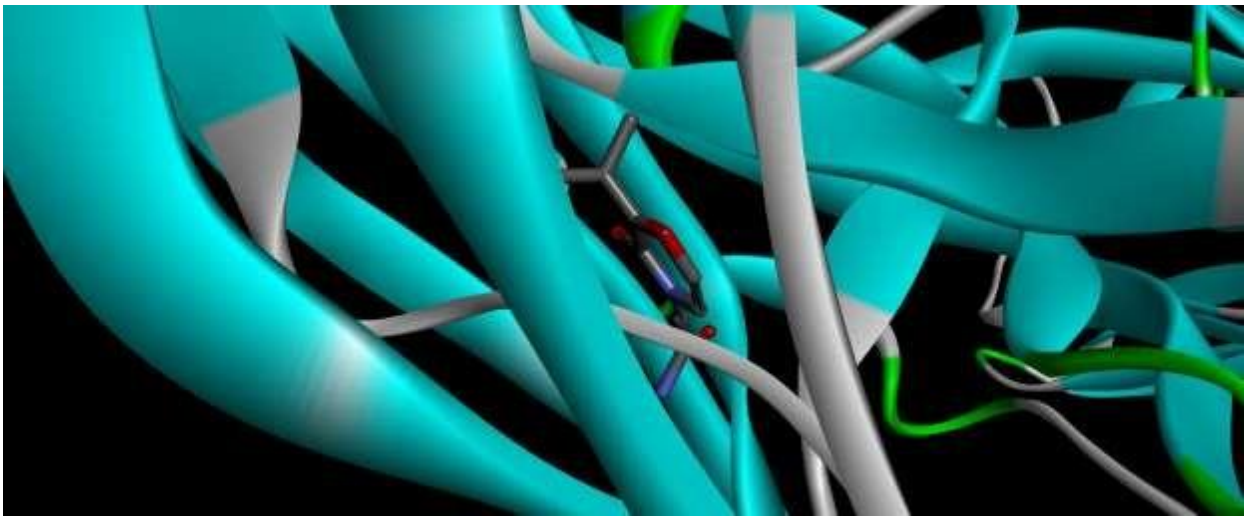


Figure 5: 3D structure of 2-(2-isopropyl-3-oxomorpholino)acetamide

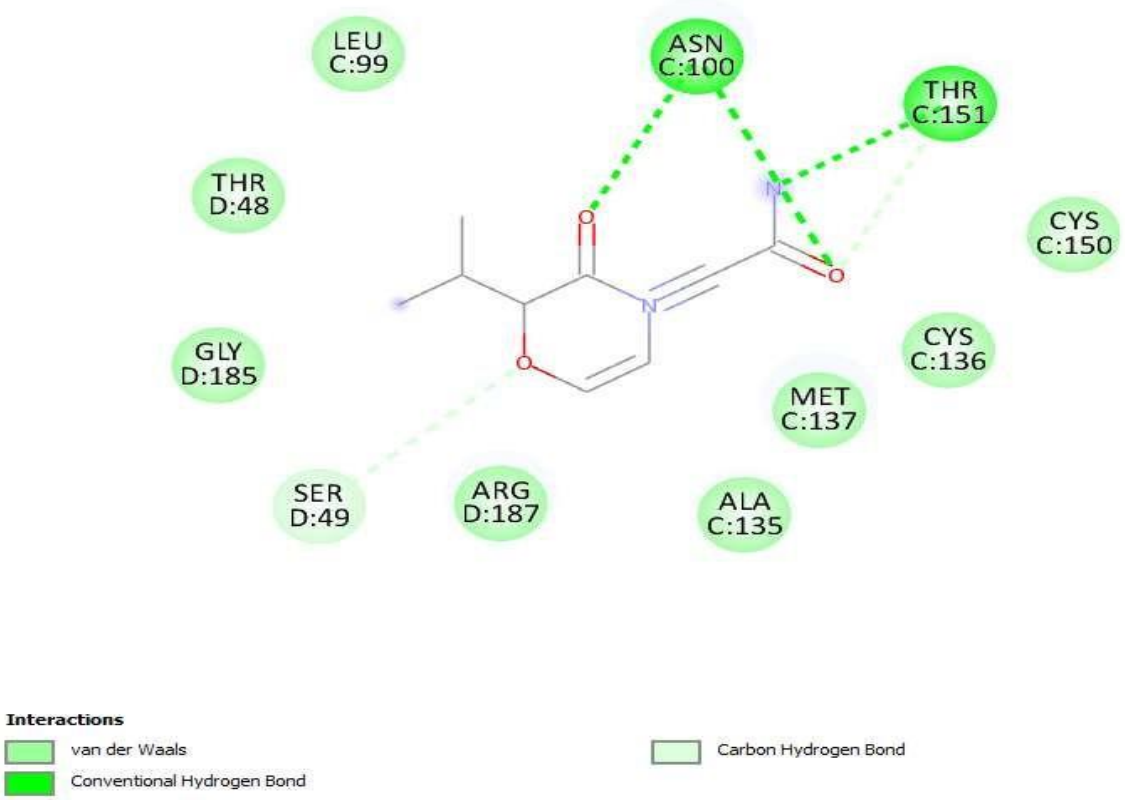


