In silico study of synthetic Bromophenol Compounds against *Staphylococcus aeurus's* target protein Dihydrofolate Reductase Enzyme

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Abstract

Natural products (NPs) serve as prototypes for a majority of antimicrobial agents currently in clinical use. The evolutionary process that gives rise to these molecules is inevitably accompanied by resistance mechanisms that curtail the clinical lifespan of any given class of antibiotics. Staphylococcus aeurus is among the class of microorganisms that exhibit resistance to multiple drugs. Dihydrofolate reductase (DHFR) enzyme is a promising target in the pursuit of mitigating S. aureus infections. This enzyme catalyzes the formation of tetrahydrofolate (THF) through the reduction of Dihydrofolate (DHF) in the presence of nicotinamide adenine dinucleotide phosphate (NADPH). Diaminopyrimidines (DAPs), such as trimethoprim (TMP), a bacterial infection treatment, which is target DHFR. DAP DHFR inhibitors have been used therapeutically for more over 30 years, and resistance to these drugs has grown prevalent. Their wide range of cellular functions make them ideal targets for antimicrobial agents. Due to the broad scope of their cellular functions, the task of developing analogues that can selectively overcome the resistance conferred by DHFR enzymes from Halopitys Incurvus Algaen's

Bromophenol Compound has posed a significant challenge. To identify the compound's drug-like properties, a pre-filtering process was conducted utilizing the Lipinski rule of five in computational analysis. Subsequently, a molecular docking study was carried out using the Chimera#AutoDock Vina 1.17.3 program between the synthetic compound and DHFR (PDB ID: 2W9S) of S. aeurus and TMP was used as control. The results demonstrated that the synthetic compound displayed a favorable binding affinity with the active site of the target protein DHFR enzyme (PDB ID: 2W9S) similar to the control (TMP).

Keywords: Bromophenol, DHFR, Molecular Docking, Molecular Dynamic, *Staphylococcus aeurus*

1. Introduction

NPs often exhibit poor therapeutic antimicrobial properties and are susceptible to resistance mechanisms that have evolved through coevolution (Waglechner N and Gerard Det al., 2017). Recent advancements in the field of chemistry have enabled the development of several antibiotic classes via fully synthetic routes, which offer fresh avenues to counter resistance (Seiple et al., 2016; Charest et al., 2005). S. aureus is a classic example of a group of microorganisms that have developed resistance to multiple medications (Lee et al., 2015). This bacterium, which is spherical in shape, gram-positive, non-spor, non-motile, and some strains are encapsulated, belongs to the phylum Firmicutes. The cell wall of this species exhibits amorphous and resilient qualities (Fisher et al.,2020). Peptidoglycan is the primary constituent of the cell wall, accounting for 50% of its total mass, while Teichoic acids contribute to 40% of the cell wall mass. The remaining 10% of the cell wall is made up of exoproteins, surface proteins, and peptidoglycan hydrolases. This bacterium is a natural inhabitant of the human body's nasopharynx and skin and can cause infections of the nose, skin, vagina, urethra, and gastrointestinal tract (Chan et al.,2013). DHFR enzyme, which catalyzes the conversion of Dihydrofolate (DHF) to THF in the presence of NADPH, is a promising target in the fight against S. aureusinfections (Sehrawat et al., 2023). Diaminopyrimidines (DAPs), such as TMP, a bacterial infection treatment, that is target DHFR. DAP, DHFR inhibitors have been used therapeutically for more over 30 years, and resistance to these drugs has grown prevalent (Heaslet et al.,2009). The synthesis of thymidylate, purines, methionine, and other essential metabolites is greatly facilitated by DHFR. This enzyme is crucial for the proliferation of cells. Hence, inhibiting DHFR activity leads to the depletion of the intracellular tetrahydrofolate pool, ultimately preventing the biosynthesis of RNA, DNA, thymidine, and protein (Kakkassery et al., 2021). Due to its multifaceted involvement in critical cellular processes, DHFR has emerged as an attractive target for the development of antimicrobial agents. However, the design of compounds that can effectively inhibit DHFR while evading resistance mechanisms remains a formidable challenge. In recent years, many studies have reported on the antibacterial activities of Marine NPs (Bourne et al., 2014). Marine NPs possess a wide array of captivating biological traits, such as the ability to act as anti-infective agents with antibacterial, antifungal, antiparasitic, and antiviral properties, thereby exhibiting immense potential for the development of alternative medicinal approaches. The

