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IN SILICO MOLECULAR DOCKING AND ADMET TOXICITY STUDIES OF POLYESTERS CONTAINING OXADIAZOLE MOIETY

C. SUBHA[1*], B. PAVITHRA[2] AND JOPHY VINCENT.V[2]

1: Assistant Professor, Department of Chemistry, Nirmala College for Women, Coimbatore, Tamil Nadu, India

2: Post Graduate Student, Department of Chemistry, Nirmala College for Women, Coimbatore, Tamil Nadu, India

***Corresponding Author: C. Subha; E Mail: subha.moses@gmail.com**

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ABSTRACT

Heterocyclic compounds are widely used in life sciences and technology. They find their application in drug industry also. Oxadiazole is a heterocyclic compound belonging to the class of diazoles which exhibit a wide variety of pharmacological activities like anti-bacterial, anti-fungal, anti-oxidant, anti-inflammatory, anti-cancer, anti-tumour, analgesic, due of the ability of the oxadiazole. Hence, we focused our attention on the study of biomedical application of aromatic polyesters containing substituted oxadiazole ring in their back bone.

Keywords: Oxadiazole, Polyesters, Anti-cancer, toxicity, Molecular docking

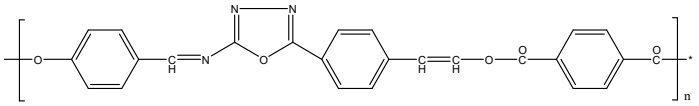
INTRODUCTION

Polymer is a class of materials which all of us use in our day-to-day life. They are the main constituents in our food, clothes, human bodies etc. Hence it is important for every chemist to understand its importance, properties and applications **[1]**. Application of polyesters is that they can used in industries because of excellent properties like high tensile strength, abrasion, resistance, and resilience and also used in making films for they are of good balance between mechanical strength and barrier properties against oxygen, smells and oils **[2]**. Computational studies are the crucial

steps in the drug designing. There are numerous areas of computational studies and one of them is identification of relationships between chemical structures and properties and recognized as QSAR. Quantitative structural activity relationship practices molecular parameters to enumerate a pharmacological or chemical property for a set of molecules **[3]**. Docking study is the computational routine to determine probable binding manners of a ligand to the dynamic site of a receptor. It makes an image of the dynamic site with interaction points known as grid. Then it fits the ligand in the binding site either by grid search or energy search **[4]**.

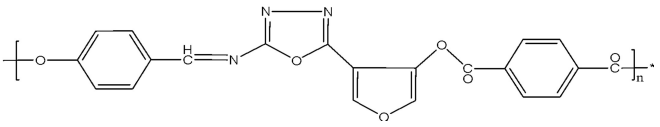
STRUCTURE OF POLYESTERS:

Polymer (P1):



(Polyester)

Polymer (P2):



METHODOLOGY

In our present study, *in silico* molecular docking and ADMET toxicity studies were carried out using BIOVIA Discovery Studio (DS) 2017 software.

1.1.Preparation of protein

The X-ray diffraction-based Crystal Structure of human HDAC8 complexed with SAHA (PDB ID: 1T69) with a resolution 2.91 Å for Anti-cancer and Structural insight into the quinolone-DNA cleavage complex of type IIA topoisomerases (PDB ID: 3FOF) for anti-bacterial analysis were selected. Hydrogen was added to the protein 1T69 and 3FOF by applied the Forcefield algorithm subsequently the energy of protein was minimized using CHARM forcefield in DS.

1.2. Ligand preparation

The polymer 1 and polymer 2 and standard drug pazopanib, Moxifloxacin were drawn in chemdraw software, subsequently, energy minimized and saved in SDF file format for docking studies.

