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Original Article

# Recent Advance Docking Sites of Novel Phenothiazine's Derivative on G Protein-Coupled Receptors (GPCRs) against Depression with Monoamine Oxidase (PDB ID: 2BXR)

**Sanket Keshav Tambe*, Rohit Jaysing Bhor, Shubham Balasaheb Mhaske, Pruthviraj Vijay Kute, Pratik Vijay Malvade, Jyoti Ramkisan Bhagat, Poonam Prakash Waykar, Vinod Rajendra Tawate, Tejaswini Bharat More, Neha Shyam Bora, Vaijanti Ashok Medge, Akanksha Kailas Nirmal**

Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy Pravaranagar, Rahata, Ahmednagar, Maharashtra, INDIA.

## ABSTRACT

**Background:** GPCRs are among the most effective therapeutic target families. They have undergone a transition from ligand screening at random to knowledge-driven drug design. We are seeing first-hand the enormous strides lately achieved in our comprehension of their structure-function linkages, which have enabled medication development at a never-before-seen rate. **Materials and Methods:** By merging two or more bioactive scaffold pharmacophores, drugs with increased effectiveness have been created by the molecular hybridization technique. In this case, the hybridization of different relevant pharmacophores with derivatives of phenothiazine has produced relevant compounds that interact with one or more targets and have a variety of biological functions. The phenothiazine system, which is often found in compounds with antipsychotic, antihistaminic and antimuscarinic properties, has actually been linked to a variety of activities that make the creation of novel medications or drug candidates based on this tricyclic system a potential strategy. **Results:** The derivatives A1, A8 and A18 were found to be the most promising options because they showed the highest binding energies and a wide range of interaction types, such as pi interactions and hydrogen bonds, over various distances. A1, A8 and A18 in particular showed the highest binding energy. Superior binding affinities and a range of interaction mechanisms with the target protein were demonstrated by these derivatives, indicating that they have considerable potential as lead compounds for the development of therapeutic medications in the future. **Conclusion:** The creation of phenothiazine hybrids is summarised in the current study report. Numerous derivatives with strong binding affinities and distinctive interaction patterns with the target protein were found, according to the molecular docking analysis. The creation of phenothiazine hybrids and their biological activity is summarised in the current study report. Numerous derivatives with strong binding affinities and distinctive interaction patterns with the target protein were found, according to the molecular docking analysis.

**Keywords:** G Protein-Coupled Receptors (GPCRs), MAO A, MAO B, Phenothiazine's.

**Correspondence:**
**Mr. Sanket Keshav Tambe**
Department of Pharmaceutical Chemistry, Pravara Rural College of Pharmacy Pravaranagar, Rahata, Ahmednagar, Maharashtra, INDIA.
Email: sanket.tambe@pravara.in

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## INTRODUCTION

The depression drugs available today either don't work to promote healing or have unpleasant side effects.[1] Thus, there is still a significant unmet clinical need. In the realm of medical chemistry, heterocyclic molecules containing nitrogen and sulphur play a major role. The primary factors in the creation of innovative antidepressants were more obvious viability, nonappearance of side effects, lack of toxicity in over measures and earlier onset of action.[2] According to WHO estimates, depression should have become the second most terrible illness globally over the next 10 years; now, one in five women and one in twelve men suffer from depression.[3] According to available data, antidepressant medications used to treat major depressive disorders are thought to function on the central monoaminergic frameworks, namely the synaptic neurotransmissions of Noradrenaline (NA) and serotonin (5-hydroxytryptamine, or 5-HT).[4] The process of finding and developing new drugs involves a number of extremely difficult and costly steps.[5] Including choosing the right condition, identifying and validating targets, finding and optimising leads.[6] And conducting preclinical and clinical trials. It has become necessary to incorporate the idea of drug-likeness at an early stage of drug discovery since an investigation into abandoned projects revealed that bad pharmacokinetic profiles and ADMET characteristics were the main reason of drug failure

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in the development stage.[7] Early drug discovery stages depend heavily on computational approaches, which are also predicted to reduce toxicity risk. Phenothiazines have been widely used in medicinal chemistry.[8] And it has been shown that their derivatives contain a variety of biological activities, such as antipsychotic and antidepressant qualities. Examining a protein's activity mechanism by confirming that its small molecule ligands are bound in the right conformation forms the foundation for drug creation.[9] It is important not only for first hit compound screening but also for computational study of lead compound binding patterns. Numerous variables, including genetic, behavioural and environmental ones, combine to produce the observable phenotype in complex disorders.[10] In actuality, many diseases have intricate aetiologies and pathsophysiologies, including cancer, Alzheimer's disease, microbial infections, obesity and inflammatory disorders. ADME or IDME describes the pharmacokinetics of the motes inside the body of an organism. Swiss ADME (http://www.swissadme.ch/) links novel derivations of indole pharmacokinetic packages *in silico* using a method similar to this one.[11] We research the Lipinski rule. The motes become orally inactive with two or more violations of Lipinski's rule of five. It consists of electronic dispersion, hydrophobicity and the existence of various pharmacophore characteristics. To predict the list commerce of the derivatives of generated phenothiazine, docking with the selected protein was carried out. We use the Auto dock Vina programme to explore molecular docking.[12] After downloading the protein from PDB, undesirable chains, cofactors, water molecules and heterotittles are eliminated and the protein is also prepared for sale.[13] Both 2 D and 3 D software are used to optimise the intended phenothiazine's derivations. The nucleus derivations of the intended phenothiazine are provided below Figure 1.

## MATERIALS AND METHODS

### Hardware and Software

It was a pre-owned computer running Windows 10 64-bit on an Intel® CoreTM i9-10900 processor clocked at 64.00 GB of RAM at 2.80 GHz. Swiss Target Prediction (STP; www.swisstargetprediction.ch) software is another option. Chem Draw Professional 17.1, Chem3D 17.1, Discovery Studio® (www.3ds.com/), AutoDockTools® (http://autodock.scripps.edu/resources/adt) 22 and AutoDock Vina23.