Figure 6: 2D structure of 2-(2-isopropyl-3-oxomorpholino)acetamide

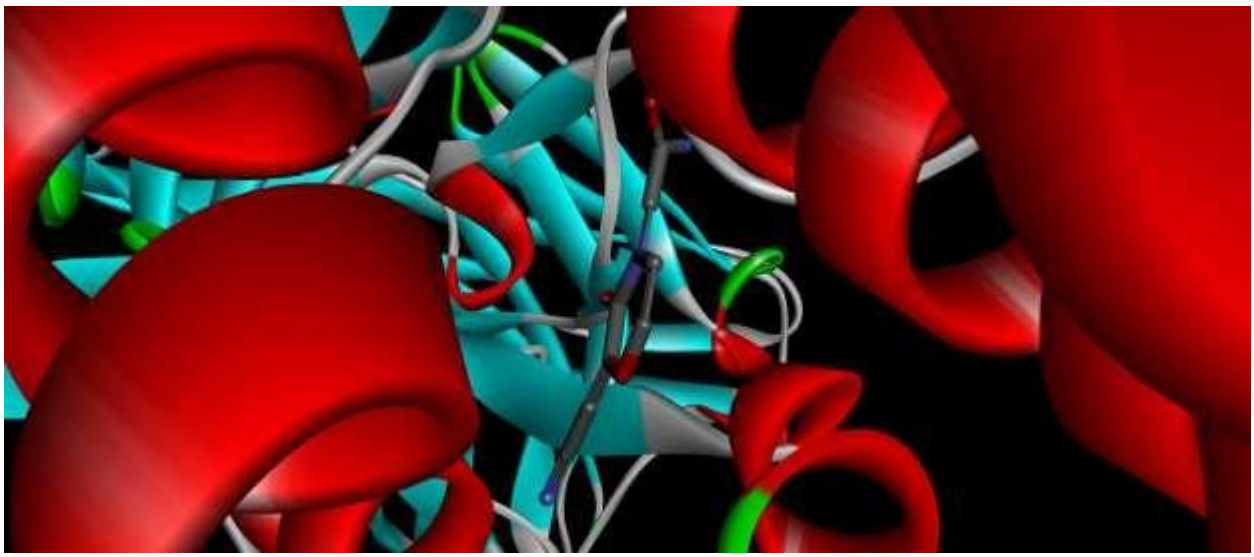


Figure 7: 3D structure of 2-(2-(2-aminoethyl)-3-oxomorpholino)acetamide

