Original Article: Quantum Chemical Calculations and Molecular Docking Studies of Some Phenothiazine Derivatives

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ABSTRACT

Phenothiazines are synthetic antipsychotics with a wide range of biological effects. Their properties are determined by the structure and variety of substituents in the heterocyclic system. It is known that various quantum chemical properties have a significant influence on drug behavior in biological systems. Because of the diversity in the chemical structure of phenothiazines and other drugs that include heterocyclic systems, quantum chemical calculations provide useful methods for predicting their effects. This study made an attempt to describe the physicochemical properties and the molecular docking simulation of phenothiazine derivatives. To predict the reactivity of phenothiazine derivatives, DFT-based descriptors including certain highest occupied molecular orbital and lowest unoccupied molecular orbital, energy gap, electronic chemical potential, chemical hardness, nucleophilicity, and electrophilicity were performed by using B3LYP / 6311 ++ G (d, p) level. The most and least active compounds were docked to the protein proteins glycosylphosphatidylinositol phospholipase D inhibitor (1GYM), anaphylatoxin receptor antagonist (6C1Q), arylacetonitrilase inhibitor (3UGC) and aspulvinone dimethylallyl transferase inhibitor (3RIX) to confirm the observations of DFT models and elucidate the mode of binding between this type of compound and the corresponding protein.

Introduction

Phenothiazines contain a tricyclic core functional group and are used in a variety of therapeutic purposes. They are a type of heterocyclic antipsychotic of the next generation that antagonizes dopamine receptors and therefore have been shown to have an antineoplastic effect [1-6]. In addition, recent research has investigated the anti-cancer effects of phenothiazines on glioblastoma cells

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that trigger a pause in the G1 cycle, suggesting a decrease in cyclins, which promote DNA replication, and an increase in cyclin-inhibiting substances [1, 2, 4]. This study mainly focused on phenothiazines as prescription drugs. This seriousness of the competing phenothiazine rivalry shows indications, effects, and contraindications as a helpful drug in the treatment and management of serious mental illnesses such as schizophrenia, cancer, and other symptoms of psychosis. This activity will also illustrate the mechanism of action, increased mortality profile, and other key indicators such as pharmacodynamics and related interactions applicable to interprofessional health team members responsible for the care of patients with schizophrenia and other comorbidities [7, 8]. They regulate the development of many interesting systems and can be viewed as the initial stages of chemical processes. The patterns of receptor-ligand interaction, which form the basis of biomolecular recognition, are part of this very important problem [2, 4]. Larger macromolecules and biological systems such as ligand receptors require a specially developed process [9].