1.3. Docking study

A molecular docking study was performed, to evaluate the most preferred geometry of the protein-ligand complex. A computational docking study was used to analyze structural complexes of the 1T69

and 3FOF with polymers in order to understand the structural basis of these target proteins. Possible binding modes between the ligands and these target proteins were studied by CDOCKER (CHARMm-based DOCKER) protocol incorporated within DS. The parameter to run the CDOCKER was tabularized in **Table 1**. The algorithm offers full ligand flexibly and employs CHARMm force fields. Ligand binding affinity was calculated using CDOCKER energy, CDOCKER Interaction energy, Hydrogen bonds, binding energies, protein energy and ligand-protein complex energy. The CDOCKER energy is mentioned in negative values. More negative value energy is indicated as a higher binding affinity of the ligands with the target protein.

Table 1: Parameter of CDOCKER protocol

Input Receptor	**Input/3FOF.dsv**
Input Ligands	**/Input/Total_min_ligands.sd**
Input Site Sphere	**-23.9454, 29.2003, 7.29961, 9**
Top Hits	**1**
Random Conformations	**10**
Random Conformations Dynamics Steps	**1000**
Random Conformations Dynamics Target Temperature	**1000**
Include Electrostatic Interactions	**True**
Orientations to Refine	**10**
Maximum Bad Orientations	**800**
Orientation vdW Energy Threshold	**300**
Simulated Annealing	**True**
Heating Steps	**2000**
Heating Target Temperature	**700**
Cooling Steps	**5000**
Cooling Target Temperature	**300**
Forcefield	**CHARMm**
Use Full Potential	**Yes**
Grid Extension	**8.0**
Ligand Partial Charge Method	**CHARMm**
Random Number Seed	**314159**
Final Minimization	**Full Potential**
Final Minimization Gradient Tolerance	**0**
Parallel Processing	**False**
Parallel Processing Batch Size	**25**
Parallel Processing Server	**localhost**
Parallel Processing Server Processes	**2**
Parallel Processing Preserve Order	**True**
Random Dynamics Time Step	**0.002**

1.4. ADMET Toxicity Analysis

Absorption, distribution, metabolism, elimination, and toxicity (ADMET) properties were predicted using ADMET descriptors in Discovery Studio (Accelrys, San Diego, CA, USA). The module uses six mathematical models, to quantitatively predict properties by a set of rules/keys that specify threshold ADMET characteristics for the chemical structure of the molecules based on the available drug information: ADMET absorption predicts human intestinal absorption (HIA) after oral administration. The model was

developed using 199 compounds in the training set based on the calculations AlogP (ADMET AlogP98) and 2D polar surface area (PSA 2D). The absorption levels of HIA model are defined by 95% and 99% confidence ellipses in the ADMET PSA 2D, ADMET AlogP98 plane. The model is based on a genetic partial least squares method on a training set of 784 compounds with experimentally measured solubilities.

RESULT AND DISCUSSION

The 3 D structure of the polymer 1 and polymer 2 were showed in **Figure 1** and **Figure 2**.

Anti-cancer activity

In silico anti-cancer activity of the polymer 1 and polymer 2 were analysed in molecular docking studies. In this docking analysis pazopanib used as a standard drug for compare the binding activity of the polymers and Crystal Structure of human HDAC8 complexed with SAHA (PDB ID: 1T69) was used for target protein **(Figure 3)**. The CDOCKER binding energy of the polymers and the standard drug were listed in **Table 2**. From the docking result the polymer 1 and polymer has higher binding affinity compared to the standard drug. **Figure 4 and Figure 5** shows the 3D and 2D binding interactions of the polymer 1. In this molecular docking analysis, the polymer 1 formed one strong hydrogen bond interaction with Arg 37 amino acid of the human HDAC8 receptor. The hydrogen bond length is 2.1Å. The His 180 amino acid formed Pi-Sigma interaction with the H atom of the polymer 1 **(Figure 5)**. Additionally, the aromatic benzene group of the polymer 1 formed two Pi-Pi stacked interaction with Phe 208 and Phe 152 amino acid respectively. Similarly, Sis 153 shows Pi-Alkyl interaction with benzene group of the polymer 1. The other active site amino acids of the human HDAC8 receptor shows non bonded Vander Waals interaction with polymer 1 and shows higher binding energy of this polymer. The above overall interactions increase the CDOCKER energy value 26.3461 $Kcal/mol^{-1}$ of polymer 1.