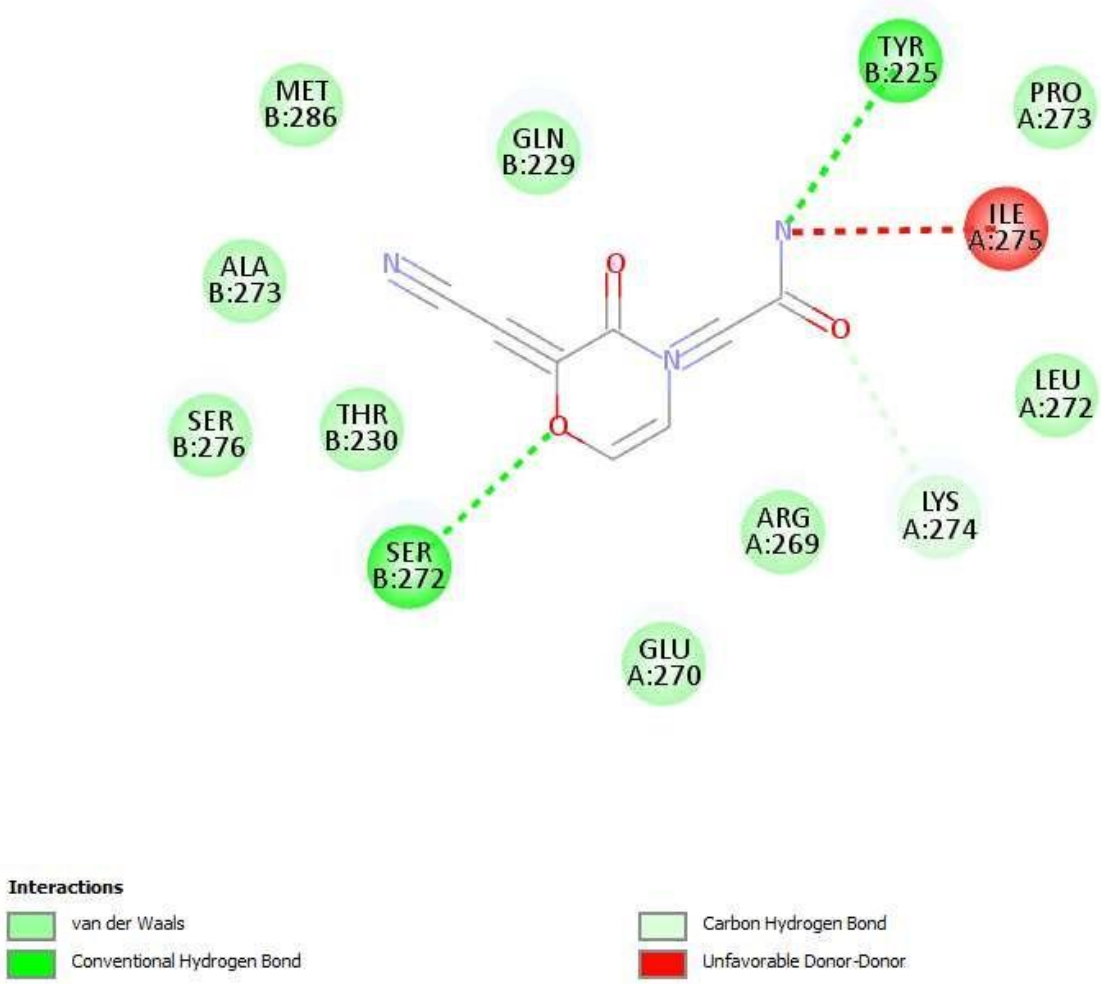


Figure 8: 2D structure of 2-(2-(2-aminoethyl)-3-oxomorpholino)acetamide

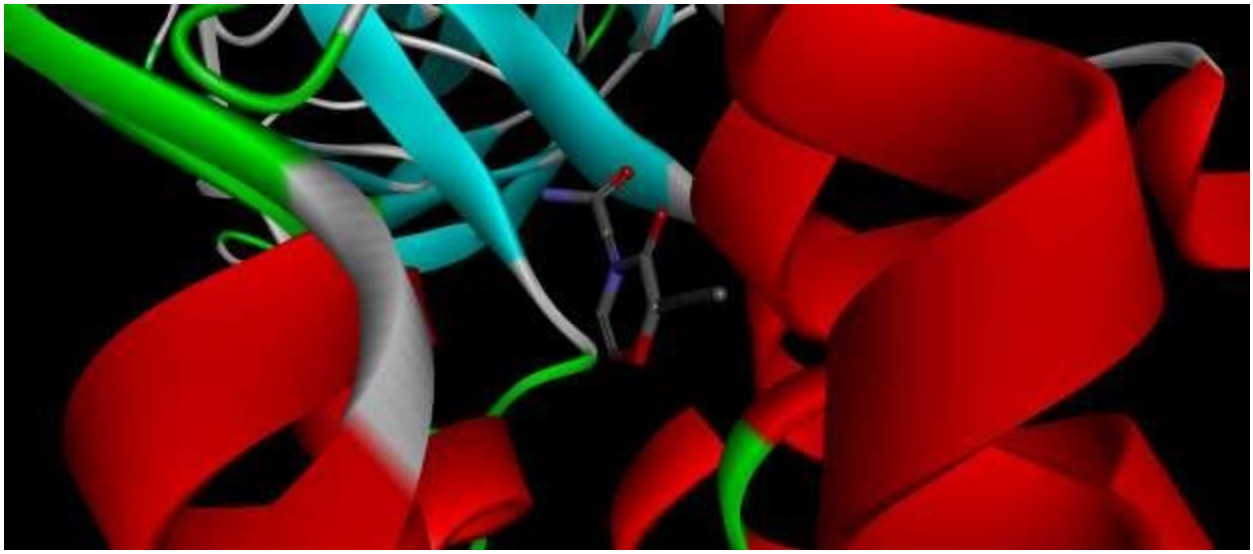