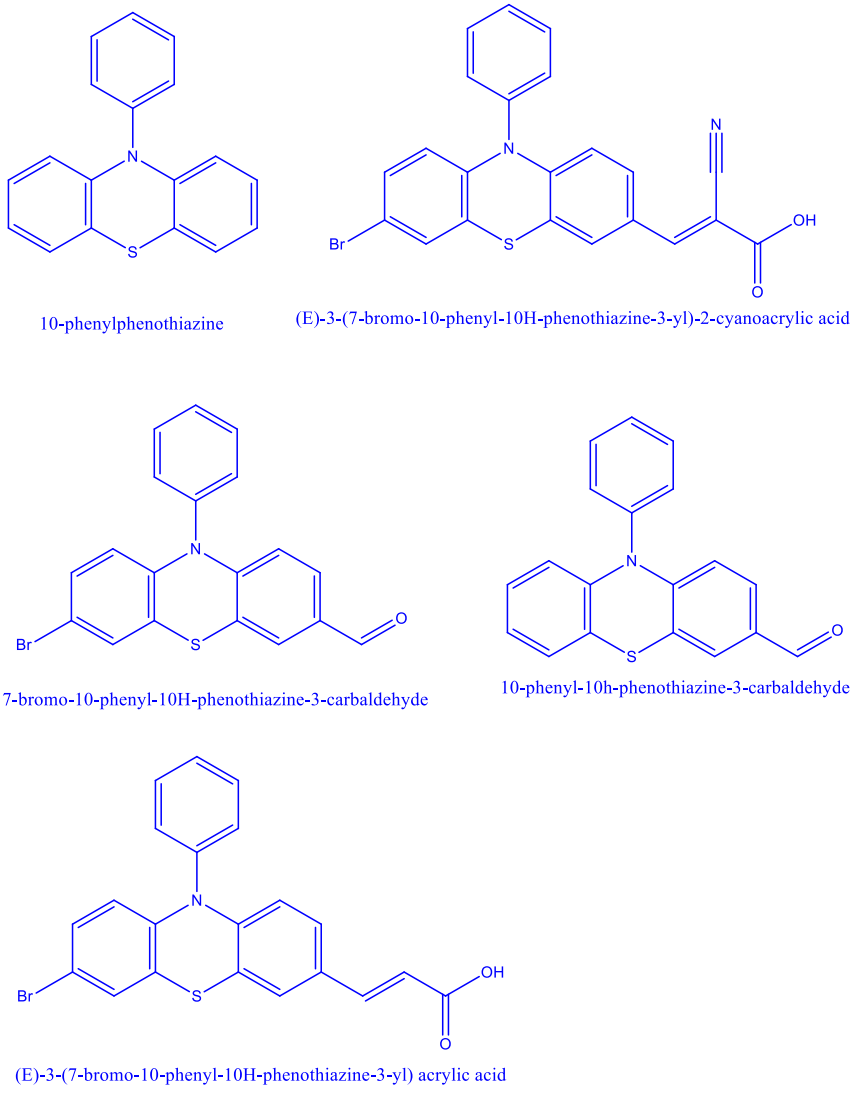

Figure1. Structure of few Phenothiazine derivatives

The Frontier Molecular Orbital (FMO) technique is one of the scaffolds that can be used to achieve energy decomposition. FMO is a recently discovered computer technology

that can perform complete quantum calculations on giant molecules with great precision and reliability [10-15]. Primary quantum chemical calculations are generally seen as more promising than the molecular mechanical approach in predicting molecular interactions. Consequently, information about the individual contribution of non-covalent interactions between each receptor residue and the respective location of ligand binding can be obtained by an FMO calculation on a ligand-receptor system. This type of study provides information about the physical nature of the interaction, comparable to that of non-covalently bound compounds with far fewer molecules. According to a study, the chemical reactivity and the molecular docking with phenothiazines and their derivatives must be comprehensively investigated. We have previously synthesized phenothiazine and its derivatives and studied their photochemical properties, but no docking study has been performed. In the present study, we analyzed the docking and quantum chemical parameters of 10-phenylphenothiazine (PP), 10-phenyl-10H-pheonothiazine-3-carbaldehyde (PPC), 7-bromo-10-phenyl-10H-phenothiazine-3-carbaldehyde (BPPC), (E) -3- (7-bromo-10-phenyl-10H-phenothiazin-3-yl) acrylic acid (BPPAA) and (E) -3- (7-bromo-10-phenyl-10H-phenothiazine -3-yl) -2-cyanoacrylic acid (BPPCA) and their molecular structure are shown in Figure 1.

Computational details

The Lee-Yang–Parr functional and Becke's three-parameter functional (B3LYP/6-311 ++ G (d, p)) were utilized as a basis set using the Gaussian 09 package for validation of reaction mechanism with specific physicochemical properties. The study of the compounds' frontier molecular orbitals is very important because of their relationship with the excitation characteristics. According to Koopmans theorem, the molecular orbital energies of E_{HOMO} and E_{LUMO} are usually related to the ionization potential (IP) and electron affinity (EA), correspondingly [16-21].

$$IP = -E_{HOMO} \quad (1)$$

$$EA = -E_{LUMO} \quad (2)$$

Electronegativity (χ) can be defined as the molecule's capacity to donate electrons and also as the inverse of the chemical potential (μ)

$$\chi = \frac{IP + EA}{2} \quad (3)$$

$$\mu = \frac{E_{HOMO} + E_{LUMO}}{2} \quad (4)$$

Hardness (η), electrophilicity index (ω) and nucleophilicity (ε) could be calculated by

$$\eta = \{\frac{E_{LUMO} - E_{HOMO}}{2}\} \quad (4)$$

$$\sigma = \frac{1}{\eta} \quad (5)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (6)$$

$$\varepsilon = \frac{1}{\omega} \quad (7)$$

Consequently, the electron-accepting capacity (ω+) may be computed as follows:

$$\omega^+ = \frac{(1+3EA)^2}{16(IP - EA)} \quad (8)$$

In order to possibly test the biological activity potential of the title molecule, we then carried out a molecular docking research with the required proteins with the AutoDock Vina software [22].

Results and Discussions

Optimized geometrical and quantum chemical calculations

The optimized structures of PP, PPC, BPPC, BPPAA and BPPCA molecules were calculated with DFT / B3LYP functional and 6-311 ++ G (d, p) level in the liquid phase and are shown in Figure 1. The global minimum energies

obtained by the DFT structure optimization for PP, PPC, BPPC, BPPAA and BPPCA are calculated as -1146.47, -1259.76, -3830.76, -3983.33 and -4058.05 Hartrees, respectively. The dipole moments PP, PPC, BPPC, BPPAA and BPPCA found 2.94, 5.77, 4.97, 5.05 and 4.34, respectively.