Receptors The molecular target, G protein-coupled receptors bound to SR348, was obtained as PDB code 6ZWP25 from the protein data bank (https://www.rcsb.org/).

## RESULTS

### Chemistry

Designed phenothiazine's nucleus and Synthetic scheme of phenothiazine's was given in Figures 1 and 2 respectively which describes the fictitious approach for avoiding phenothiazine use.[14] The preparation of phenothiazine derivatives involved refluxing several aniline derivatives with 2-chlorobenzoic acid in ethanol. It was prepared by refluxing 2-chlorobenzoic acid and various aniline derivatives. 2-(phenylamino)benzoic acid converted into 10*H*-phenothiazine-1-carboxylic acid and then ethyl 10*H*-phenothiazine-1-carboxylate and (hydrazinyloxy)(10*H*-phenothiazin-1-yl)methanone by adding ethyl alcohol and hydrazine hydrate respectively.[15] cyclization of phenothiazine compounds using acids that have been substituted (A1-A20) in the presence of a catalyst and different solvents. Scheme: Synthetic pathways for synthesising the required derivatives of phenothiazine. The important intermediate of phenothiazine, the sulfonyl chloride derivative, was obtained by cyclizing ethyl 10H-phenothiazine-1-carboxylate acid. The active amino residues, bond length, bond category, bond type, ligand energies, and docking scores were given in Table 3.

### Drug likeness analysis

For the novel compounds, the phenothiazine's anti-cancer activity was stated in Table 1. Successful novel treatments are often defined as substances or drugs having high biological activity at low doses, low toxicity, or minimal side effects.[16] There are several studies on the application of the nucleus of heterocyclic phenothiazine in the management of bacterial and fungal illnesses. Phenothiazine chemicals that are more effective against fungi are being developed. It functions as an inhibitor of the synthesis of ergosterol. A list of every suggested chemical may be seen in Figure 3. It was shown that the suggested compound exhibited minimal risk of adverse drug responses while demonstrating efficacy as an ergo sterol biosynthesis inhibitor.

## DISCUSSION

### Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET)

The increasing number of crystal structures of these proteins has greatly aided in the development of new drugs and improved our comprehension of the mechanisms of action of these proteins. Drug development benefits greatly from a number of computational techniques, including molecular docking, molecular dynamics

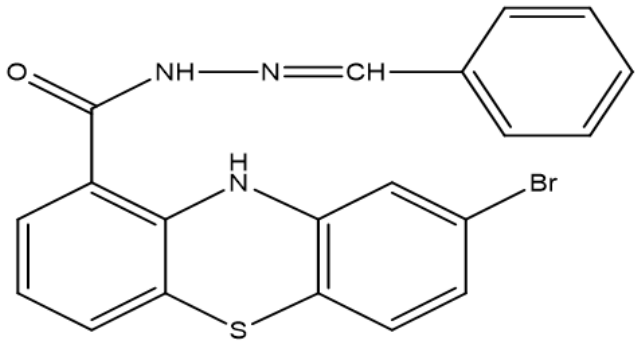
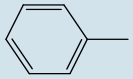
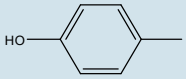
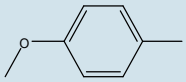
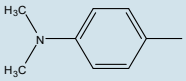
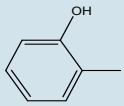
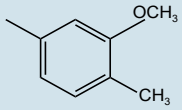
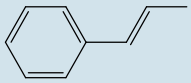
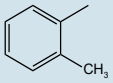
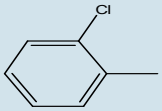
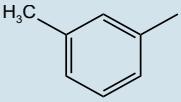
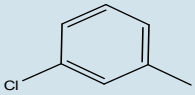
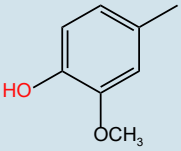
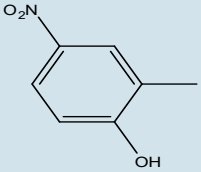
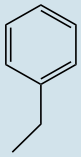
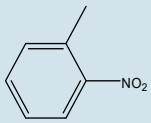
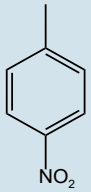
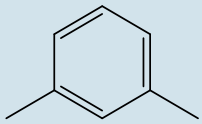
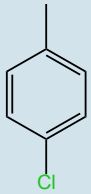
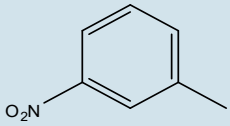
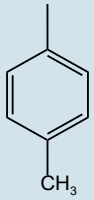



**Figure 1:** Designed phenothiazine's nucleus.

**Table 1: Derivatives of designed compound of phenothiazine's.**

| Comp. Code | Ar | R | Comp. Code | Ar | R |
|---|---|---|---|---|---|
| $A_1$ |  | $NO_2$ | $A_{11}$ |  | $NO_2$ |
| $A_2$ |  | Cl | $A_{12}$ |  | $NO_2$ |
| $A_3$ |  | Cl | $A_{13}$ |  | Br |
| $A_4$ |  | Cl | $A_{14}$ |  | Br |
| $A_5$ |  | $NO_2$ | $A_{15}$ |  | Cl |
| $A_6$ |  | $NO_2$ | $A_{16}$ |  | $NO_2$ |
| A7 |  | Cl | $A_{17}$ |  | Cl |
| $A_8$ |  | Br | $A_{18}$ |  | Cl |
| $A_9$ |  | Cl | $A_{19}$ |  | Br |
| $A_{10}$ |  | $NO_2$ | $A_{20}$ |  | Cl |