Figure 9: 3D structure of 2-(2-ethynyl-3-oxomorpholino)acetamide

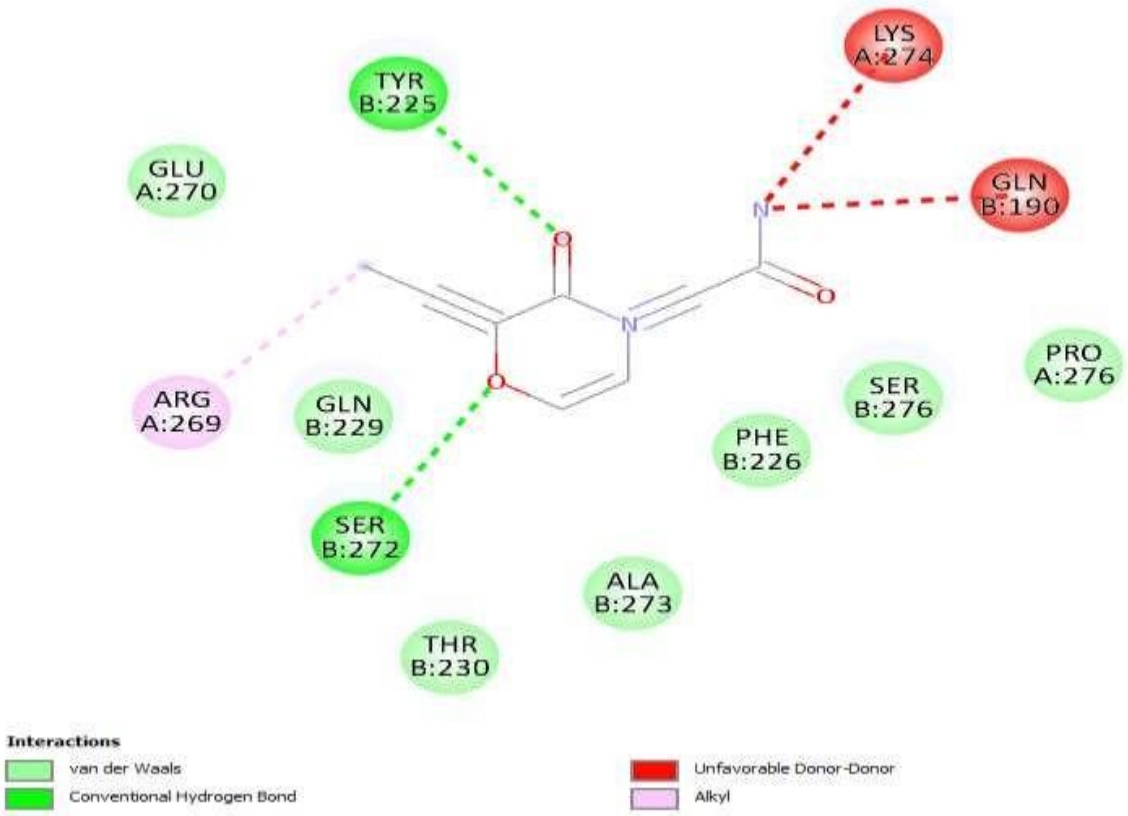
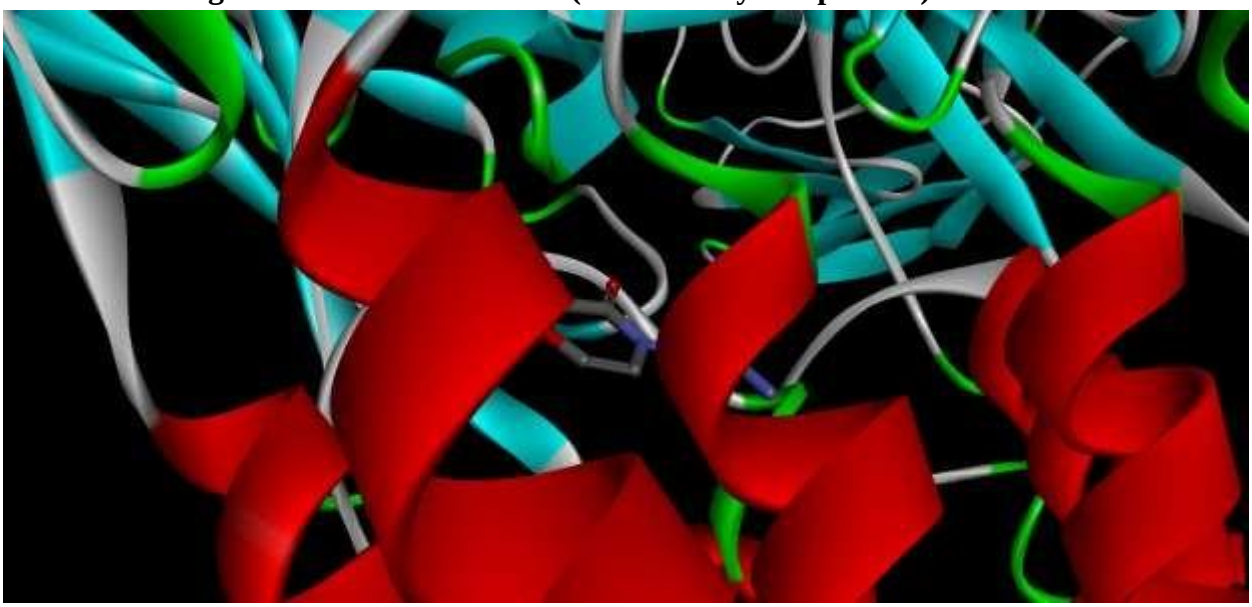