The physicochemical parameters of the title compounds were calculated in the liquid phase using the B3LYP / 6-311 ++ G (d, p) functional level (Table 1). Every molecular interaction includes the interaction of the EHOMO orbital with the ELUMO orbital. The molecular energy of EHOMO and ELUMO is decisive for the definition of electronic energy gaps and how a chemical reaction takes place [23-27]. Since EHOMO and ELUMO energies are essential quantum mechanical descriptors, they also play a role in generating charge transfer within the molecule. The EHOMO energy indicates the ionization energy potential and determines the sensitivity of a molecule to electrophilic attacks. The inherent EHOMO of the aromatic ring is delocalized over the entire carbon-carbon bond. The energy of ELUMO influences the electron affinity and defines the tendency of the molecule to attack nucleophiles.

As a result, the HOMO-LUMO transition indicates a transfer of electron density from the aromatic ring to the substituted group. A density functional calculation serves as the theoretical basis for the new quantities. A narrow HOMO-LUMO gap implies a low excitation energy for a wide range of excited states. This suggests that soft molecules with a small gap appear to be more polarizable than hard molecules. The main distinguishing features of soft acids and bases were their high polarizability. Energy gaps should be kept to a minimum and molecules should be soft for effective binding. Table 1 simply proves that BPPAA is a dynamically more stable molecule than BPPCA. The contour regions of the frontier molecular orbitals are shown in Figure 2.

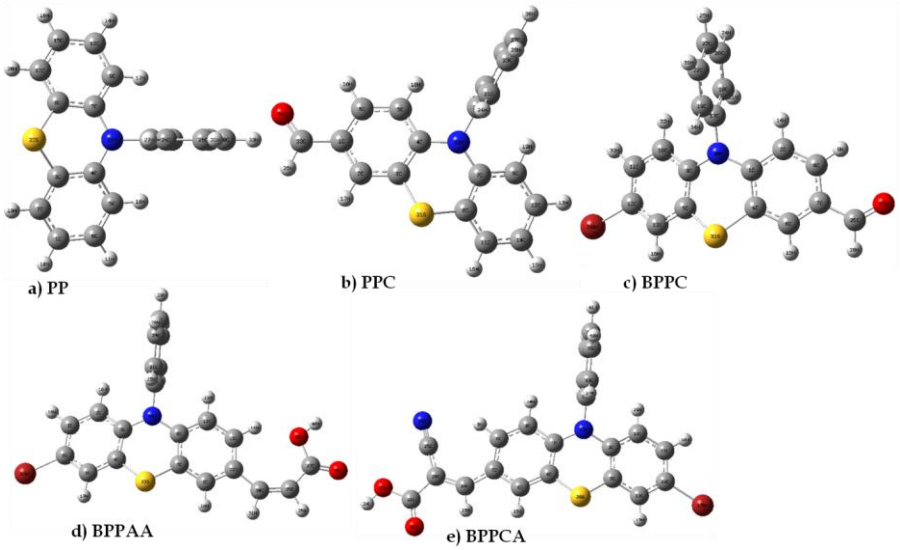

Figure 2. The optimized geometrical structure of title compounds at DFT/6-311 ++ G (d, p) basis set

Table 1. Chemical parameters of title compounds aqueous phase

Compounds	E_{HOMO}	E_{LUMO}	IP	EA	ΔE	χ	μ	η	σ	ω	ε	ω⁺
PP	-5.00	-0.58	5.00	0.58	4.41	-2.79	-2.79	2.21	0.45	1.76	0.57	0.11
PPC	-5.37	-1.71	5.37	1.71	3.66	-3.54	-3.54	1.83	0.55	3.42	0.29	0.64
BPPC	-5.53	-1.85	5.53	1.85	3.68	-3.69	-3.69	1.84	0.54	3.71	0.27	0.73
BPPAA	-6.45	-2.03	6.45	2.03	4.43	-4.24	-4.24	2.21	0.45	4.06	0.25	0.71
BPPCA	-5.55	-2.48	5.55	2.48	3.07	-4.02	-4.02	1.54	0.65	5.25	0.19	1.45