exploration of distinctive chemical variations in marine sources enables the discovery of new anti-infective compounds (Kumar et al., 2021; Rezaie et al., 2018). Moreover, the identification of drug-like molecules necessitates the consideration of pertinent pharmacodynamics and pharmacokinetics properties, and molecular descriptors play a crucial role in identifying the primary chemical characteristics required for drug development (Wang et al., 2021). The computational analysis of new synthetic compounds to overcome resistance to the DHFR inhibitor has not yet to be investigated. In this paper, we have conducted a study on the docking of a new synthetic compound with the target protein DHFR of S. aeurus and TMP inhibitör of DHFR applied as control. Our findings reveal that the synthetic compound displayed a significant binding affinity with the DHFR enzyme (PDB ID: 2W9S) in the active site similar to the control. Based on our computational analysis, we report that this new synthetic compound can be used as inhibitor of DHFR.

2. Material and methods

2.1. Synthesis of a bromphenol compound biomimetic to marine algae

For Synthesis of a bromphenol compound from Halopitys Incurvus Algae, Rezaei et al, (2018) methodes was used (Rezaei et al.,2018).

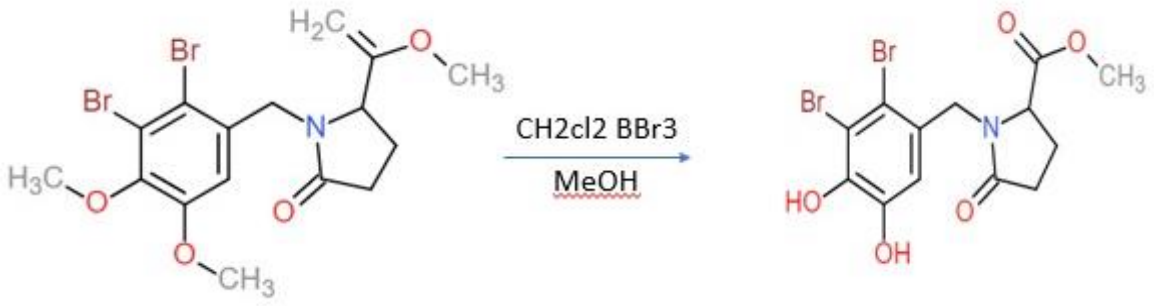

Figure 1. Synthetic compound, 2-D structure

2.2. Preparation of synthetic bromphenol Compound for Molecular Modeling

First, ZINC22 database used for geting canonical smile by drawing 2D structure of synthetic compound ((https://zinc.docking.org) (Figure 1). Second, 3D structure drawn in ChemBioOffice sotware (Kerwin 2010).

2.3. Synthetic ligand and Protein preparation for docking

The PDB fomat of the DHFR target protein of S. aeurus (PDB ID: 2W9S) obtained from PDB RCSB database (https://www.rcsb.org) (Table 1). The software UCSF# Chimera used to prepar the synthetic ligand and receptor. Adding hydrogen bond, remove non-standard

residue, remove water molecule, and add charge are all steps included in this process. At the end the minimization structure to increase stability was done (Bietz et al.,2014) (Fig. 2; Table 1).

2.4. Molecular docking protocol

After preparation and minimization of DHFR and synthetic ligand, the active site (*LEU 20, SER 49*) Chain A of DHFR was determined (Kakkassery et al.,2021; Fig 3). Then, rigid receptor and flexibility synthetic ligand Docking was selected. This type of docking is important to drug discovery (Nguyen et al., 2019). This process was run by Chimera#AutodockVina software to predict the structure of the DHFR-synthetic ligand complexes and DHFR-TMP (control) complex. Grid box center; 7,81993, -2,79912, 37,1565, size; X10, Y 13,3794, Z15,795 was set. The results of molecular docking were analized by PLIP (Protein-Synthetic ligand Interaction Profiler) online server in order to prediction the ideal mode of binding between the DHFR (IDs:2W9S) and synthetic ligand as well as TM-DHFR (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index)

2.5. SWISStarget and SWISSADME/ADMET Prediction

SMILES (Simplified Molecular Input Line Entry System) canonical of synthetic ligand was submitted in (www.swisstargetprediction.com) server to predict targets (Li et al.,2022). Then pharmakinitic, toxicity and druglikness properties was predicted for synthetic ligand and TMP. Furthermore, adherence to crucial criteria such as the 5 rules of Lipinski's, Veber's Rule, Egan's Rule, and polar surface area (TPSA), as well as considerations of rotatable bonds, ADME (Absorption) (http://www.swissadme.ch ; https://preadmet.webservice.bmdrc.org) (Bakchi et al.,2022).