Figure 10: 2D structure of 2-(2-ethynyl-3-oxomorpholino)acetamide

Figure 11: 3D structure of 2-(3-oxo-2-vinylmorpholino)acetamide



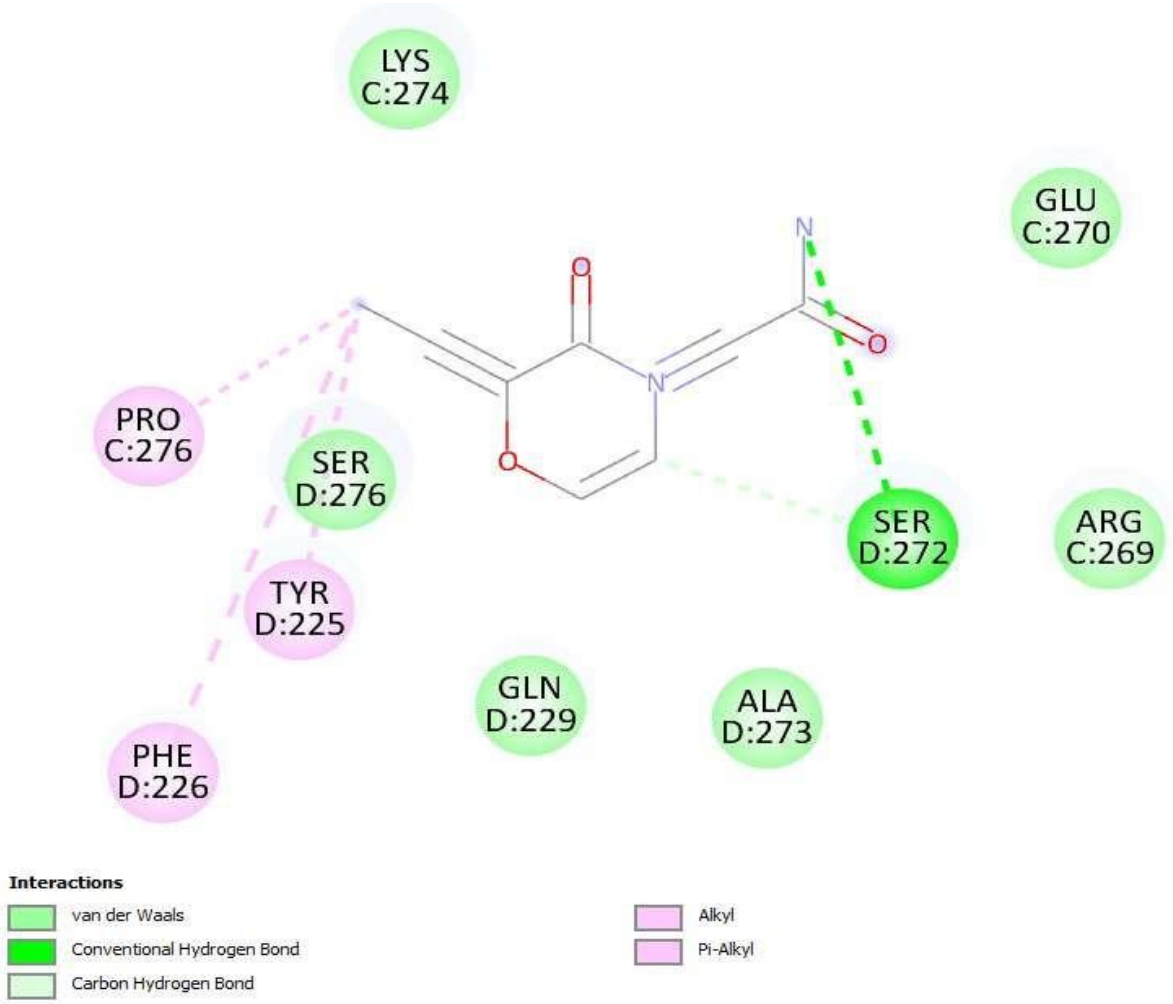
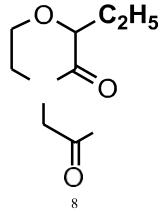
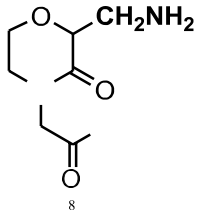
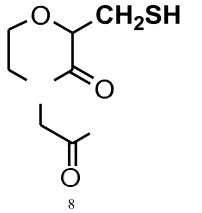
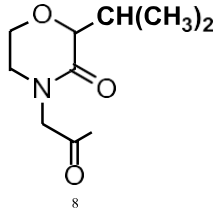
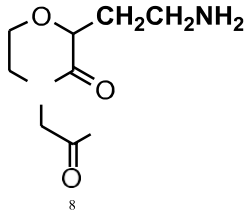
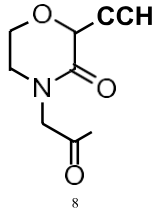
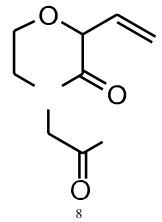
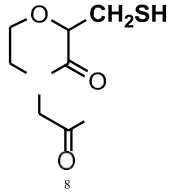
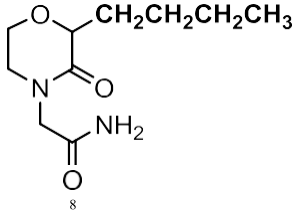
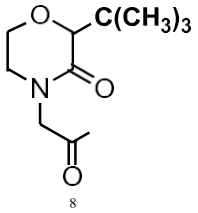
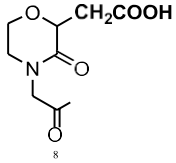
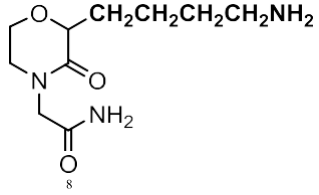