## Synthetic scheme 1:

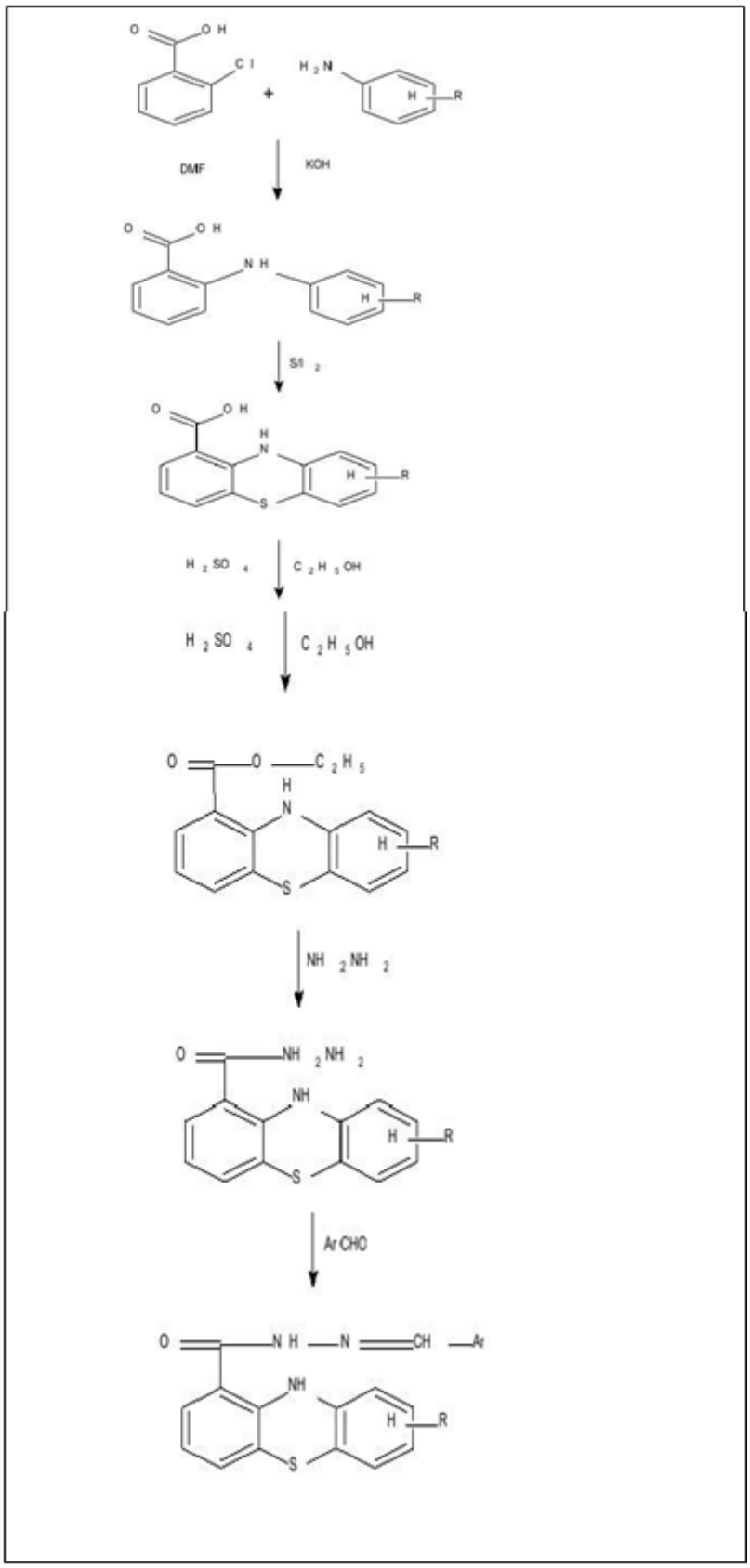



**Figure 2:** Synthetic scheme of phenothiazine's.

**Table 2: *In silico* ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties of phenothiazine's.**

| Molecule Code | Formula | MW | Rotatable bonds | #H-bond acceptor | #H-bond donors | iLOGP | GI absorption | Lipinski #violation | Bioavailability score |
|---|---|---|---|---|---|---|---|---|---|
| A1 | $C_{20}H_{14}BrN_3OS$ | 424.31 | 4 | 2 | 2 | 2.96 | High | 1 | 0.55 |
| A2 | $C_{21}H_{16}BrN_3O_2S$ | 454.34 | 5 | 3 | 2 | 3.47 | High | 1 | 0.55 |
| A3 | $C_{20}H_{14}BrN_3O_2S$ | 440.31 | 4 | 3 | 3 | 2.93 | High | 0 | 0.55 |
| A4 | $C_{22}H_{16}BrN_3OS$ | 450.35 | 5 | 2 | 2 | 3.29 | High | 1 | 0.55 |
| A5 | $C_{20}H_{13}Br_2N_3OS$ | 503.21 | 4 | 2 | 2 | 3.31 | High | 2 | 0.17 |
| A6 | $C_{20}H_{13}Br_2N_3OS$ | 503.21 | 4 | 2 | 2 | 3.63 | High | 2 | 0.17 |
| A7 | $C_{20}H_{15}BrN_4O_4S$ | 487.33 | 5 | 5 | 3 | 0 | Low | 0 | 0.55 |
| A9 | $C_{21}H_{14}BrN_3O_2S$ | 452.32 | 5 | 3 | 2 | 3.08 | High | 0 | 0.55 |
| A10 | $C_{20}H_{15}BrN_4O_3S$ | 471.33 | 5 | 4 | 2 | 0 | High | 0 | 0.55 |
| A11 | $C_{20}H_{14}BrN_3O_2S$ | 440.31 | 4 | 3 | 3 | 2.95 | High | 0 | 0.55 |
| A12 | $C_{22}H_{19}BrN_4OS$ | 467.38 | 5 | 2 | 2 | 3.3 | High | 1 | 0.55 |
| A13 | $C_{22}H_{18}BrN_3O_2S$ | 468.37 | 5 | 3 | 2 | 3.76 | High | 1 | 0.55 |
| A14 | $C_{21}H_{16}BrN_3OS$ | 438.34 | 4 | 2 | 2 | 3.32 | High | 1 | 0.55 |
| A15 | $C_{21}H_{16}BrN_3OS$ | 438.34 | 4 | 2 | 2 | 3.59 | High | 1 | 0.55 |
| A16 | $C_{21}H_{16}BrN_3O_3S$ | 470.34 | 5 | 4 | 3 | 3.42 | High | 0 | 0.55 |
| A17 | $C_{21}H_{16}BrN_3OS$ | 438.34 | 5 | 2 | 2 | 3.22 | High | 1 | 0.55 |
| A18 | $C_{20}H_{14}BrN_4O_3S$ | 470.32 | 5 | 4 | 2 | 0 | High | 0 | 0.55 |
| A19 | $C_{20}H_{13}Br_2N_3OS$ | 503.21 | 4 | 2 | 2 | 3.58 | High | 2 | 0.17 |
| A20 | $C_{21}H_{16}BrN_3OS$ | 438.34 | 4 | 2 | 2 | 3.6 | High | 1 | 0.55 |