Table.1. DHFR Target protein of S. aureus

Proteins	Methods	Revaluein	Resolution	ResiduesNumber	Control	Docking score Kcal/mol
DHFR PDB ID: 2W9S	X-ray Diffraction	0.237	1,80 A	161	TMP	-7

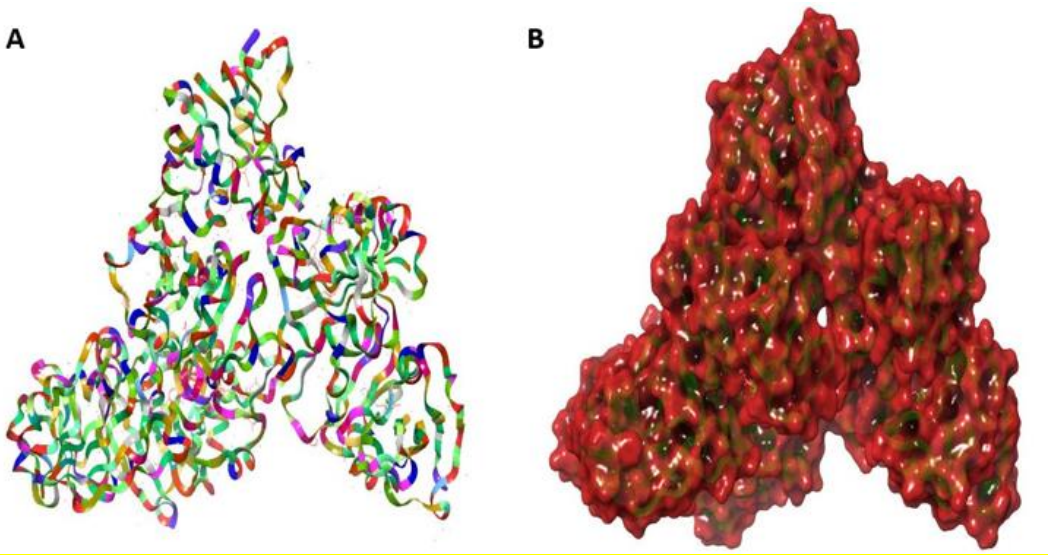

Figure 2. 3D Structure (PDB ID:2W9S), the structure was taken Maestro Shrodinger Software

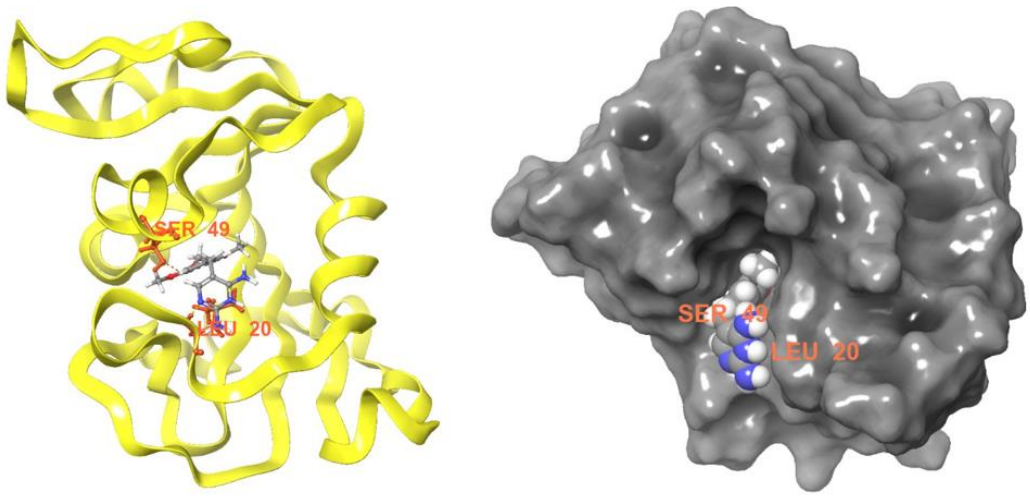

Figure 3. 3D Structure of active site DHFR- chain A (*LEU 20*, *SER49*), the structure was taken Maestro Shrodinger Software.