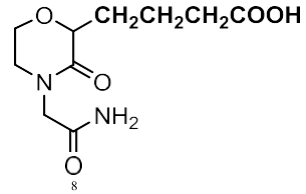
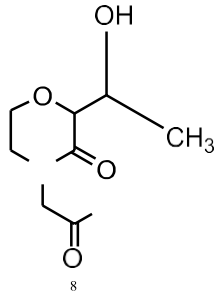
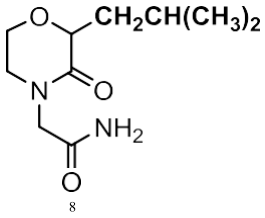
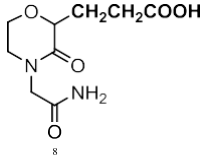
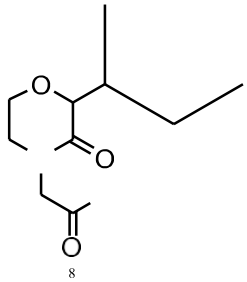
Figure 12: 2D structure of 2-(3-oxo-2-vinylmorpholino)acetamide

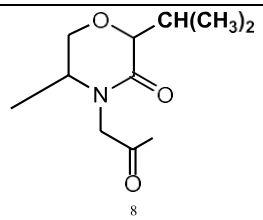
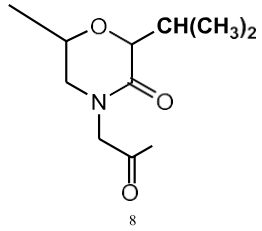
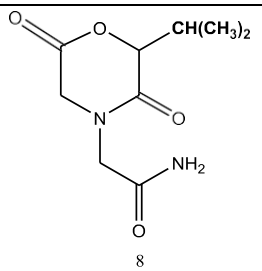
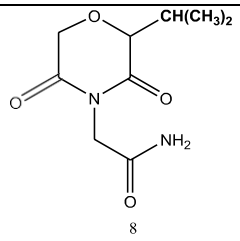
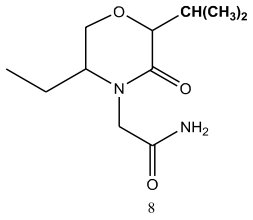
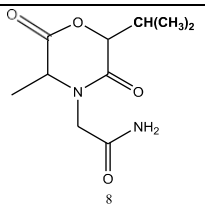
Table: 1 Binding affinity of Piracetam derivatives (N-(N-acyl-3-oxomorpholino) acetamide with gabaergic receptor (4COF)

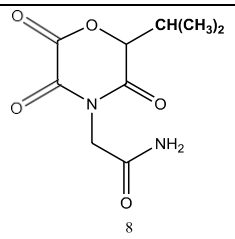
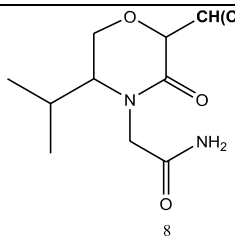
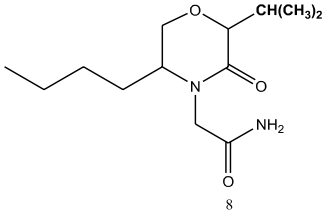
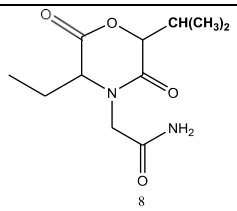
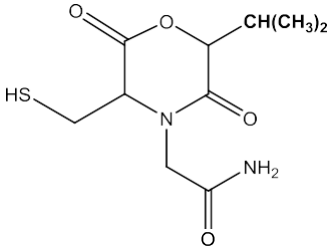
S.NO.	Derivatives	With GABAA (4COF) Docking
1.	 2-(2-ethyl-3-oxomorpholino)acetamide	

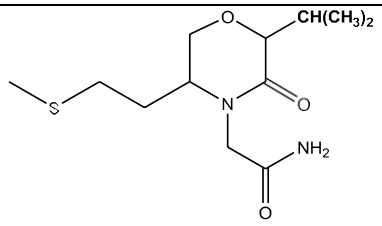
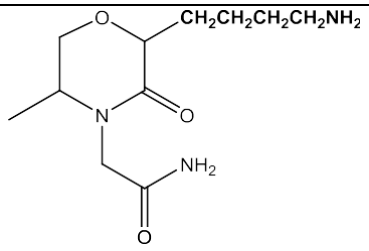
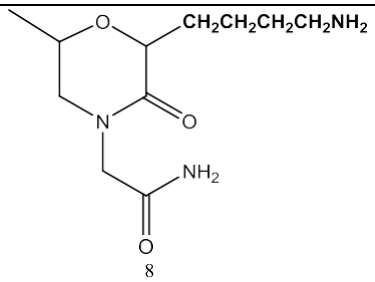
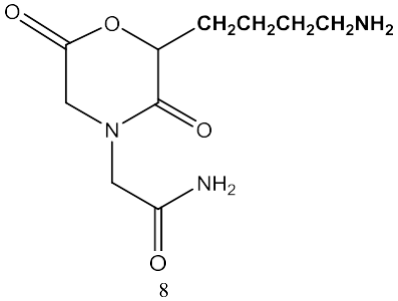
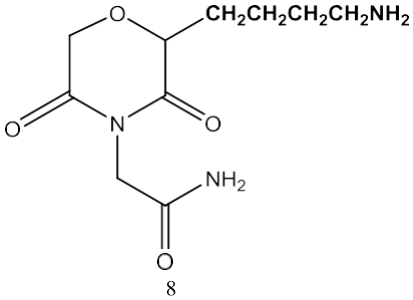
		-6.2
2.	 2-(2-(aminomethyl)-3-oxomorpholino)acetamide	**-5.6**
3.	 2-(2-(mercaptomethyl)-3-oxomorpholino)acetamide	**-6.4**
4.	 2-(2-isopropyl-3-oxomorpholino)acetamide	**-6**
5.	 2-(2-(2-aminoethyl)-3-oxomorpholino)acetamide	**-5**
6.	 2-(2-ethynyl-3-oxomorpholino)acetamide	**-4.9**