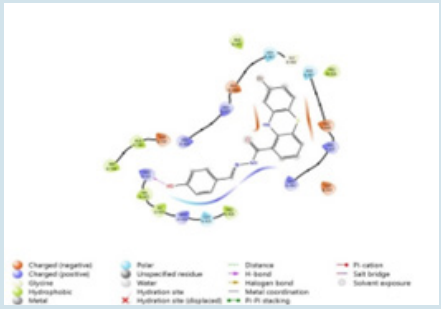
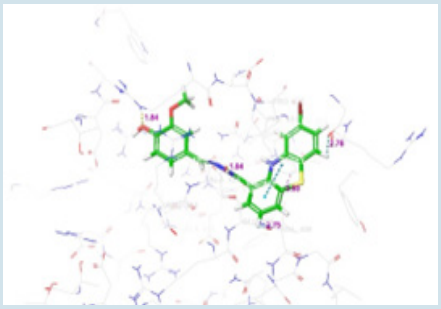
**Table 3: The active amino residues, bond length, bond category, bond type, ligand energies and docking scores.**

| Active Amino Acid | Bond length | Bond type | Hydrogen Bond | Van Der Waals Energy | Ligand Energy | Docking score |
|---|---|---|---|---|---|---|
| A1 | | | | | | |
| ARGA421 | 1.84 | Hydrogen Bond | -0.376748902 | -40.45968628 | 61.906863 | -5.288915392 |
| GLUB458 | 1.84 | Halogen Bond | | | | |
| GLUA458 | 2.75 | Halogen Bond | | | | |
| ARGA424 | 2.78 | Hydrogen Bond | | | | |
| A2 | | | | | | |
| ASPB141 | 4.64 | Hydrogen Bond | -0.161353705 | -37.20854568 | 63.880476 | -1.773097124 |
| A3 | | | | | | |
| ARGB424 | 1.99 | Hydrogen Bond | 0 | -45.43943787 | 70.740336 | -5.401243556 |
| GLUB458 | 1.71 | Hydrogen Bond | | | | |
| A4 | | | | | | |
| ASPA414 | 1.96 | Hydrogen Bond | -0.32 | -42.82445526 | 57.407798 | -5.614208154 |
| PROA426 | 2.65 | Hydrophobic | | | | |
| GLUB458 | 2.40 | Hydrogen Bond | | | | |
| A5 | | | | | | |
| GLNB425 | 2.29 | H Hydrogen Bond | -0.16 | -43.68091965 | 62.929513 | -5.228596886 |
| A6 | | | | | | |

| Active Amino Acid | Bond length | Bond type | Hydrogen Bond | Van Der Waals Energy | Ligand Energy | Docking score |
|---|---|---|---|---|---|---|
| GLNA425 | 2.11 | Hydrophobic | -0.24354132 | -42.84318924 | 55.560202 | -5.602788164 |
| GLUA458 | 2.42 | Halogen Bond | | | | |
| GLUB458 | 2.36 | Halogen Bond | | | | |
| A7 | | | | | | |
| ARGA424 | 2.12 | Hydrogen Bond | -0.16 | -42.44791794 | 62.889949 | -5.363857918 |
| A8 | | | | | | |
| ARGB424 | 3.48 | Hydrogen Bond | 0 | -40.71807098 | 63.005712 | -4.616632428 |
| ASNA461 | 2.27 | Hydrogen Bond | | | | |
| GLYB428 | 3.67 | Halogen Bond | | | | |
| ASNB461 | 3.29 | Halogen Bond | | | | |
| A9 | | | | | | |
| ARGA421 | 2.13 | Hydrophobic | -0.16 | -41.3778038 | 64.261883 | -4.918377203 |
| A10 | | | | | | |
| ARGA429 | 3.45 | Halogen Bond | -0.276391912 | -41.12136078 | 67.583437 | -4.980830702 |
| ASPA141 | 2.75 | Hydrogen Bond | | | | |
| A11 | | | | | | |
| ARGA424 | 2.14 | Hydrophobic | -0.392640171 | -41.01231766 | 67.691654 | -5.465086107 |
| A12 | | | | | | |
| ARGB424 | 3.35 | Hydrogen Bond | -0.054773303 | -43.37104797 | 62.277097 | -5.095658522 |
| GLUA458 | 3.40 | Halogen Bond | | | | |
| A13 | | | | | | |
| GLUA458 | 3.46 | Halogen Bond | 0 | -44.63956833 | 77.267631 | -5.158781647 |
| ARGA424 | 2.31 | Hydrogen Bond | | | | |
| GLUB458 | 1.91 | Halogen Bond | | | | |
| A14 | | | | | | |
| GLNB425 | 1.89 | Hydrogen Bond | 0 | -47.21842575 | 68.389809 | -5.289796014 |
| ARGA457 | 2.29 | Hydrophobic | | | | |
| A15 | | | | | | |
| GLNB425 | 2.41 | Hydrogen Bond | 0 | -43.95074463 | 63.299668 | -5.523633753 |
| GLU458 | 2.66 | Halogen Bond | | | | |
| A16 | | | | | | |
| LYSA199 | 2.66 | Halogen Bond | 0 | -47.21842575 | 68.389809 | -5.289796014 |
| ASPA141 | 2.11 | Hydrogen Bond | | | | |
| A17 | | | | | | |
| GLNA425 | 2.46 | Hydrogen Bond | -0.32 | -40.08344269 | . | -6.123262202 |
| ARGB457 | 2.03 | Hydrogen Bond | | | | |
| ARGA421 | 2.43 | Hydrogen Bond | | | | |
| A18 | | | | | | |
| ASPA141 | 2.63 | Halogen Bond | 0 | -45.83961487 | 85.206754 | -4.946783785 |
| ARGA424 | 2.62 | Halogen Bond | | | | |
| GLUB458 | 2.26 | Halogen Bond | | | | |