2.6. Moleculer Dynamic smulations

For analysing Molecular Dynamics (MD) simulation, IMOD online server was used. MD is a computer simulation tool used to examine the physical motions of atoms and molecules. In MD simulations, atoms and molecules are allowed to interact for a set amount of time, offering a glimpse of the dynamic evolution of the system (Hollingsworth et al.,2018). This is analyse the stability of receptor and synthetic ligand complex stability (Kirar et al.,2022). It included the results of B-factor, deformability, co-varience map, eigenvalues, and elastic network and variance (https://imods.iqfr.csic.es).

Table 2. Interaction results of synthetic ligand and DHFR enzyme

Hydrogen Bond									
Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle	Protein Donor	Side Chain	Donor Atoms	Acceptor Atoms
1	7A	ALA	3,22	4	137,11	V	X	45(Nam)	1292(OCO2)
2	49A	SER	1,74	2,7	171,34	V	V	398 (O3)	1295(O3)
3	49A	SER	2,08	2,7	122,7	X	V	1295 (03)	398(O3)
4	98A	TYR	2,24	3,09	149,57	V	V	784 (O3)	1292 (Oco2)
5	98A	TYR	2,24	3,09	150,15	X	V	1292 (OCO2)	784 (O3)

Table 3. SWISSADME/ADMET Prediction

		TMP	Synthetic ligand
	Cannonical Smiles	COC1=CC(=CC(=C1OC)OC)CC2=CN=C(N=C2N)N	OC(=O)C1CCC(=O)N1CC1=CC(O)=C(O)C(Br)=C1Br
Physicochemical Properties	Molecular Formula	C14H18N4O3	C12H11Br2NO5
	Molecular weight g/mol	290.32 g/mol	409.03 g/mol
	Num. Rotatable Bonds	5	3
	Num. H-bond acceptors	5	5
	Num. H-bond Donor	2	3
	Molar Refractivity	79.77	81.56
	TPSA	105,51 Å²	98.07 Å²
Lipophilicity	Consensus Log P o/w	1.16	1.57
Water Solubility	Log S (ESOL)	-2.31	-3,40
Pharmacokinetics and Toxicity	GI absorption	High	High
	Ames_test	Mutagen	Mutagen
	Caecino_Mouse	Positive	Negative
	hERG_inhibition	Low risk	Low_risk
	BBB permaent	No	No
	P-gp substrate	Yes	No
	CYP1A2 inhibitor	No	Yes
	CYP2C19 inhibitor	No	No
	CYP2C9 inhibitor	No	No
	CYP2D6 inhibitor	No	No
	CYP3A4 inhibitor	No	No
Drugliken ess	Lipsinki	Yes	Yes
	Ghose	Yes	Yes
	Veber	Yes	Yes
	Egan	Yes	Yes
	Muegge	Yes	Yes
	Bioavability Score	0.55	0.56
Medicinal Chemistry	Syntetic accessibility	2.58	2.51

3.Results and Discussion

3.1. Moleculer Docking Simulation

3.1.1. Intreaction Analyses of the synthetic ligand into DHFR

As shown in table 2, the DHFR - synthetic ligand has one hydrogen bond with SER49 residue and TMP have one hydrogen bond with SER 49 residue in active site of DHFR. Hydrogen bonds assume a central role in the stabilization of protein-synthetic ligand complexes, thus playing a critical role in determining the selectivity of these interactions (Nittinger et al.,2017; Kretschmer et al.,2012). Regarded to the our results, synthetic ligand present dock score –6,7 Kcal/mol (9 pose), the dock score of TMP -7 Kcal/mol (6 pose). Docking scores serve as valuable metrics for approximating the binding affinity between a synthetic ligand and its target. This critical aspect of docking analysis enables the assessment and comparison of potential synthetic ligand-protein affinities, guiding the selection and optimization of synthetic ligands with superior binding characteristics for further study or development (Paulsen et al.,2013). These findings indicate that the synthetic ligand qualifies as a potent inhibitor of the DHFR enzyme, similar to the control (TMP). (Table 2; Fig 4).