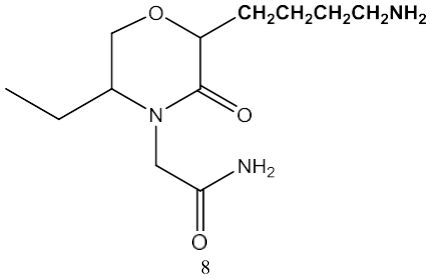
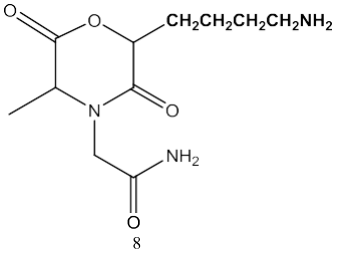
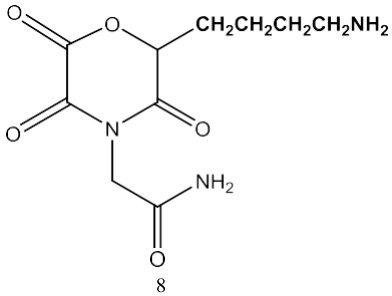
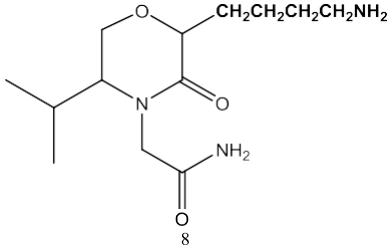
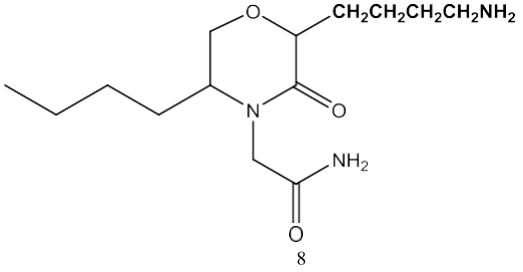
7.	 2-(3-oxo-2-vinylmorpholino)acetamide	**-5.7**
8.	 2-(2-(mercaptomethyl)-3-oxomorpholino)acetamide	**-5.1**
9.	 2-(2-butyl-3-oxomorpholino)acetamide	**-6.4**
10.	 2-(2-butyl-3-oxomorpholino)acetamide	**-6.8**
11.	 2-(4-(2-amino-2-oxoethyl)-3-oxomorpholin-2-yl)acetic acid	**-5.4**
12.	 2-(2-(4-aminobutyl)-3-oxomorpholino)acetamide	**-6**

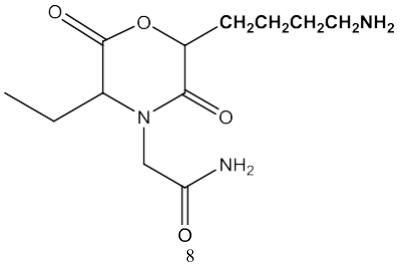
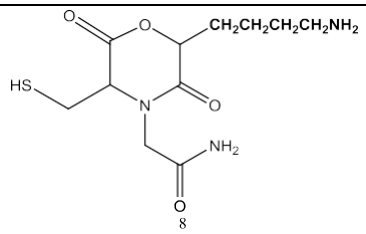
13.	 2-(2-(4-aminobutyl)-3-oxomorpholino)acetamide	**-6.2**
14.	 2-(2-methyl-3-oxomorpholino)acetamide	**-4.9**
15.	 2-(2-isobutyl-3-oxomorpholino)acetamide	**-5.8**
16.	 3-(4-(2-amino-2-oxoethyl)-3-oxomorpholin-2-yl)propanoic acid	**-5.7**
17.	 2-(2-(*sec*-butyl)-3-oxomorpholino)acetamide	**-6**

