DESIGNING AND DOCKING STUDIES OF ARYL BIOISOSTERES OF ENZALUTAMIDE FOR PROSTATE CANCER THERAPY

Abstract

Cancer is a major health problem throughout the world. Androgens like testosterone and dihydrotestosterone are essential for the growth and development of the prostate gland. Androgenic receptors are overexpressed, which promotes the progression of prostate cancer (PC) therefore, androgenic receptors are a key target in the therapy of PC. A non-steroidal antiandrogen drug called enzalutamide (ENZ) is used to treat PC; however, it also causes toxicities such as cardiovascular toxicity, acute myocarditis, hypertension, and seizures. The study's goal is to use a bioisosteric approach to replace the aryl group in the ENZ molecule in order to generate a less toxic analogues with improve pharmacokinetic properties and reduce toxicity. The physicochemical, medicinal, pharmacokinetic, and toxicological characteristics of the designed analogues were calculated using ADMETlab 2.0. Drug likeness (DL) and drug score (DS) of analogues were calculated using OSIRIS property explorer (PEO). The docking analysis of designed ENZ analogues was carried out with the help of AutoDock Vina (ADV). Designed analogues met the requirements for acceptability and followed the Lipinski rule of five. The ADMET profile of designed analogues was found to be optimal to good. However, no hydrogen bond was found in docking interactions between ligands and protein. Based on their QED score, ADMET properties, toxicity score, DL, DS and docking interactions, ligands E6 and E20 may be used for further screening as androgen receptor (AR) antagonists in management of PC.

Keywords: Enzalutamide; Bioisosteric Approach; Prostate Cancer; ADMET; Molecular Docking

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I. INTRODUCTION

The Global Cancer Observatory (GLOBOCAN) forecasts 19.3 million new cases of cancer globally in 2020. India came in third in term of cancer cases after China and the United States. According to GLOBOCAN, there will be 2.08 million new cases of cancer in India by 2040, an increase of 57.5% from 2020. The estimated number of cancer cases in India for the year 2022 was 1.46 million (100.4 for every 100,000). PC is the third leading site of cancer (6.1%) in men, causing a significant portion of all cancer-related mortalities [1, 2]. The prostate gland is a male sexual accessory that is situated in the pelvic area and is encircled by the urethra. For the growth and development of the prostate gland, androgenic hormones such as testosterone and dihydrotestosterone are essential. However, overexpression of testosterone and dihydrotestosterone may cause the proliferation of prostate cells [3-5].

PC is treated with antiandrogen drugs. Anti-androgen therapy was often first intended to be used in conjunction with castration, however, it has since been reported to be used alone. Castration is preferable to antiandrogen therapy in cases of metastatic cancer. In 1940, Hoggins and Hodges claimed that PC was an androgen-dependent disease. Since then, gonadal androgen deprivation and other techniques have advanced hormonal treatment via iterative development. Gonadotropin-releasing hormone (GnRH) agonists (Leuprolide), androgen biosynthesis inhibitors (Abiraterone), first generation non-steroidal AR antagonists (Flutamide) and second-generation non-steroidal AR antagonists (Enzalutamide) are among the therapies used in PC treatment [6,7].

ENZ is a first-generation nonsteroidal antiandrogen inhibitor that is taken orally and is intended to overcome acquired resistance to bicalutamide, nilutamide, and flutamide, among other first-generation nonsteroidal antiandrogens. Enzalutamide enhanced overall survival in castration-resistant prostate cancer regardless of whether it was administered before or during docetaxel treatment, according to prior studies. Furthermore, ENZ is used as the initial androgen deprivation treatment for metastatic prostate cancer [8,9]. Patients treated with ENZ significantly increased the incidence of cardiovascular toxicity, acute myocarditis,and arterial hypertension[10].

Therefore, it is necessary to modify the ENZ molecule to get a novel ENZ derivative with less toxicity. Bioisosterism is a strategy of medicinal chemistry for the rational design of new drugs, applied to a lead compound as a special process of molecular modification. A bioisosteric replacement transforms an active compound into another compound by swapping functional groups of a molecule with other substructures that share similar shapes, volumes, electronic distributions and physiochemical properties, which produce similar biological properties. Bioisosteric replacement is widely used in drug discovery to improve potency and selectivity, solve problems associated with drug pharmacokinetics and remove unwanted side effects such as toxicity and metabolic liabilities [11]. The aim of the study is to develop novel analogues of ENZ by modifying the aryl group in the ENZ molecule using a bioisosteric approach with less toxic effects.