| Active Amino Acid | Bond length | Bond type | Hydrogen Bond | Van Der Waals Energy | Ligand Energy | Docking score |
|---|---|---|---|---|---|---|
| A19 | | | | | | |
| GLUB458 | 4.14 | Hydrogen Bond | 0 | -45.12250137 | 67.251696 | -4.757187342 |
| A20 | | | | | | |
| ASPB141 | 2.70 | Halogen Bond | 0 | -42.22762299 | 65.205399 | -4.871783081 |

**Table 4: 2 D and 3 D Structure of designed Phenothiazine's derivatives.**

| 3D-docking poses | 2D-docking poses |
|---|---|
| A1 | |
|  |  |
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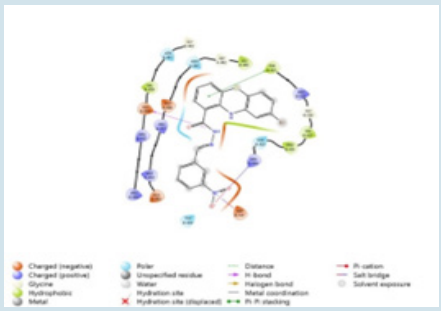
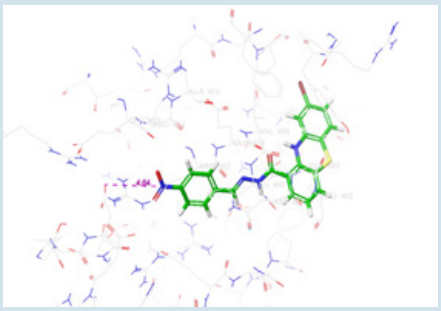
|  |  |
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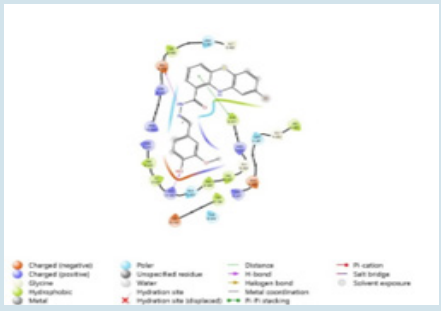
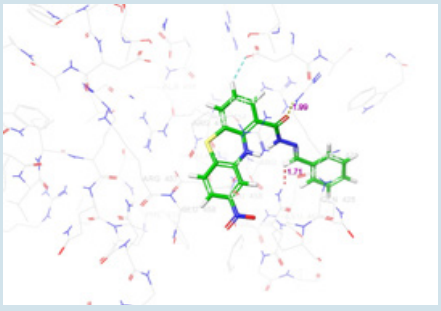
|  |  |
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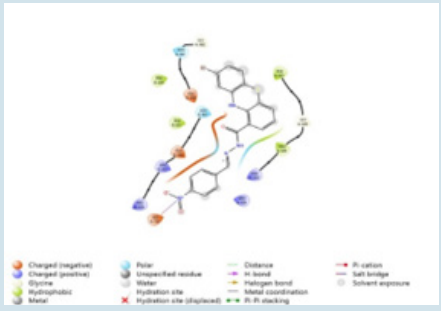
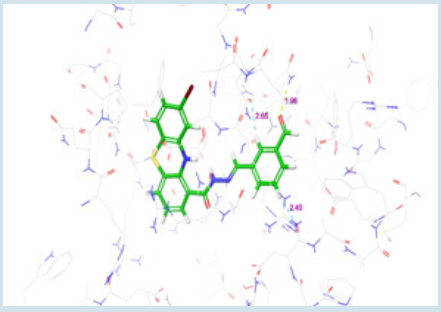
|  |  |