18.	 2-(2-isopropyl-5-methyl-3-oxomorpholino)acetamide	**-5.6**
19.	 2-(2-isopropyl-5-methyl-3-oxomorpholino)acetamide	**-6.5**
20.	 2-(2-isopropyl-3-oxomorpholino)acetamide	**-6.4**
21.	 2-(2-isopropyl-3,6-dioxomorpholino)acetamide	**-5.5**
22.	 2-(5-ethyl-2-isopropyl-3-oxomorpholino)acetamide	**-6.5**
23.	 2-(2-isopropyl-5-methyl-3,6-dioxomorpholino)acetamide	**-6.3**

24.	 2-(2-isopropyl-3,5,6-trioxomorpholino)acetamide	**-6.9**
25.	 2-(2,5-diisopropyl-3-oxomorpholino)acetamide	**-4.6**
26.	 2-(5-butyl-2-isopropyl-3-oxomorpholino)acetamide	**-6.9**
27.	 2-(3-ethyl-6-isopropyl-2,5-dioxomorpholino)acetamide	**-6.5**
28.	 2-(2-isopropyl-5-(mercaptomethyl)-3,6-dioxomorpholino)acetamide	**-6.6**

29.	 8 2-(2-isopropyl-5-(2-(methylthio)ethyl)-3-oxomorpholino)acetamide	**-6.2**
30.	 8 2-(2-(4-aminobutyl)-5-methyl-3-oxomorpholino)acetamide	**-6.2**
31.	 8 2-(2-(4-aminobutyl)-6-methyl-3-oxomorpholino)acetamide	**-6.6**
32.	 8 2-(2-(4-aminobutyl)-3,6-dioxomorpholino)acetamide	**-6**
33.	 8 2-(2-(4-aminobutyl)-3,5-dioxomorpholino)acetamide	**-6.1**

34.	 2-(2-(4-aminobutyl)-5-ethyl-3-oxomorpholino)acetamide	**-6.2**
35.	 2-(2-(4-aminobutyl)-5-methyl-3,6-dioxomorpholino)acetamide	**-5.3**
36.	 2-(2-(4-aminobutyl)-3,5,6-trioxomorpholino)acetamide	**-5.7**
37.	 2-(2-(4-aminobutyl)-5-isopropyl-3-oxomorpholino)acetamide	**-4.9**
38.	 2-(2-(4-aminobutyl)-5-butyl-3-oxomorpholino)acetamide	**-6**

39.	 2-(2-(4-aminobutyl)-5-ethyl-3,6-dioxomorpholino)acetamide	**-6.6**
40.	 2-(2-(4-aminobutyl)-5-(mercaptomethyl)-3,6-dioxomorpholino)acetamide	**-5**

RESULTS AND DISCUSSION:

The binding energies of all the proposed structures are given in table 1. This study was done to evaluate the novel proposed derivatives for the treatment of treat peripheral neuropathy by observing the receptor interactions. The 2D and 3D interactions of few derivatives are given from figure 3 to figure 12. The planning and creation of novel medications heavily relies on molecular docking. It accurately predicts a native molecule's experimental binding mechanism and affinities within the drug target's binding site. Glide XP docking and induced fit docking (IFD) were used to investigate the molecular underpinnings of contact and conformation of hit compounds inside the binding pose of our protein target. Schrödinger Maestro software is used to prepare the prospective ligands' 3D structures. The OPLS-2005 force field module was used to minimize all ligands Using ESP atomic charges from the OPLS2005 force field, the electrostatic potential values were displayed on the surface of the ligands. Induced fit docking approach, which uses Glide and refinement module, was further used for precise prediction. It calculates the binding energy of ligand with receptor based on concurrent structural changes of the ligand within the binding pocket of the protein target. The receptor is held stiff when the ligand is docked into its binding site in the Glide docking algorithm (HTVS, XP, and SP). It is a common misconception that a receptor's stiffness might cause a docking score to be invalid since proteins undergo certain motions (side-chain or backbone) when they attach to tiny ligands. However, these structural alterations provide the receptor the ability to alter its binding site such that it more closely resembles the form and binding mode of the ligand. Calculating the binding free energy of protein-ligand complexes served to validate the docking studies of the lead compounds. The validity of the MM-GBSA (Molecular Mechanism Surface Area Continuum Salvation) post docking approach for determining the protein-ligand complex's affinities has been established by two separate investigations. Total of 40 proposed synthesized derivatives docking studies was executed and out of which only 20 derivatives (2,4,5,6,7,8,11,12,14,15,16,17,18,21,25,35,36,37,38 and 40) was found to have low

binding energy and are efficiently docked. The proposed synthesized derivatives were also found to have lower binding energy than the established drug used for the treatment of peripheral neuropathy example amitriptyline, duloxetine, pregabalin and gabapentin and hence it opens new avenues for the research in this field.

Conflict of interest

Authors declare no conflict of interests.

Conclusion

To assess potential medicines against Peripheral neuropathy molecular docking studies, were carried out using 40 proposed piracetam derivatives with their structures drawn from the chemdraw software. 20 top docked compounds were found efficiently docked through analysis, and only this compound synthesis is considered. Docking score of all the synthesized compounds was identified. This work makes it easier to start the process of finding novel derivatives against peripheral neuropathy. As a result, we conducted an in-silico analysis on potential derivatives to determine whether they could treat peripheral neuropathy.

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