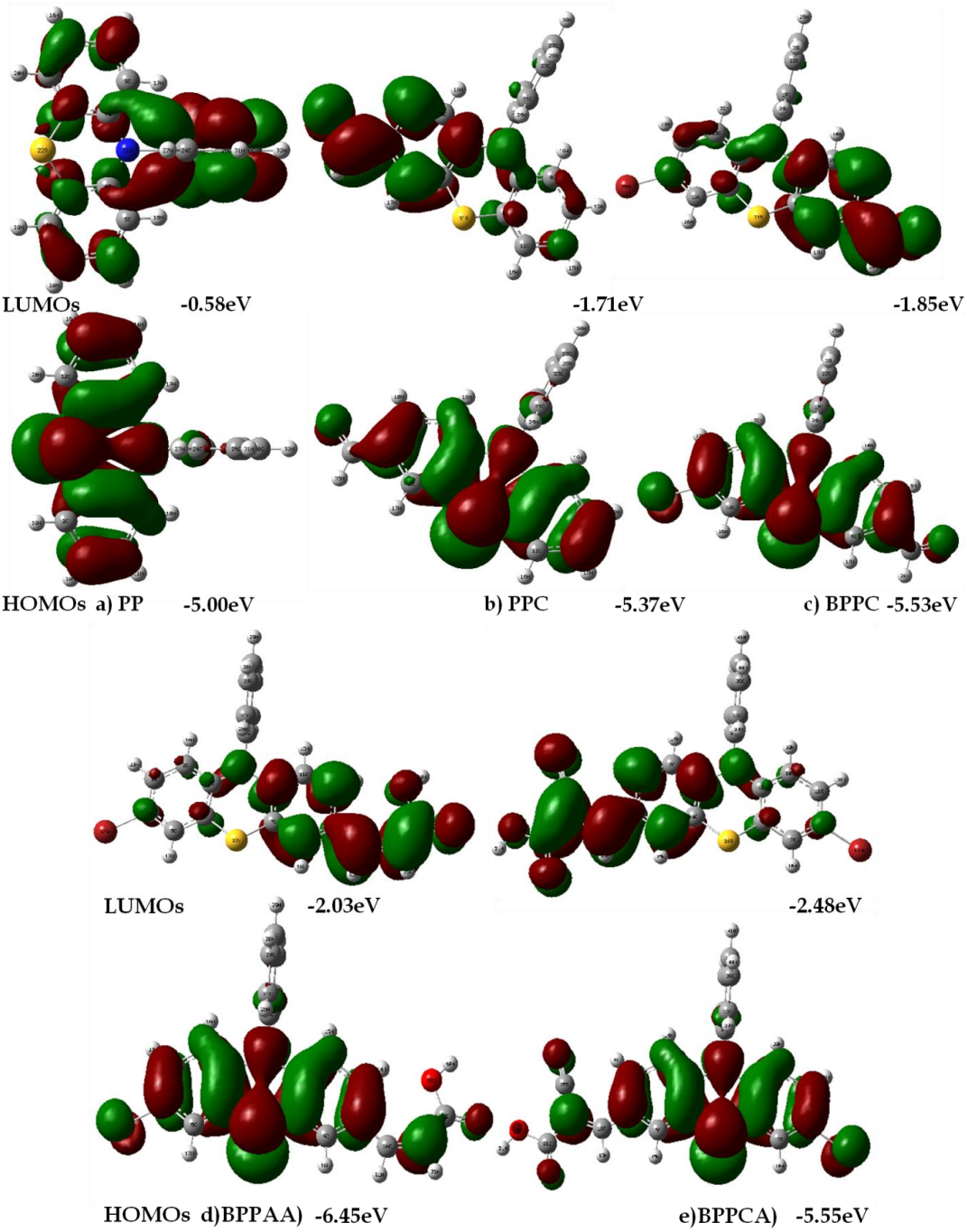

Figure 3. HOMO-LUMO depiction of title compounds

Molecular Docking

The title compound's PASS analysis predicts the behavior of glycosylphosphatidylinositol phospholipase D inhibitor, anaphylatoxin receptor antagonist, arylacetonitrilase inhibitor and aspulvinone dimethylallyltransferase inhibitor with active probabilities of 0.935, 0.920, 0.885 and 0.867, respectively, as shown in Table 2. The corresponding proteins, 1GYM, 6C1Q, 3UGC and 3RIX were downloaded from the protein data bank and the title compounds were docked by using Autodock-Vina. The AutoDock Tools graphical interface was used to calculate Kollman charges. The polar hydrogen and

partial charges were calculated by Geistenger method and the active site of the enzyme was defined to include residues of the active site within the grid size of 40×40×40Å. The docking protocol was tested by extracting co-crystallized inhibitor from the protein and then the same docking and the protocol predicted the same conformation as it was present in the crystal structure with RMSD value well within the reliable range of 2Å. The ligand binds at the active site of substrate and the amino acid interactions with the ligands are given in Table 3. The docked ligand forms stable complexes with binding affinities of -6.4, -8.0, -7.8 and -7.5 kcal/mol for PP, -6.7, -7.7, -8.1 and -7.4 kcal/mol for PPC, -7.2, -7.6, -7.9 and -7.7 kcal/ mol for PPCA, -8.2, -8.3, -8.6 and -7.7 kcal/mol for BPPAA and -8.2, -8.1, 8.5 and -7.5 kcal/mol for BPPCA for the proteins, 1GYM, 6C1Q, 3UGC and 3RIX, respectively. All the ligands showed good binding affinities; as a result, PP, PPC, PPCA, BPPAA and BPPCA have inhibitory action and can be utilized as innovative medicines.