The 3D and 2D binding interactions of the polymer 2 is shown in **Figure 6 and Figure 7**. In polymer 2 interaction analysis, the ketone atom of the polymer 2 form one strong hydrogen interaction with Tyr 100 amino acid **(Figure 7)**. The same Tyr 100 amino acid interacted with the polymer by Pi-Pi- stacked interaction. Further, the furan ring forms two Pi-Pi- T shaped interaction with the Phe 208 and Phe 207 residues. The His 180 and Trp 141 forms Pi-Alkyl interaction with polymer 2 **(Figure 7)**. Moreover, Cys 153 and other active site residues forms Pi- sulfur and van der Waals interaction with the polymer 2.

The CDOCKER energy of the polymer 2 is 25.8961 Kcal/mol^{-1}.

In this anti-cancer molecular docking studies, pazopanib drug used as standard for compared activity of the polymer 1 and polymer 2. The DOCKER energy of the pazopanib is 22.3864 Kcal/mol^{-1}. Its shows low binding energy compared to polymer 1 and polymer 2. 3D and 2D interactions of the pazopanib shows in **Figure 8 and Figure 9**. The ketone group of the pazopanib forms two strong hydrogen bond interaction with Lys 33 and Tyr 100 residues. The Phe 152 and Phe 208 forms Pi-Pi stacked interactions with pazopanib drug **(Figure 9)**.

Antibacterial activity

The secondary structure of the quinolone-DNA cleavage complex of type IIA topoisomerases receptor is shown in **Figure 10**. In this in silico molecular docking studies of antibacterial activity, moxifloxacin used as a standard drug. From the result, the polymer 1 and polymer 2 shows good binding affinity compared to the moxifloxacin drug.

In this anti-bacterial docking studies, the polymer 1 was integration with the DNA which bind with the type IIA topoisomerases receptor. This polymer forms Van der Waals interaction with guanine and thymine nucleotides. Fuhrer the benzene group form Pi-Pi stacked interaction with adenine nucleotide **(Figure 12)**. In polymer 2 interaction analysis, the guanine forms strong hydrogen bond with the ketone group of the polymer 2. The adenine nucleotide forms carbon hydrogen bond interaction with polymer 2 **(Figure 14)**. The CDOCKER energy of the polymer 1 and polymer 2 is 27.2594 Kcal/mol^{-1} and 24.9743 Kcal/mol^{-1} respectively. The moxifloxacin drug shows low binding energy (-20.3572 Kcal/mol^{-1}) compared to the polymer 1 and polymer 2. It forms carbon hydrogen bond with adenine of the DNA. The guanine forms van der Waals interaction with polymer 2 **(Figure 16)**.

ADMET analysis

Chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET), play key roles in drug discovery and development. A high-quality drug candidate should not only have sufficient efficacy against the therapeutic target, but also show appropriate ADMET properties at a therapeutic dose. A lot of in silico models are hence developed for prediction of chemical ADMET properties. However, it is still not easy to evaluate the drug-likeness of compounds in terms of so many ADMET properties.

The ADMET result of polymer 1 and polymer 2 are declared in **Table 4** and the plot of polar surface area (2D PSA) and AlogP for these compounds are represented

in **Figure 17**. The intestinal absorption and blood brain barrier penetration were predicted by 2D PSA and AlogP that include 95% and 99% confidence ellipses in ADMET study. The region of ellipses defines, where the compounds are expected as well-absorbed. The absorption level (human intestinal absorption-HIA) of all the molecules shows good absorption (value 0 as good absorption). The absorption levels of HIA model are defined by 95% and 99% confidence ellipses in the ADMET.