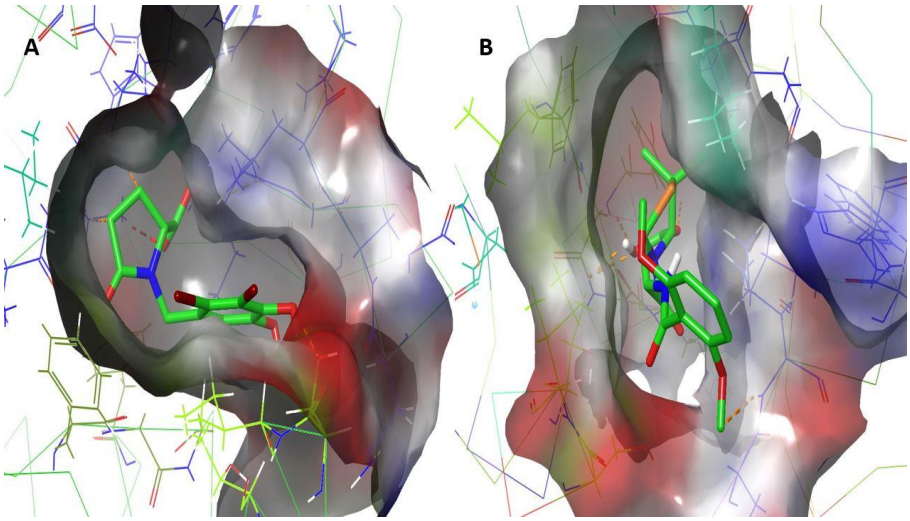

Figure 4. Intreaction synthetic ligand into DHFR (A); Intreaction TMP (control) into DHFR (B).

3.2. Result of SWISSADME/ADMET Prediction

Absorption, distribution, metabolism, and excretion (ADME) are all factors to consider while developing a new drug (Daina et al.,2017). ADME studies performed early in the drug discovery process can aid in minimizing

pharmacokinetics-related failure of compounds during clinical phase trials (Alqahtani et al.,2017). The typical method for researching pharmacokinetics (ADME) qualities is to split the target influencing effects into different parameters (Prakash et al.,2021). Several strategies have been developed to learn about the ADME characteristics of emerging compounds. Due to a lack of pharmacokinetic qualities, the majority of substances reported to date to be successful in their respective backgrounds could not be maintained for clinical reasons (Hao et al.,2015). When developing novel drugs, five Lipinski's Rules frequently used to determine if a naturally occurring compound will likely be effective when taken orally (Protti et al.,2021). The rule is based on a number of distinct characteristics, such as a molecular mass of less than 500 Dalton, low lipophilicity (LogP) of less than 5, less than 5 donors and acceptors of hydrogen bonds <10, and a molar refractive range of between 40 and 130 (Lipinski 2002). As shown in Table 3, the five Lipinski's rules was confirmed for the synthetic ligand produced from marine life. Veber's rule, which depicts a potential therapeutic molecule's oral bioavailability, is supported for the synthetic ligand under investigation. We also point out that the synthetic ligand is verified by Ghose's and Muegge's rules as well as another Egan's rule, which determines the absorption of the drug molecule (Ghosh et al.,2021; Vélez et al.,2022; Muegge et al.,2001). A Synthetic Accessibility Score (SA) is used to evaluate how simple it is to synthesize a medicinal molecule. The SA score is calculated by adding up the contributions made by each molecule's fragments, then dividing that total by the number of fragments in the molecule. This rating is useful for drug discovery since it assesses a molecule's ease of synthesis, assisting with several steps in the drug development process (Thakkar et al., 2021; Ertl et al., 2009). Low-scoring molecules are simple to make, hence the SA for a synthetic ligand is 2,51. Therefore, based on our findings, the synthetic ligand is simpler to synthesis and also displayed favorable Druglikness, Solubility, and Drug Score values. As a result, the synthetic ligand complied with the Lipinski, Veber, Egan, Ghose, and Muegge guidelines, making it simple to produce and suitable for use as an effective medicine. Based on ADME/T results the synthetic ligand has a strong gastrointestinal tract absorption capacity, demonstrating its potential for effective absorption in this physiological setting (Table 3). These tests were run to find out how a medicine behaved within the body's pharmacological and pharmacodynamic parameters. As the physiologically active form of the medication must be in its unbound state in