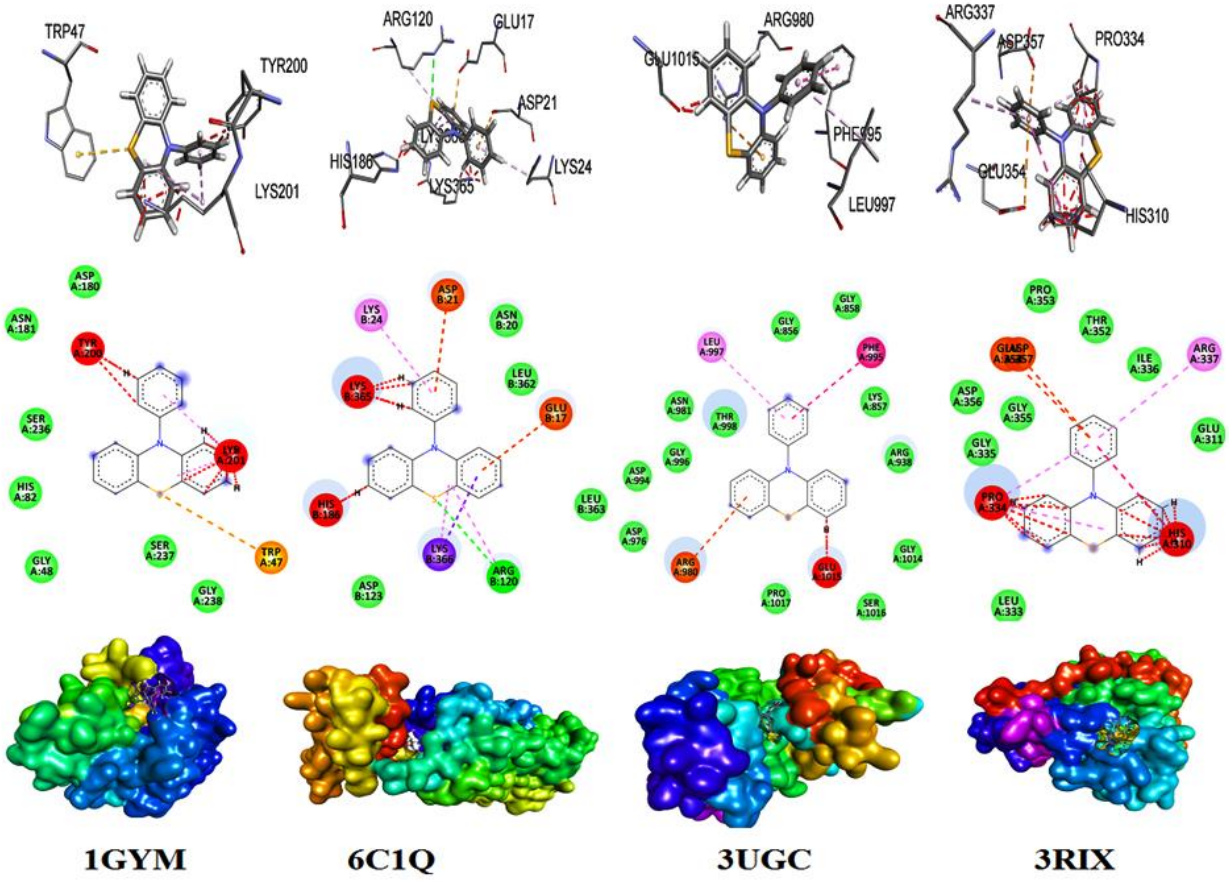

Figure 4. 2D Figure 2D interactions of amino acids with the molecule PP for (a) 1GYM (b) 6C1Q (c) 3UGC (d) 3RIX