Similarly, aqueous solubility of all the compounds has good solubility and absorption nature in aqueous media. Further, all compounds are satisfactory with respect to CYP2D6 liver, suggesting that PA are non-inhibitors of CYP2D6. The model orders either as "toxic" or "nontoxic" and gives a certainty level pointer of the probability of the model's prescient exactness. Our results indicate that all compounds are nontoxic to liver and thus they experience significant first-pass effect. According to the model for the all compounds to have an optimum cell permeability should follow the criteria (PSA < 140 $Å^2$ and AlogP98 < 5). Further, the hepatotoxicity level of all the molecules were calculated, the molecules with liver toxic nature were filtered out. Similarly, all the molecules were found to be satisfactory with respect to CYP 450 2D6 liver enzyme, suggesting that the derivatives molecules were non inhibitors of the metabolic enzyme. Finally, the PPB prediction denotes that all the molecules have binding ≤90 % clearly revealing that the molecules have good bioavailability and are not likely to be highly bound to carrier proteins in the blood. All the compounds showed polar surface area (PSA) < 140 $Å^2$. Since the AlogP98 criteria, all the compounds had AlogP98 value <5. From the result of ADMET, we found that the molecules have drug likeness properties and also it will be useful as a potent new drug in anti-cancer and anti-bacterial activity.

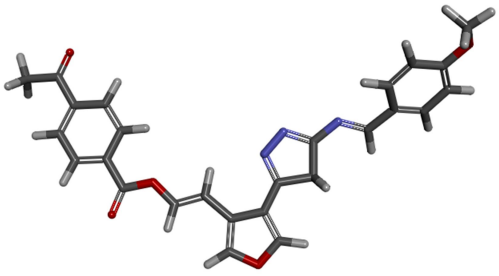


Figure 1: 3D structure of the polymer 1

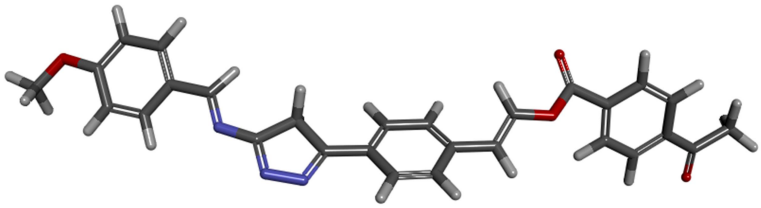


Figure 2: 3D structure of the polymer 2

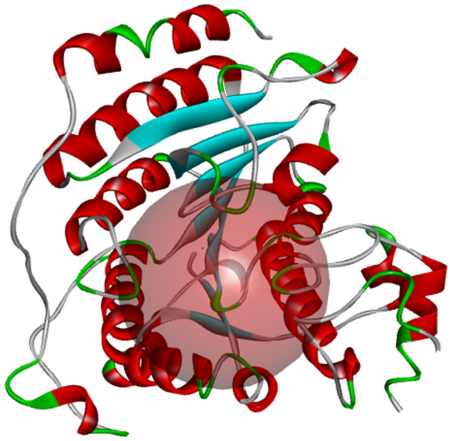


Figure 3: Secondary structure of the human HDAC8 receptor with active site sphere

Table 2: CDOCKER energy of the polymers in human HDAC8 receptor

Molecules	-CDOCKER energy (Kcal/mol)
Polymer 1	26.3451
Polymer 1	25.8961
pazopanib	22.3864