II. MATERIAL AND METHODS

1. **Designing Enzalutamide Bioisosteres:** MolOpt is used for the generation of bioisosteres based on navigating historical bioisosteric group space and identifying new bioisosteric transformation ideas [12]. Bioisosteres of ENZ were designed by modifying the aryl group in the ENZ molecule is shown in Figure 1.

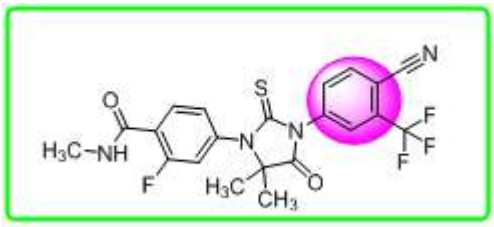


Figure 1: Structure of the enzalutamide and modified group

2. **Prediction of Pharmacokinetic and Toxicological (ADMET) Properties:** Screening of the absorption, distribution, metabolism and excretion and toxicological (ADMET) properties of designed ENZ bioiosteres was computed using ADMETlab 2.0. It is an integrated online platform with eighty-four quantitative and four qualitative regression models with authentic and extensive predictions of ADMET properties for new ligands that mimic mammalian ADMET properties [13-16].

3. **Prediction of Drug Likeness and Drug Score:** There are several ways to evaluate a DL as a medicine, some of which use topological descriptors, fingerprints of MDL structure keys, or other factors like cLogP and molecular weights. DS combines the drug likeness, cLogP, logS, molecular weight, and toxicity concerns into a single, useful number that may be used to assess the compound's overall ability to be approved as a drug. DL and drug score DS were predicted using the PEO web tool [17].

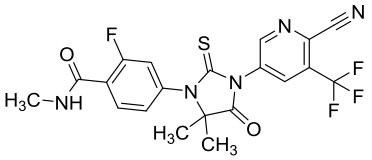
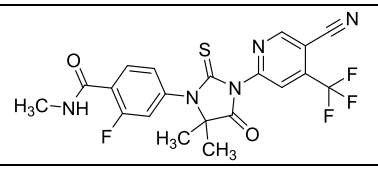
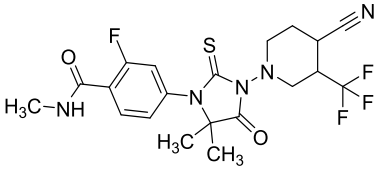
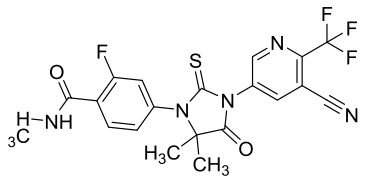
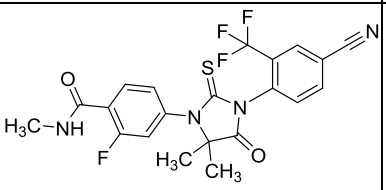
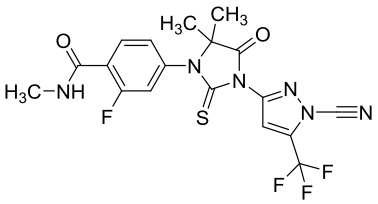
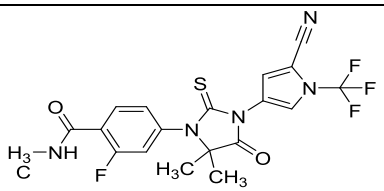
4. **Molecular Docking Study:** Now a days, molecular docking is extensively used in drug design and discovery. It is broadly used for the study of binding interactions between target and ligand. The molecular docking approach can represent the atomic-level interaction between a small molecule and a protein, allowing us to characterise small molecules in target protein binding sites and understand key biological processes [18, 19]. A molecular docking study of designed analogues was carried out using the crystal structure of the androgen receptor (PDB ID: 2OZ7), and this study involved a number of steps like preparation of the ligand structures, preparation of the protein structures and protein-ligand docking using ADV.