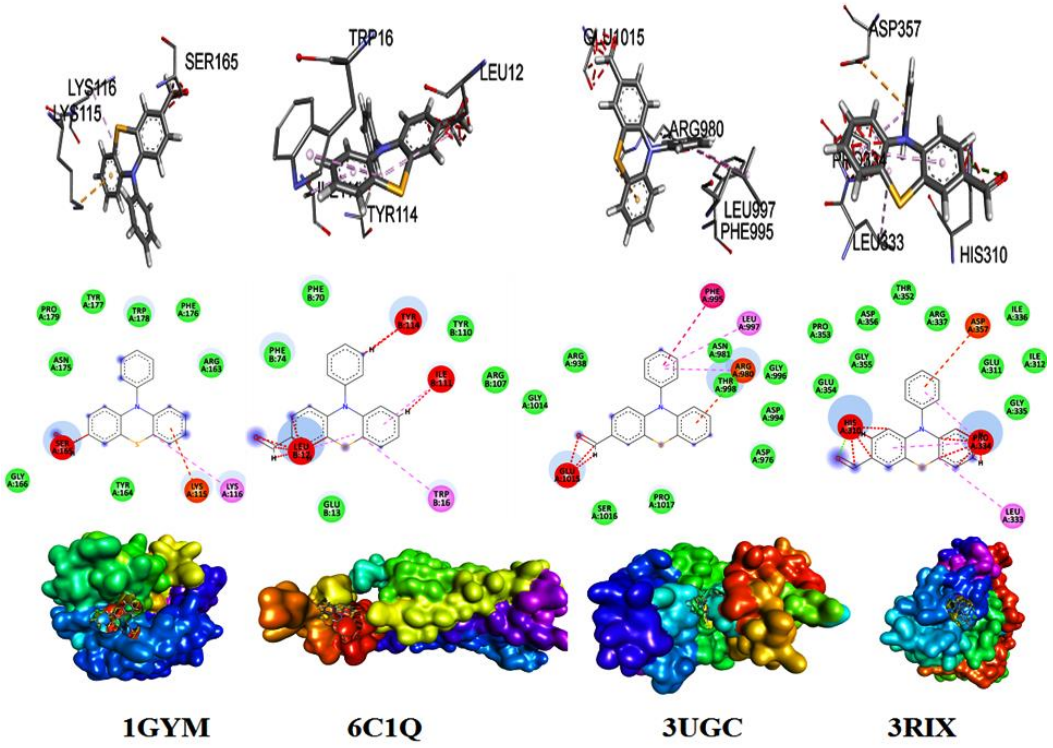

Figure 5. 2D Figure 2D interactions of amino acids with the molecule PPC for (a) 1GYM (b) 6C1Q (c) 3UGC (d) 3RIX

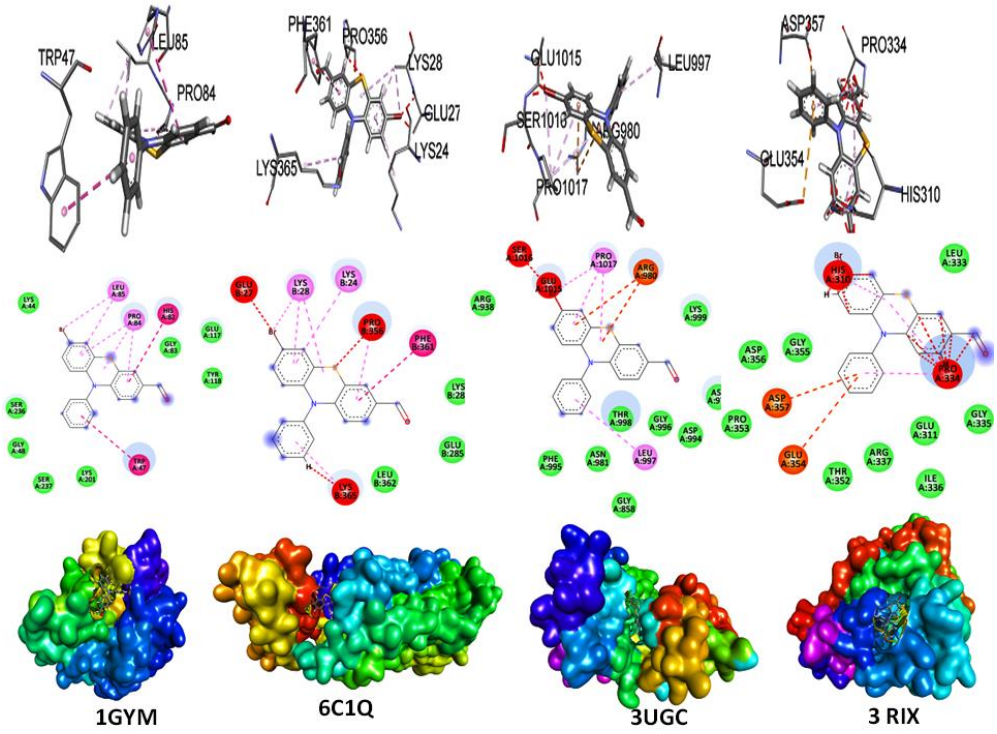

Figure 6. 2D Figure 2D interactions of amino acids with the molecule BPPC for (a) 1GYM (b) 6C1Q (c) 3UGC (d) 3RIX