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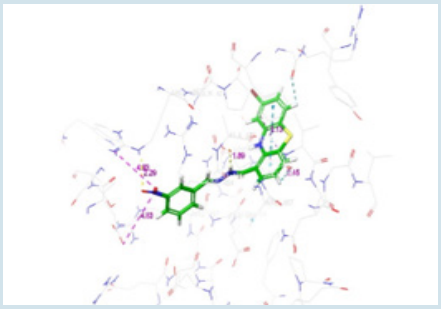
|  |  |
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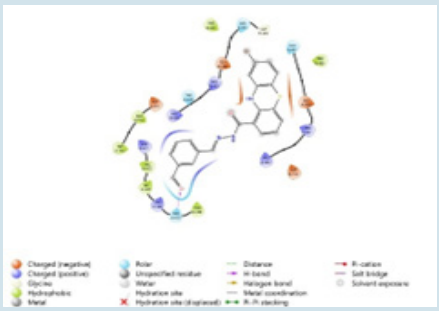
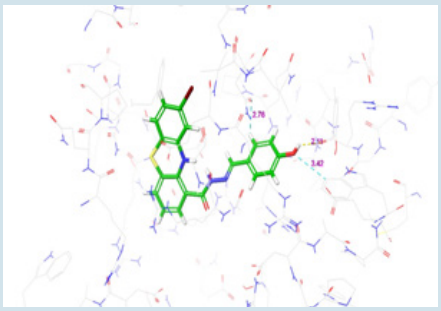
|  |  |
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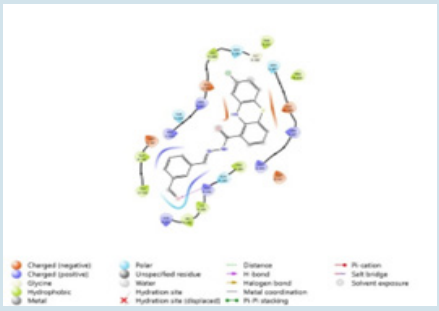
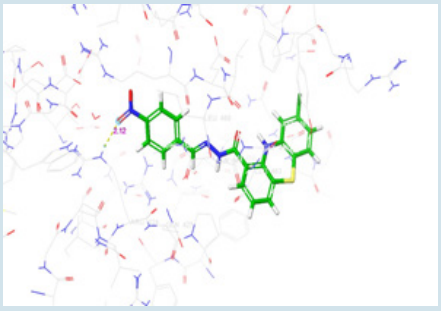
|  |  |
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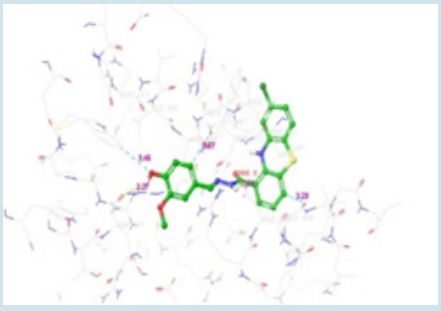
|  |  |
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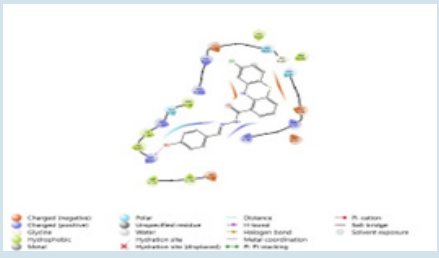
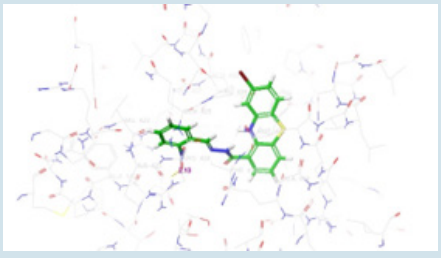
|  |  |

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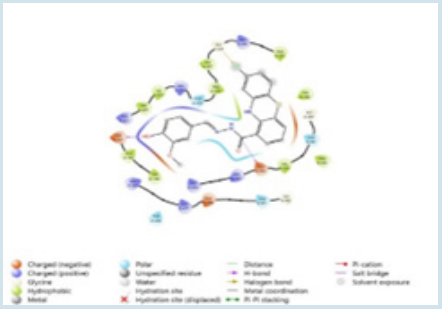
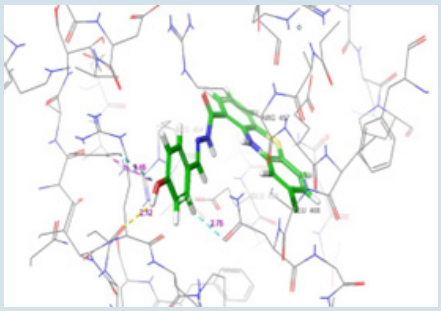
|  |  |
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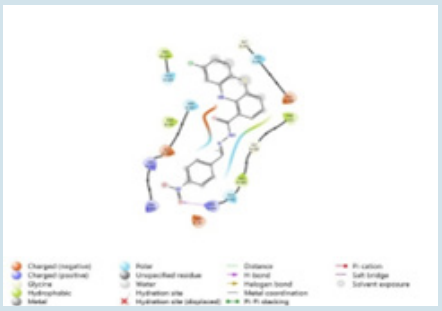
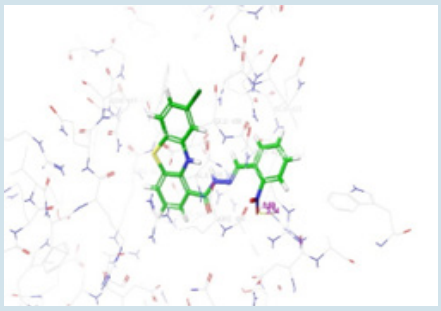
|  |  |
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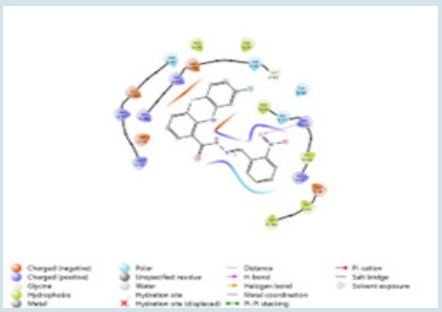
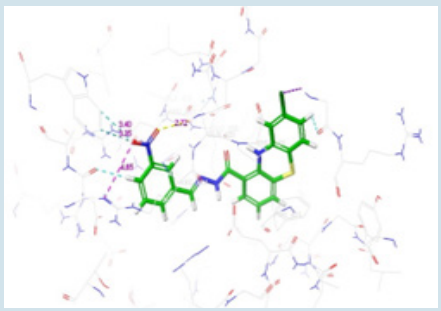
|  |  |
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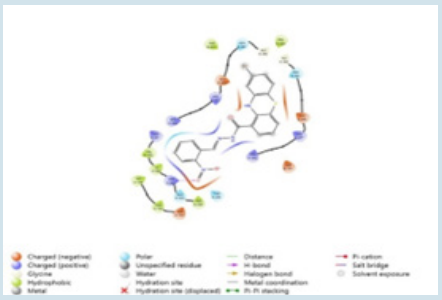
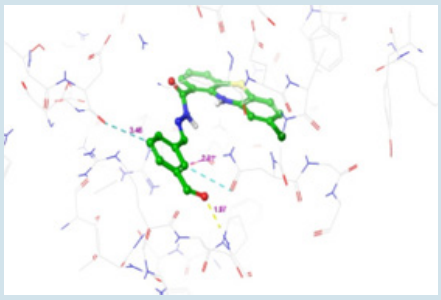
|  |  |
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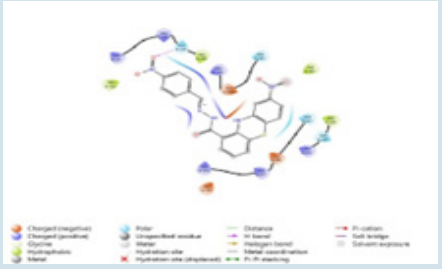
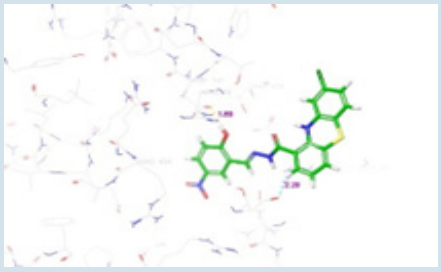
|  |  |