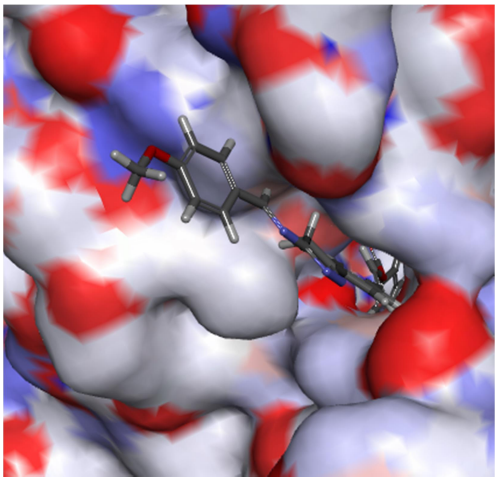


Figure 4: 3D binding interaction of the polymer 1 with the human HDAC8 receptor

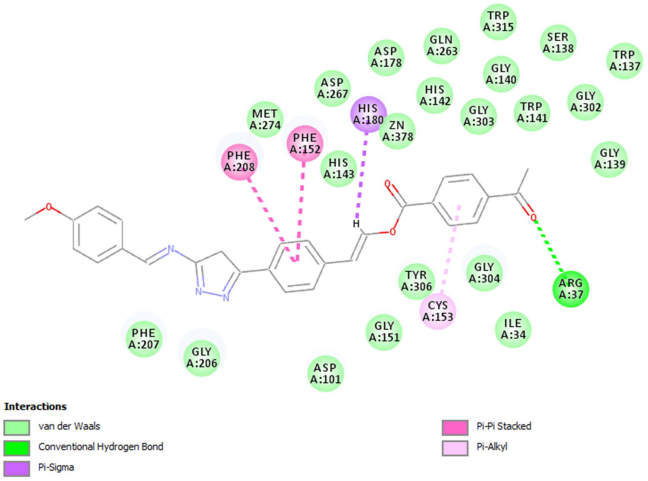


Figure 5: 2D binding interaction of the polymer 1 with the human HDAC8 receptor

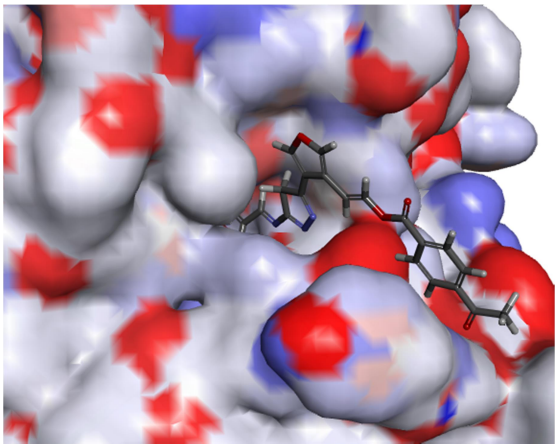


Figure 6: 3D binding interaction of the polymer 2 with the human HDAC8 receptor

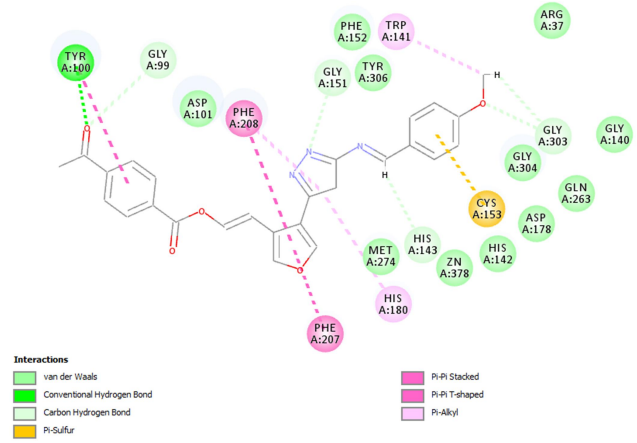


Figure 7: 2D binding interaction of the polymer 2 with the human HDAC8 receptor

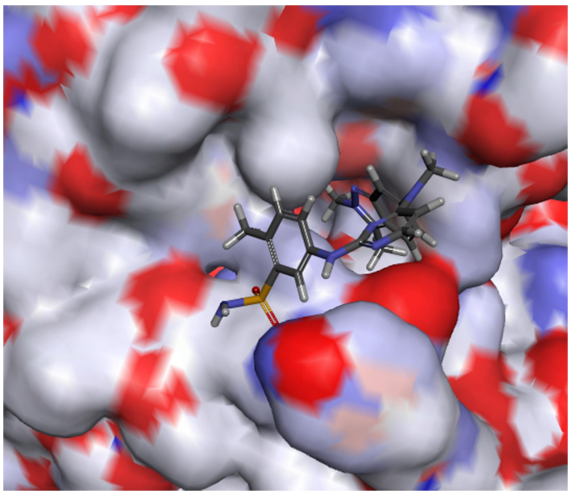


Figure 8: 3D interaction of the pazopanib drug in human HDAC8 receptor