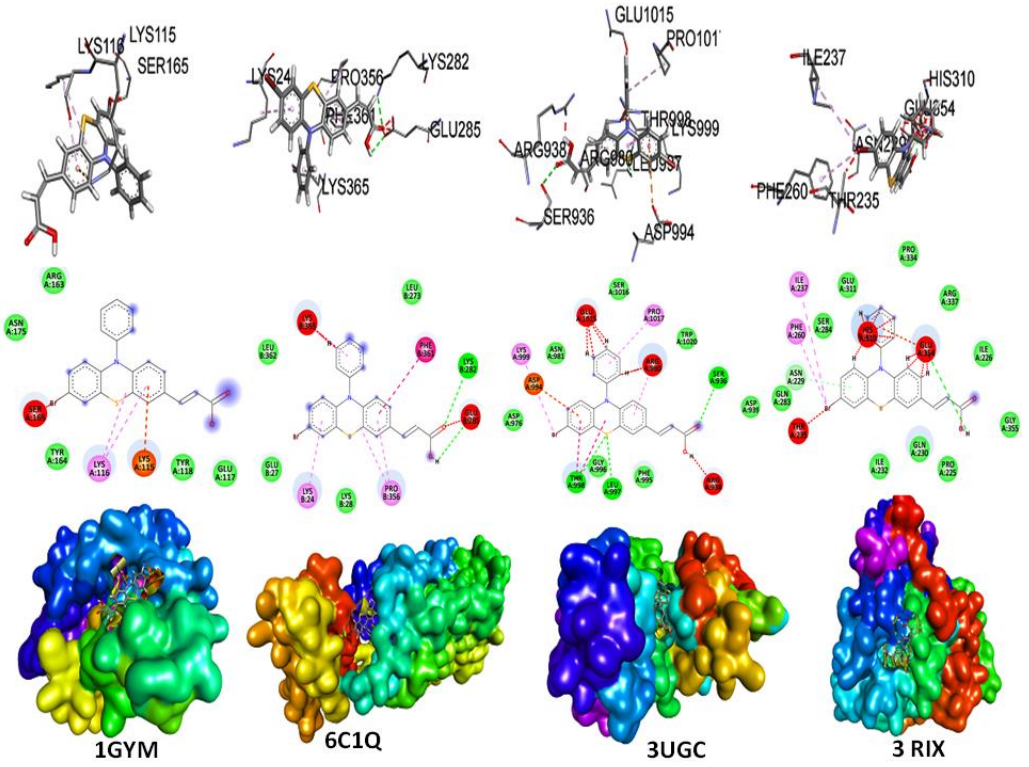

Figure 7. 2D Figure 2D interactions of amino acids with the molecule BPPAA for (a) 1GYM (b) 6C1Q (c) 3UGC (d) 3RIX