| 3D-docking poses | 2D-docking poses |
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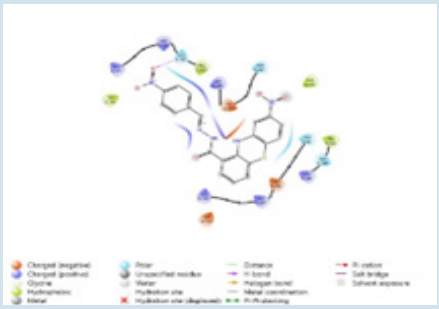
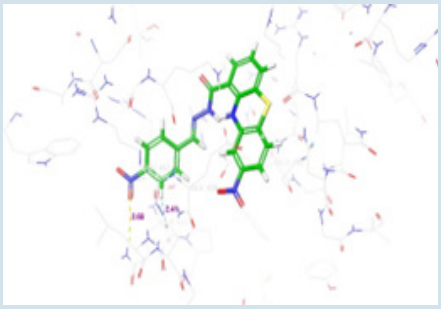
|  |  |
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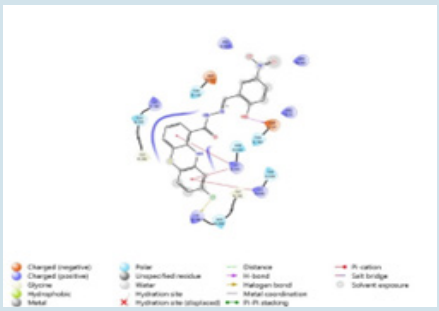
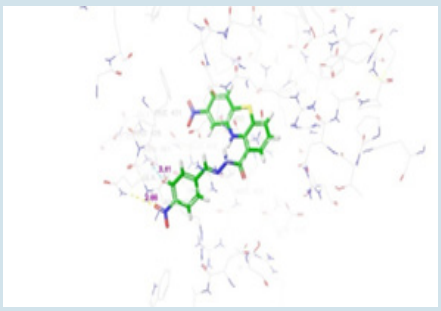
|  |  |
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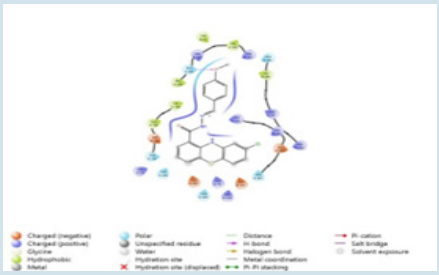
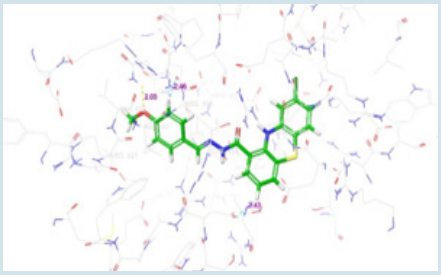
|  |  |
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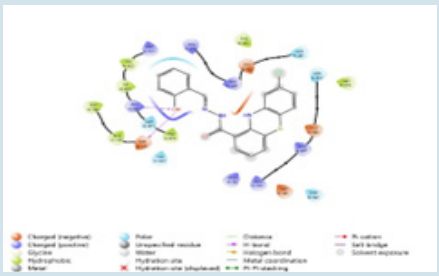
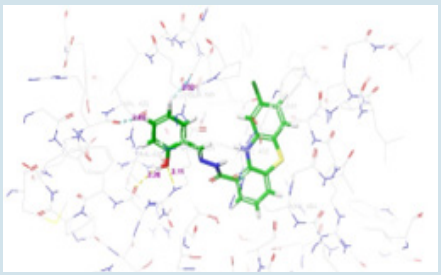
|  |  |
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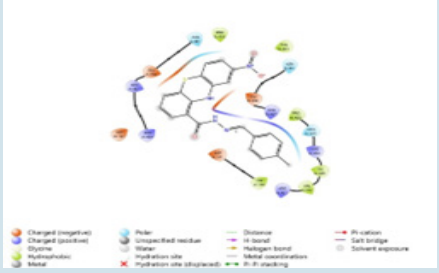
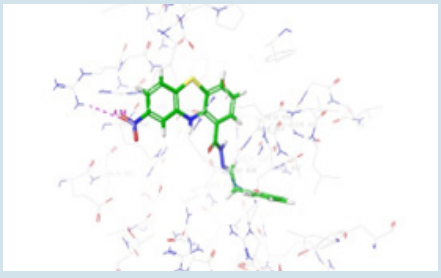
|  |  |
| A20 | |