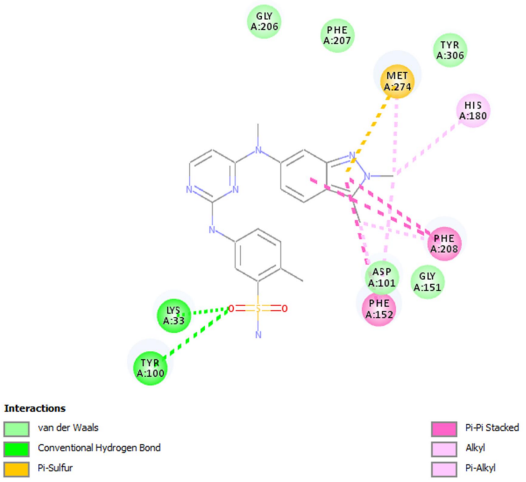


Figure 9: 2D interaction of the pazopanib drug in human HDAC8 receptor

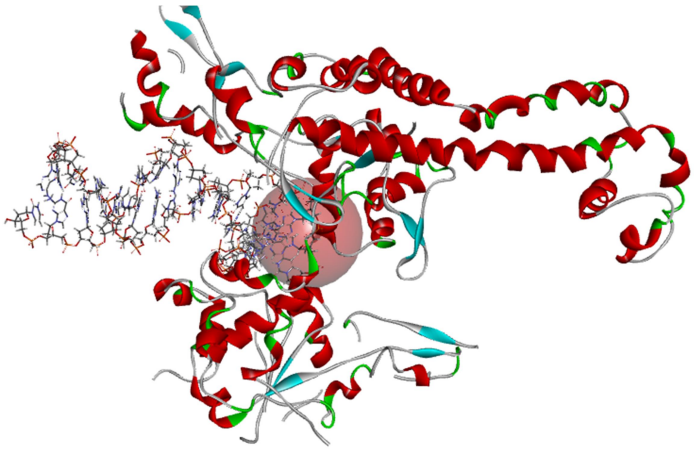


Figure 10: Quinolone-DNA cleavage complex of type IIA topoisomerases

Table 3: CDOCKER energy of the polymers in type IIA topoisomerases receptor

Molecules	-CDOCKER energy (Kcal/mol)
Polymer 1	27.2594
Polymer 1	24.9743
Moxifloxacin	20.3572

Polymer 1

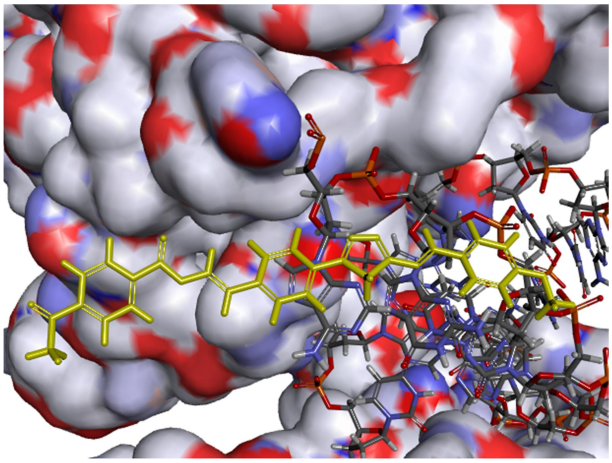


Figure 11: 3D binding interaction of polymer 1 with the type IIA topoisomerases receptor