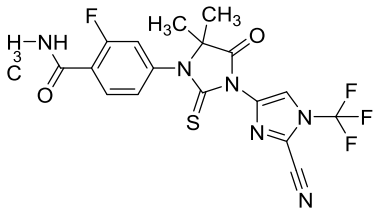
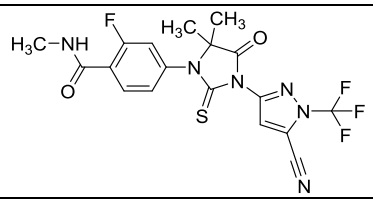
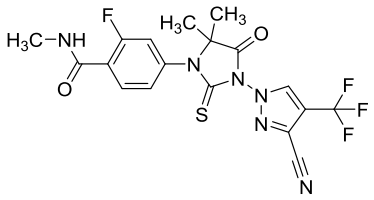
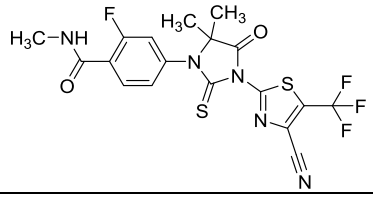
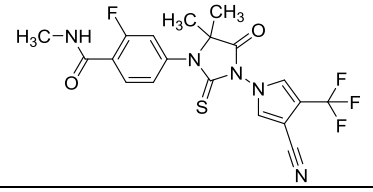
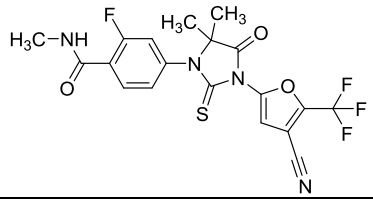
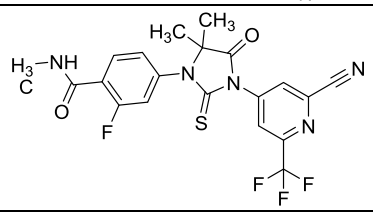
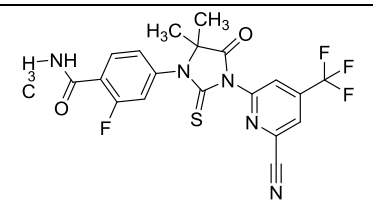
III. RESULTS AND DISCUSSION

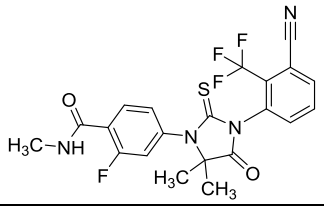
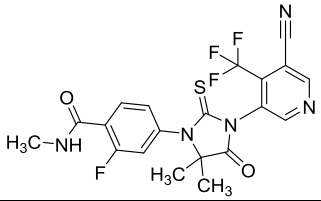
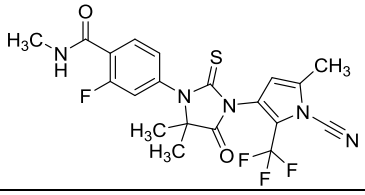
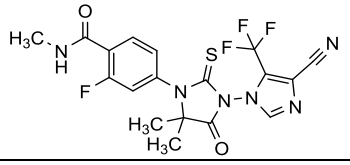
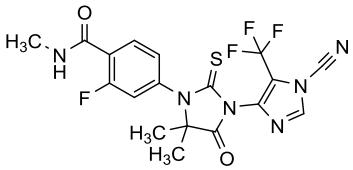
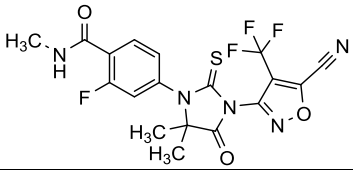
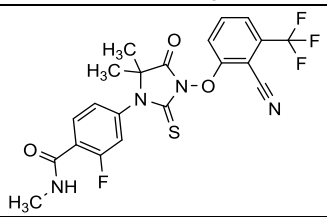
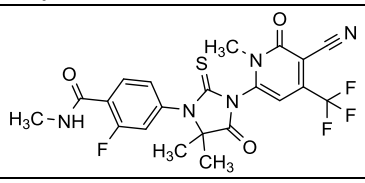
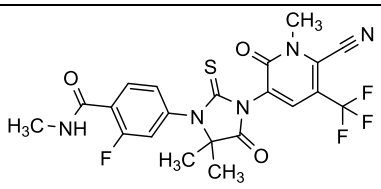
1. **Bioisosteres of the Aryl Group in Enzalutamide:** In the drug discovery techniques, the bioisosteric approach is generally used to alter pharmacokinetic and pharmacodynamic properties. MolOpt generated 200 replaceable groups for the aryl group in the ENZ molecule and their ADMET properties were also computed. Among those, the structure of selected ENZ analogues is shown in Table 1.