order to cross biological barriers and provide a therapeutic effect, this factor is crucial in the creation of innovative pharmaceuticals (Bitew et al., 2021; Zadorozhnii et al., 2021). Synthetic bromophenols compound have a wide spectrum of bioactivities that indicate potential for therapeutic uses (Dong et al., 2020).

3.3. Target prediction

According to Gfeller et al. (2014), Swiss target prediction is a web service that can anticipate the most likely protein targets for small compounds. In order to detect phenotypically undesirable effects or probable cross-reactivity resulting from the activity of marine-derived material (synthetic ligand), it is crucial to investigate targets. Figure 5 displays the findings of the top 25 targets ((http://www.swisstargetprediction.ch). The majority of the potential targets for the compound's binding are enzymes that promote the drug reaction, family Protease, and targets for Kinase.

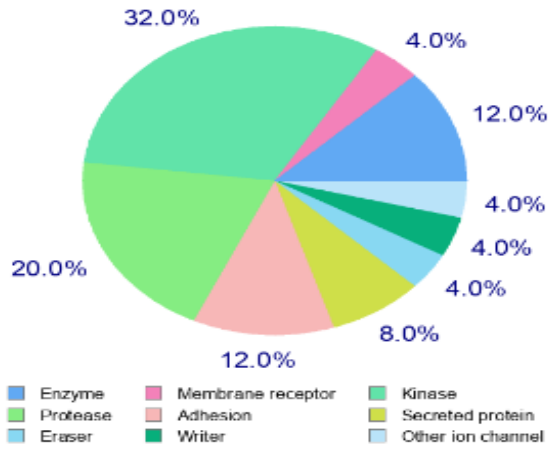

Figure 5. Graph displaying the predicted target structure of the synthetic ligand (Smile canonical: OC(=O)C1CCC(=O)N1CC1=CC(O)=C(O)C(Br)=C1Br).

3.4. Molecular dynamics simulations

MD analysed physical interaction of heavy atom and protein (Karplus and McCammon 2002). A molecular dynamics (MD) simulation study was conducted to assess the stability of the synthetic ligand-DHFR receptor complex (Figure 6). For this, Imod online server (http://imods.chaconlab.org) was uesd. MD results in figure 6, including NMA in (A), the peaks reveal the deformability of the respective synthetic ligand (B),the empirical B-factor graphs were derived from the relevant PDB data and NMA mobility of the complexes (C). Computed eigenvalues of the docked complex, which depict the rigidity of protein motion Synthetic ligand-DHFR complex stands out for requiring the least energy to undergo structural deformation, as indicated by the lowest eigenvalue (4.671985e-04) compared to the synthetic ligand-DHFR complex compare to the TMP (4.706842e-04) (D), as shown in (E) the inverse relationship between eigenvalue and

associated variance is demonstrated (E). Individual variance is represented with red color, while variance is depicted with green color. The interaction patterns between residue pairs are showcased in the co-variance map (F), where red indicates correlated motion, white signifies uncorrelated motion, and blue denotes anti-correlated motion between residue pairs. The elastic network model, depicted in the elastic map (G), illustrates inter-atomic connections using dots. The color gradient of these dots corresponds directly to their stiffness, with darker spots representing stiffer connections.