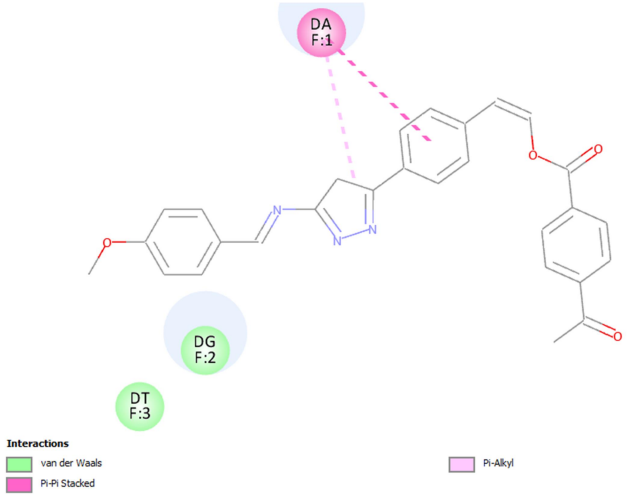


Figure 12: 2D binding interaction of polymer 1 with the type IIA topoisomerases receptor

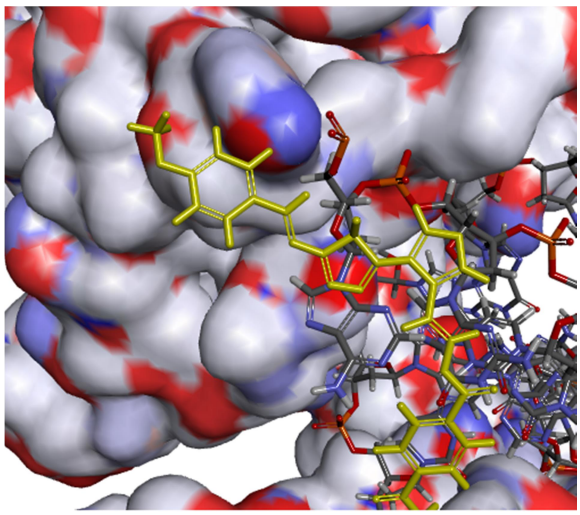


Figure 13: 3D binding interaction of polymer 2 with the type IIA topoisomerases receptor

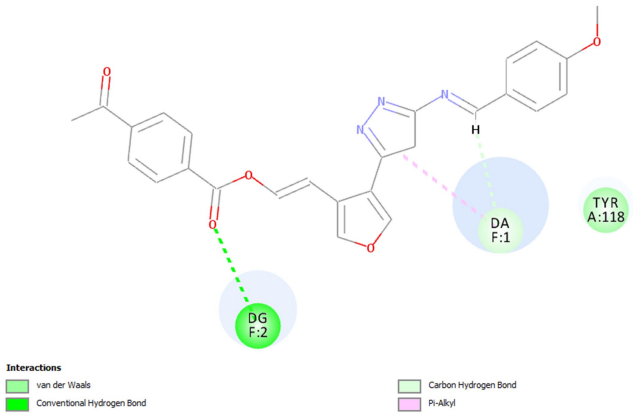


Figure 14: 2D binding interaction of polymer 2 with the type IIA topoisomerases receptor

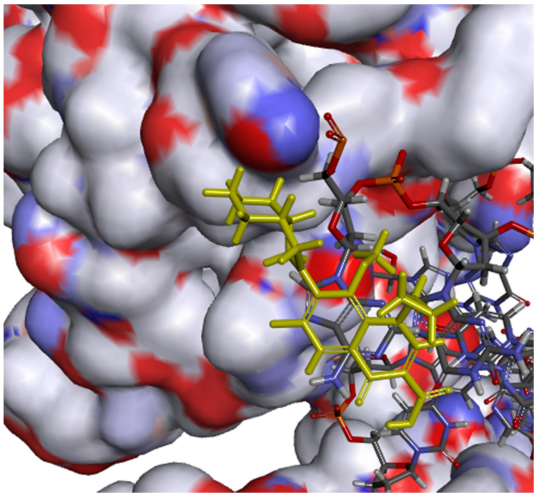


Figure 15: 3D binding interaction of moxifloxacin with the type IIA topoisomerases receptor