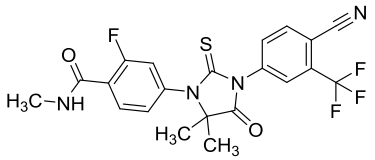
2. **Prediction of Molecular Properties:** The molecular properties of the designed analogues were calculated using ADMETlab 2.0, as shown in Table 1. Lipinski's rule of five predicts the absorption, permeation and bioiavailability of the drug candidates [20]. The result indicates that all analogues with ENZ follow the lipinski rule, indicating designed analogues may be considered as drug candidates.

Table 1: Molecular Structure and Physicochemical Properties of ENZ Analogues

S. No.	Entry No.	Structure	MW	nHA	nHD	LogP	LogS	nRot	TPSA
1	E1		465.09	7	1	2.28	-4.86	5	89.33
2	E2		465.09	7	1	2.545	-4.89	5	89.33
3	E3		471.14	7	1	1.874	-4.38	5	79.68
4	E4		465.09	7	1	2.215	-4.87	5	89.33
5	E5		464.09	6	1	3	-4.98	5	76.44
6	E6		454.08	8	1	2.71	-4.92	5	94.26
7	E7		453.09	7	1	3.06	-5.23	5	81.37

8	E8		454.08	8	1	2.67	-4.93	5	94.26
9	E9		454.08	8	1	2.82	-5.13	5	94.26
10	E10		454.08	8	1	2.24	-4.44	5	94.26
11	E11		471.04	7	1	3.24	-5.02	5	89.33
12	E12		453.09	7	1	2.69	-4.51	5	81.37
13	E13		454.07	7	1	2.59	-4.83	5	89.58
14	E14		465.09	7	1	2.44	-4.97	5	89.33
15	E15		465.09	7	1	2.85	-5.00	5	89.33

16	E16		464.09	6	1	2.91	-4.96	5	76.44
17	E17		465.09	7	1	1.96	-4.59	5	89.33
18	E18		467.1	7	1	2.68	-4.92	5	81.37
19	E19		454.08	8	1	1.81	-4.43	5	94.26
20	E20		454.08	8	1	2.05	-4.65	5	94.26
21	E21		455.07	8	1	2.49	-4.79	5	102.47
22	E22		480.09	7	1	2.99	-4.99	6	85.67
23	E23		495.1	8	1	1.83	-4.93	5	98.44
24	E24		495.1	8	1	2.19	-4.95	5	98.44

STD	ENZ		464.09	6	1	3.01	-5.04	5	76.44

MW; molecular weight, nHA; number of hydrogen bond acceptors, nHD; number of hydrogen bond donors, nRot; number of rotatable bonds, TPSA; topological polar surface area, logP; the logarithm of partition coefficient value, logS; the logarithm of aqueous solubility value.

3. **Prediction of Medicinal Properties:** The medicinal properties of designed analogues were calculated using ADMETlab 2.0 is shown in Table 2. QED is based on the eight drug-like related properties and used to measure drug-likeness. The QED value of all ENZ analogues was greather than 0.5. All analogues will be easy to synthesise as per synthetic accessibility prediction criteria (<6). Lipinski, Pfizer and golden triangle (GT) rule for all analogues has been found acceptable, indicating good bioavailability.