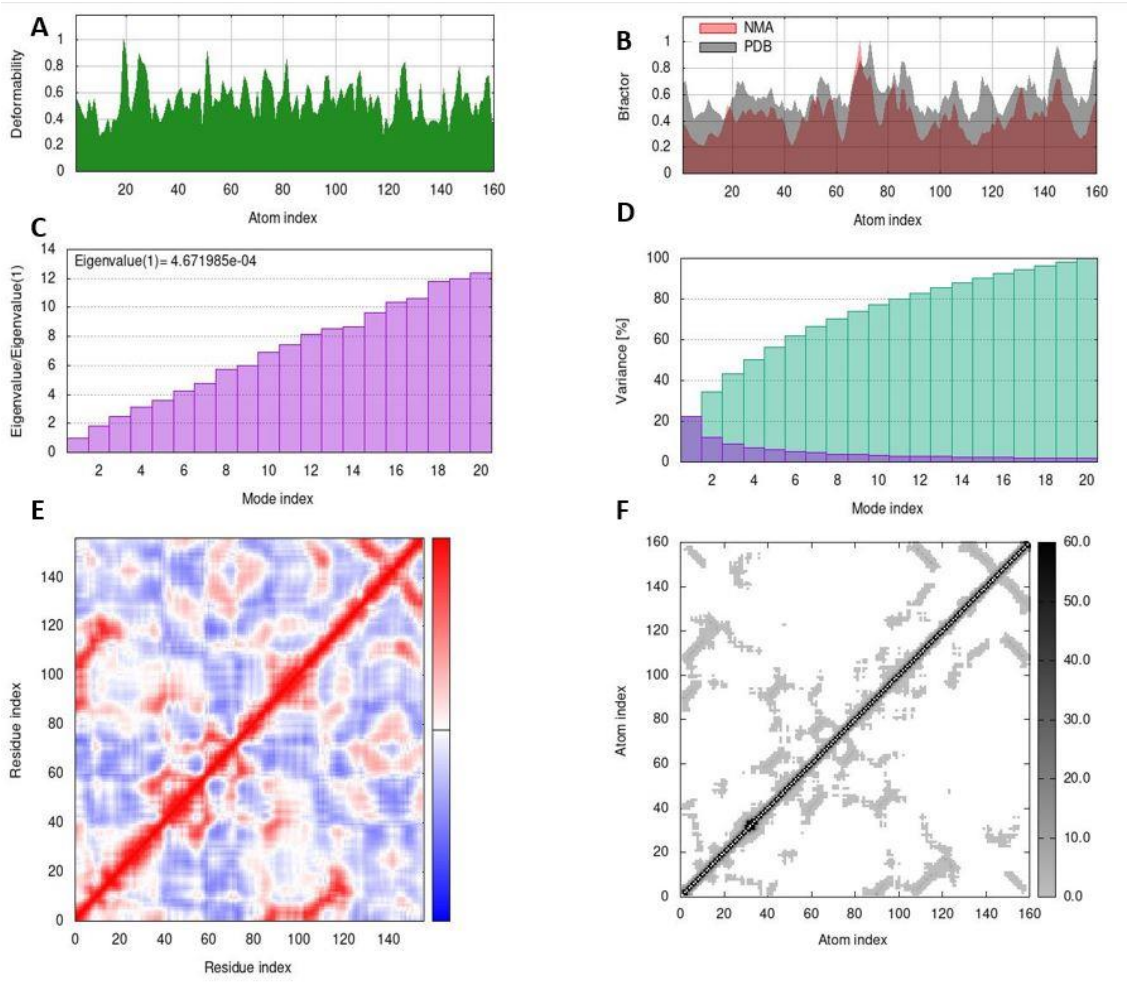

Figure 6. MD results (complex synthetic ligand-DHFR) (a) NMA, (b) deformability, (c) B-factor, (d) eigenvalues, (e) variance (f) co-variance mapand (g) elastic network

4. Conclusıon

The results of this investigation strongly suggest that the boromophenole compound derived from marine sources displays significant potential as an innovative therapeutic agent for the Staphyloccocos aeurus. The comprehensive evaluation of diverse parameters demonstrated substantial enhancements when compared to the control, thus

indicating the robustness and feasibility of the synthetic ligand as a potential drug candidate. The amplified scores across a range of critical parameters emphasize its appropriateness for further exploration and experimental validation. These discoveries unveil novel avenues for pharmaceutical research directed towards mitigating the S. aureusinfection. While in-silico studies provide a foundational understanding, subsequent in vitro and in vivo experiments will be imperative to validate the efficacy and safety of the synthetic ligand as a treatment option. Collaborative efforts between computational biologists, medicinal chemists, and microbiologist will be crucial to advance this discovery from a theoretical concept to a tangible therapeutic solution.

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