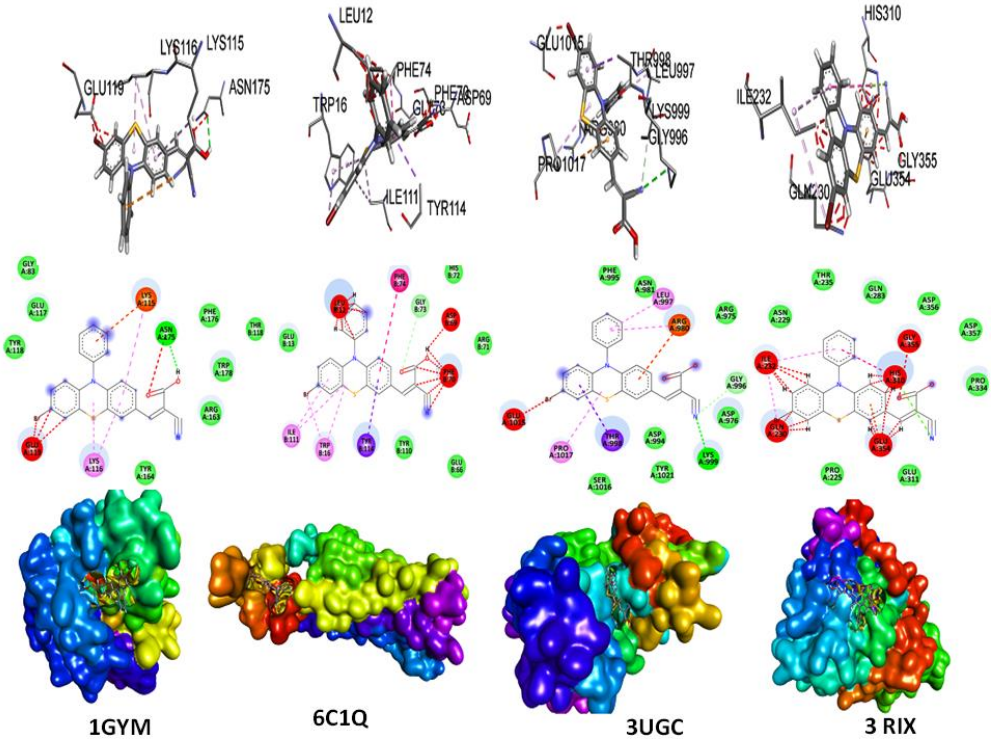

Figure 8. 2D Figure 2D interactions of amino acids with the molecule BPPCA for (a) 1GYM (b) 6C1Q (c) 3UGC (d) 3RIX

Table 2. Analysis of receptor-ligand docking

Compound	Receptor	Binding energy (kcal/mol)	Residues potentially participating in hydrogen bonding	Electrostatic interactions involving residues	Residues implicated in hydrophobic interactions
PP	1GYM	-6.4	TRP47	LYS201	LYS201
	6C1Q	-8.0	ARG120, LYS365, HIS186	GLU17, ASP21	LYS366, ARG120, LYS24
	3UGC	-7.8	GLU1015	ARG980	PHE995, LEU997
	3RIX	-7.5	PRO334,	GLU354, ASP357	HIS310, PRO334, ARG337
PPC	1GYM	-6.7	SER165	LYS115	LYS116
	6C1Q	-7.7	TYR114		LEU12, TRP16, ILE111
	3UGC	-8.1	GLU1015	ARG980,	PHE995, ARG980, LEU997
	3RIX	-7.4	HIS310, PRO334	ASP357	LEU333, PRO334,
BPPC	1GYM	-7.2	PRO84, LEU85	PRO84	TRP47, HIS82, LEU85, PRO84
	6C1Q	-7.6	LYS24, LYS365	LYS28	PHE361, LYS28, PRO356, LYS24, L YS365
	3UGC	-7.9	ARG980, PRO1017, GLU1015, SER1016,	ARG980, PRO1017,	PRO1017, LEU997
	3RIX	-7.7	PRO334	GLU354, ASP357	PRO334, HIS310
BPPAC	1GYM	-8.2	LYS115, SER165		LYS116
	6C1Q	-8.3	LYS282, GLU285	PRO356	PHE361, PRO356, LYS24 , LYS365
	3UGC	-8.6	SER936, LEU997, THR998, ARG938	ASP994, TH998, GLU1015	THR998, LYS999, ARG980, PRO1017
	3RIX	-7.7	GLU354, ASN229, THR235	GLU354	ILE227, PHE260, HIS310

Table 3. PASS prediction for the title compound's activity spectrum

Pa	Pi	Activity
0.935	0.002	Glycosylphosphatidylinositol phospholipase D inhibitor (1GYM)
0.921	0.003	Anaphylatoxin receptor antagonist (6C1Q)
0.885	0.004	Arylacetonitrilase inhibitor (3UGC)
0.867	0.016	Aspulvinone dimethylallyltransferase inhibitor (3R1X)
		PASS evaluation
0.838	0.004	Complement factor D inhibitor
0.831	0.002	Taurine-2-oxoglutarate transaminase inhibitor
0.831	0.008	NADPH peroxidase inhibitor
0.799	0.003	Tetrahydroxynaphthalene reductase inhibitor
0.776	0.004	Thioredoxin inhibitor
0.769	0.008	Bisphosphoglycerate phosphatase inhibitor

Conclusion

The quantum chemical calculations of phenothiazine derivatives were done and discussed. The calculated EHOMO-LUMO gap is 4.41 (PP), 3.66 (PPC), 3.68 (BPPC), 4.43 (BPPAC) and 3.07 (BPPCA) eV, which explains the charge transport within the molecule. The narrow HOMO-LUMO gap and the high dipole moment value ensure the reactivity of the phenothiazine derivative molecules. Docking on different proteins illustrates the binding affinity and other ligand-target interactions. The validation through molecular docking in connection with molecular interactions shows the stability with the specific proteins. BPPC, BPPAA, and BPPCA are suitable candidates for a topical cancer drug.

Conflict of Interest

The authors affirm that they did not have any conflicts of interest in the present study

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