Table 2: Medicinal Chemistry of Analogues

Entry No.	QED	Synth	Fsp3	MCE-18	Lipinski	Pfizer	GSK	GT
E1	0.552	3.07	0.25	54	Accepted	Accepted	Rejected	Accepted
E2	0.552	3.05	0.25	54	Accepted	Accepted	Rejected	Accepted
E3	0.540	4.23	0.5	88	Accepted	Accepted	Rejected	Accepted
E4	0.552	3.11	0.25	54	Accepted	Accepted	Rejected	Accepted
E5	0.549	2.89	0.238	54	Accepted	Accepted	Rejected	Accepted
E6	0.566	3.41	0.278	54	Accepted	Accepted	Rejected	Accepted
E7	0.570	3.39	0.263	54	Accepted	Accepted	Rejected	Accepted
E8	0.566	3.47	0.278	54	Accepted	Accepted	Rejected	Accepted
E9	0.566	3.41	0.278	54	Accepted	Accepted	Rejected	Accepted
E10	0.565	3.44	0.278	54	Accepted	Accepted	Rejected	Accepted
E11	0.545	3.32	0.278	54	Accepted	Accepted	Rejected	Accepted
E12	0.571	3.41	0.263	54	Accepted	Accepted	Rejected	Accepted
E13	0.563	3.30	0.263	54	Accepted	Accepted	Rejected	Accepted
E14	0.552	3.08	0.25	54	Accepted	Accepted	Rejected	Accepted
E15	0.552	3.13	0.25	54	Accepted	Accepted	Rejected	Accepted
E16	0.549	3.00	0.238	54	Accepted	Accepted	Rejected	Accepted
E17	0.552	3.19	0.25	54	Accepted	Accepted	Rejected	Accepted
E18	0.552	3.39	0.3	56	Accepted	Accepted	Rejected	Accepted
E19	0.565	3.42	0.278	54	Accepted	Accepted	Rejected	Accepted
E20	0.566	3.45	0.278	54	Accepted	Accepted	Rejected	Accepted
E21	0.561	3.34	0.278	54	Accepted	Accepted	Rejected	Accepted
E22	0.530	3.19	0.238	54	Accepted	Accepted	Rejected	Accepted
E23	0.520	3.20	0.286	58	Accepted	Accepted	Rejected	Accepted
E24	0.520	3.33	0.286	58	Accepted	Accepted	Rejected	Accepted
ENZ	0.549	2.83	0.238	54	Accepted	Accepted	Rejected	Accepted

QED; a measure of drug-likeness based on the concept of desirability, Synth; synthetic accessibility score, Fsp3; the number of sp3 hybridized carbons/total carbon count, MCE-18; medicinal chemistry evolution in 2018, GT; golden triangle.

4. **Prediction of Pharmacokinetic (ADME) Properties:** Pharmacokinetic properties such as absorption (Caco-2, MDCK and HIA), distribution (BBB, PPB and VD), metabolism (CYP1A2) and excretion (CL and $T_{1/2}$) have been calculated using ADMETlab 2.0 and results are shown in Table 3. The caco-2 score of all analogues was found excellent (> -5.15) with the exception of E1, E3, E6, E7, E14, E18, E23, E24 and ENZ, which indicate proper *in- vivo* drug permeability. HIA scores of designed analogues in the range between 0 and 0.3 indicate excellent oral bioavailability. The MDCK score that predicts the *in-vitro* permeability of analogues was found to be excellent. The BBB prediction of analogues found in the range between 0.823-0.983 means they can cause central nervous system (CNS) side effects. Analogues E3, E4, E6-E9, E17, E18 and E20 have proper plasma protein binding (PPB) found less than 90%, which indicates the increase in distribution volume and a decrease in the half-life of elimination. The volume of distribution (VD) of all designed analogues was found to have anexcellent score in the range between 0.04 and 20. Cytochrome P450 (CYT P450) plays a crucial role in the metabolism of drugs. The CYT P450 enzyme is a substrate for analogues, which cause molecules to undergo metabolism. If analogues inhibit the enzyme, however, metabolism will not occur. All designed analogues have excellent clearance, with the score of ≥ 5 indicating a low risk of toxicity with the exception of E18 and E20. All analogues have a $T_{1/2}$ score in the range (0 to 0.3) with exception of E8 and E18-E20, which indicate proper clearance from the body.