**Figure 3:** 3D Structure of monoamine oxidase (PDB ID: 2BXR).

and virtual screening, which clarify the mechanisms of action of pharmaceuticals. G proteins may have a function in the onset and management of mood disorders in addition to being crucial in the transmission of signals from receptors to cells. Initially, following lithium treatment, alterations in G protein activity or concentration have been noted in post mortem tissues and peripheral blood components of individuals with bipolar disorder and other mood disorders. G protein expression is unchanged, according to other research employing different antidepressants. These observations support the notion that hMAO A comprises a dimer to monomer switch through the hMAO A specific Glu-151->Lys mutation in addition to providing the foundation for the creation of an inhibitor unique to hMAO A. The use of MAO A form non-human sources in the production of human drugs is questioned in light of these factors. All of the suggested drugs, including phenothiazine molecules, exhibit oral action. The study results from ADME were shown in Table 2 containing *in silico* ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties of phenothiazine's. Research led us to believe that the suggested compounds would have a good oral bioavailability since they don't exceed greater than five in the octanol-water partition coefficient (mol log P), which means they follow the rule of five. The distribution of the substances throughout the body was predicted using the BBB, % unbound and VD. When the VD value is greater, the medicine is being absorbed by the tissues more efficiently than by the plasma. Every chemical shows a modest distribution in tissues. An interesting technique for predicting a ligand's principal list mechanism with a target protein that is structured in a known three dimensions is called molecular docking. It is an essential tool for designing computer-supported, structure-based medicine. The precisely engineered phenothiazine derivatives effectively bind to the target protein, G Protein-Coupled Receptors (GPCRs), with the aid of auto dock software. The study molecular docking results from ADME were shown in Table 3 containing the active amino residues, bond length, bond category, bond type, ligand energies and docking scores. The suggested derivatives A1, A8 and A18 show great list via hydrophobic bonds, whereas A4 and A13 with ASPA414, PROA426 and GLUB458 display hydrophobic interaction. All of the composites in this investigation are active, but the most active derivatives A1, A8 and A18 with the least list affinity are identified as strong obstacles. A1, A8 and A18 engage in hydrophobic trade with GLUA458, ARGA421, ARGA424 and GLUB458, a unique group. Docking investigations revealed that the list mode of the most active composites was the desired emulsion and target protein. 2 D and 3 D structures of the planned phenothiazine derivations were given in Table 4. The following (Table 4) shows the 2 D and 3 D structures of the planned phenothiazine derivations of A1, A8 and A18. Compared to other compounds, molecule A17 exhibits more activity and has a high docking score of -6.123262202. It binds to amino acids that include ARGB457, ARGA421 and GLNA425. bond lengths of 2.46, 2.03 and 2.43 for the relevant sequences. Hydrogen bonding is a form of bond. The molecules' ligand energy is 60.696523.

## CONCLUSION

The *in silico* ADMET parameter of phenothiazine was investigated and its derivatives created. The docking score, drug likeness analysis of phenothiazine derivatives and ADME investigations indicate that the developed mixtures are super eminent compounds. According to a molecular docking analysis, A1, A8 and A18 exhibit the most powerful asset among the derivatives. They interact with PHE and MET to produce hydrogen cleave and with GLUA458, ARGA421, ARGA424 and GLUB458 to form hydrophobic commerce. These mixtures are qualified for drug-likeness because they pass the ADME test. Strong intestinal and PPB absorption capabilities are possessed by these substances. The 20 derivatives and aldehyde derivatives of phenothiazine are drawn for their antidepressant efficacy in this study. ADME studies are conducted on all buildings and 35 of those structures exhibit zero breaches of the Lipinski rule. We have considered the compounds' bioavailability, hydrogen bond acceptors, donors and log p values in the ADME Studies. Following ADME research, the target protein, monoamine oxidase (PDB ID: 2BXR), was identified. After all 20 structures were analysed, it was found that molecule number 18 had the highest antidepressant activity.

## ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**mg/kg:** Milligram/kilograms; **sec:** Seconds; **kcal:** Kilocalorie; **Mol.Wt:** Molecular Weight; **gm:** Gram; **LEU:** Leucine; **THR:** Threonine; **ALA:** Alanine; **MET:** Methionine; **PHE:** Phenylalanine; **Gpcrs:** G Protein-Coupled Receptors; **MAO:** Monoamine Oxidase; **Log P:** Partition Coefficient; **PDB:** Protein Drug Bank.

## SUMMARY

The application of computational docking in structure-based drug design allows for the prediction of bond conformations and free energies of binding between small molecule ligands and macromolecular targets of Phenothiazine. Molecular docking methods, ADMET and 2D and 3D Structure of different Phenothiazine were intended to support the creation of medicinal substances.

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