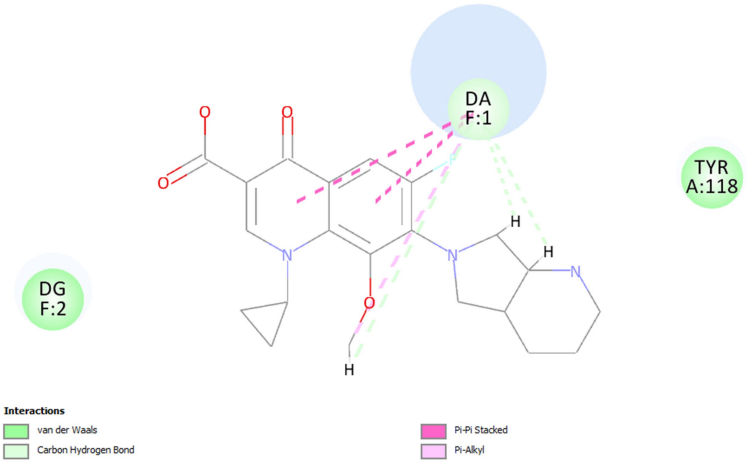


Figure 16: 2D binding interaction of moxifloxacin with the type IIA topoisomerases receptor

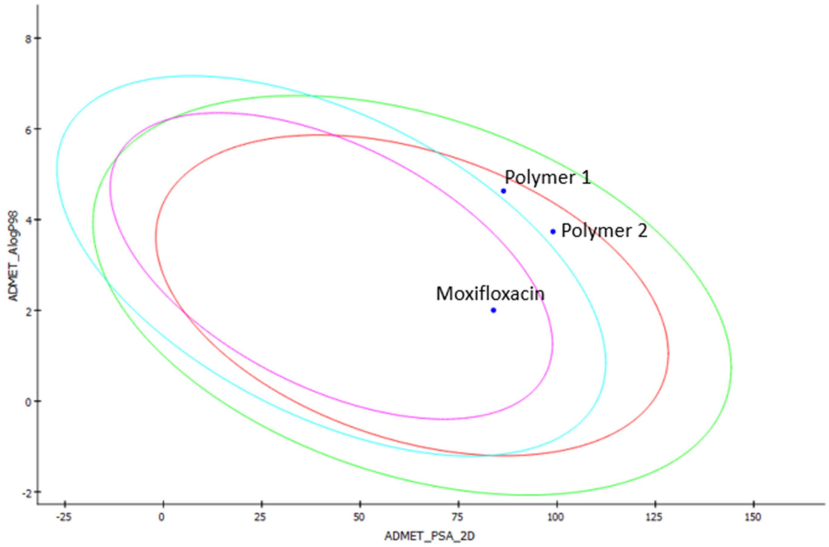


Figure 17: ADMET prediction analysis of polymer 1, polymer 2 and moxifloxacin drug

Table 4: ADMET properties of polymer 1 and polymer 2

Mol. Name	Absorption level	Solubility level	BBB level	PPB level	Hepatotoxic level	CYP 2D6	PSA 2D	AlogP98
Polymer- 1	Good	Good	Low	<90%	No	No	45.24	3.48
Polymer- 2	Good	Good	Low	<90%	No	No	65.38	3.94
Moxifloxacin	Good	Good	Low	<90%	No	No	82.34	4.19

CONCLUSION

In the present work the molecular docking study of polymer 1 and polymer 2 molecules was performed by Discovery studio software. In this study we have used human HDAC8 receptor and quinolone-DNA cleavage complex of type IIA topoisomerases identified best anticancer target. Molecular docking results displayed polymer 1 and polymer 2 showed the better docked score with good binding affinity of receptor and comparable to the standard drug. Also, these polymers show good drug likeness properties. From these in silico results, in future we can use this polymer as suitable drug molecules in anti-cancer and anti-bacterial activity.

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