Table 3: ADME Profile of Analogues

Entry No.	Caco-2	HIA	MDCK	BBB	PPB (%)	VD	Fu (%)	CYP1A2		CL	$T_{1/2}$
								Inh	Sub		
E1	-5.188	0.018	EX	0.962	91.18	1.126	2.84	-	+	6.782	0.183
E2	-5.046	0.017	EX	0.965	91.80	0.981	3.61	-	+	6.661	0.121
E3	-5.237	0.018	EX	0.823	78.33	1.104	9.89	-	+	6.703	0.091
E4	-5.143	0.018	EX	0.956	89.10	1.095	4.50	-	+	5.376	0.22
E5	-5.125	0.02	EX	0.976	93.77	0.97	2.06	-	+	6.982	0.107
E6	-5.194	0.036	EX	0.933	73.61	1.362	9.87	+	-	6.596	0.216
E7	-5.210	0.022	EX	0.979	83.67	1.033	5.55	-	+	6.825	0.258
E8	-5.075	0.021	EX	0.976	83.90	0.711	6.21	-	+	6.786	0.319
E9	-5.134	0.041	EX	0.972	83.38	0.93	3.96	-	+	6.466	0.181
E10	-5.060	0.06	EX	0.943	95.89	0.868	2.59	-	+	7.804	0.196
E11	-4.886	0.029	EX	0.855	97.12	0.758	1.48	-	+	6.666	0.092
E12	-4.982	0.019	EX	0.944	91.69	0.874	3.87	-	+	7.407	0.188
E13	-5.031	0.026	EX	0.852	94.66	1.241	1.82	+	-	7.558	0.115
E14	-5.154	0.022	EX	0.958	91.82	0.697	2.27	-	+	5.284	0.178
E15	-5.095	0.023	EX	0.929	94.76	0.602	2.12	+	-	6.788	0.127
E16	-5.141	0.016	EX	0.976	94.56	1.116	2.03	-	+	6.564	0.163
E17	-5.070	0.015	EX	0.919	87.04	1.245	6.33	-	+	5.513	0.289
E18	-5.183	0.04	EX	0.967	77.58	1.891	8.65	-	+	4.851	0.393
E19	-5.098	0.029	EX	0.956	92.85	0.89	3.81	-	+	7.398	0.545
E20	-5.043	0.029	EX	0.867	66.93	1.362	40.61	-	+	4.464	0.457
E21	-4.932	0.048	EX	0.823	93.67	1.338	2.82	+	-	6.441	0.246
E22	-5.094	0.033	EX	0.837	98.11	0.827	1.23	-	+	7.904	0.108

E23	-5.252	0.041	EX	0.983	91.35	1.251	4.05	-	+	5.485	0.174
E24	-5.205	0.041	EX	0.983	90.52	1.202	4.16	-	+	5.953	0.147
ENZ	-5.184	0.014	EX	0.964	94.90	1.047	1.92	-	+	6.997	0.122

Caco-2; the human colon adenocarcinoma cell lines, MDCK; Madin−Darby canine kidney cells, HIA; human intestinal absorption, PPB; plasma protein binding, BBB; blood-brain barrier, VD; volume distribution, Fu; the fraction unbound in plasms, EX; Excellent. (-);inhibitor, (+); substrate of human cytochrome P450 (five isozymes-1A2), CL; the clearance of a drug, $T_{1/2}$; the half-life of a drug.

5. **Prediction of Toxicity Properties:** Toxicological properties of analogues such as DILI, Ames, NR-AR and others that were calculated using ADMETlab 2.0 are shown in Table 4. The DILI and H-HT scores for analogues were found to the same as those ENZ with tocxic effects. The mutagenicity effects of all analogues were predicted to be safer with expection of E19, indicating that the analogues could not cause mutagenesis. The ROA prediction of analogues E3 and E13 were found in a safer range (< 0.3) which is an important safety profile for drug candidates, whereas ENZ is toxic. The carcinogenicity of analogues are a serious issue because of their powerful effects on wellness and because they can damage the genome or disrupt cellular metabolism. According to the results of the carcinogenicity scores, E17 and E24 were moderately safe (0.3-0.7). NR-AR plays a crucial role in AR-dependent PC as well as androgen-related diseases. ENZ and their analogues were predicted to bind to the NR-AR, which could inhibit the activity of the androgen receptor.

Table 4: Toxicity Profile of Analogues

Entry No.	H-HT	DILI	Ames	ROA	Carc.	NR-AR	NR-AR-LBD
E1	0.976	0.989	0.030	0.778	0.786	0.036	0.050
E2	0.981	0.990	0.043	0.655	0.818	0.138	0.016
E3	0.990	0.985	0.149	0.226	0.961	0.051	0.003
E4	0.974	0.991	0.039	0.444	0.693	0.088	0.052
E5	0.956	0.985	0.062	0.485	0.769	0.052	0.011
E6	0.951	0.984	0.070	0.677	0.879	0.035	0.017
E7	0.977	0.985	0.079	0.471	0.968	0.005	0.005
E8	0.978	0.988	0.063	0.338	0.965	0.004	0.004
E9	0.968	0.986	0.132	0.580	0.965	0.003	0.006
E10	0.978	0.990	0.693	0.808	0.946	0.014	0.009
E11	0.972	0.993	0.083	0.848	0.876	0.009	0.335
E12	0.972	0.989	0.756	0.378	0.954	0.030	0.003
E13	0.985	0.992	0.328	0.791	0.923	0.024	0.017
E14	0.966	0.984	0.044	0.812	0.796	0.082	0.050
E15	0.967	0.984	0.038	0.645	0.754	0.072	0.018
E16	0.970	0.988	0.130	0.761	0.810	0.083	0.021
E17	0.969	0.991	0.029	0.785	0.563	0.031	0.013
E18	0.938	0.982	0.095	0.531	0.920	0.070	0.010
E19	0.976	0.990	0.931	0.284	0.951	0.014	0.004
E20	0.956	0.990	0.133	0.365	0.882	0.024	0.013

E21	0.997	0.997	0.228	0.587	0.936	0.021	0.039
E22	0.982	0.986	0.867	0.838	0.953	0.057	0.061
E23	0.969	0.979	0.211	0.320	0.755	0.059	0.008
E24	0.961	0.980	0.074	0.353	0.619	0.061	0.010
ENZ	0.975	0.986	0.062	0.668	0.850	0.155	0.036

H-HT; human hepatotoxicity, DILI; drug-induced liver injury, Ames; test for mutagenicity, ROA; rat oral acute toxicity, NR-AR; androgen receptor - a nuclear hormone receptor, NR-AR-LBD; molecule binds with LBD of androgen receptor.

6. **Drug Likeness and Drug Score Prediction:** In the current work, we have carried out a DL and DS analysis of ENZ analogues by the PEO. The findings are shown in Table 5. Table 5 clearly shows that E6 and E20 may be non-toxic as well as having good DL and DS. The DL score for ligand E6 was higher -4.54, followed by E20 (-5.92). The positive values for DS of ligands E6 and E20, with scores of 0.32 and 0.33, respectively indicate that E6 and E20 can act as potential drugs.

Table 5: Prediction of Drug Likeness and Drug score

Entry No.	Toxicity				DL	DS
	M	T	I	R		
E1	G	R	G	G	-8.57	0.16
E2	G	G	G	G	-8.57	0.24
E3	R	G	G	R	-6.01	0.11
E4	G	G	G	G	-8.57	0.27
E5	G	G	G	G	-813	0.22
E6	G	G	G	G	-4.54	0.32
E7	G	G	O	G	-6.72	0.19
E8	G	G	O	G	-6.68	0.21
E9	G	G	O	G	-5.21	0.19
E10	R	G	G	R	-6.69	0.10
E11	G	G	G	G	-7.28	0.23
E12	R	G	G	R	-7.61	0.08
E13	O	G	G	G	-10.0	0.19
E14	G	G	G	G	-10.1	0.27
E15	G	G	G	G	-10.1	0.24
E16	G	G	G	G	-8.54	0.22
E17	G	G	G	G	-6.57	0.27
E18	G	G	G	G	-6.28	0.31
E19	R	G	G	R	-7.46	0.08
E20	G	G	G	G	-5.92	0.33
E21	G	G	R	R	-8.58	0.09
E22	G	G	G	G	-8.03	0.22
E23	G	G	G	G	-6.47	0.25
E24	G	G	G	G	-6.80	0.30
ENZ	G	G	G	G	-8.17	0.22

M; mutagenic, T; tumorigenic, I; irritant, R; reproductive, G; no toxicity risk, O; toxicity risk, R; high toxicity risk, DL;drug Likeness, DS; drug Score.

7. Molecular Docking Study

- **Molecular Docking:** Molecular docking study of designed analogues of ENZ was carried out using ADV (https://vina.scripps.edu) [21]. The 3D crystallographic structure of protein was taken from the protein data bank (PDB ID: 2OZ7). ADV is an open-source programme offering a complete molecular viewer and graphical support for all the steps inevitable for setup and docking analysis. ADV produces a high-quality 3D image of protein as well as its visualization. The discovery studio visualizer is used for docking analysis.
- **Protein Preparation:** The structure taken from the PDB database is unsuitable for docking studies. ADV produces high-quality 3D images of the protein. The structure should clear up with water molecules. Hydrogen atoms and charges (Kollman charges) should be added to the structure of the protein, followed by the protein being saved in PDBQT format.
- **Ligand Preparation:** The 2D chemical structures of ligands are drawn using ChemDraw Professional 16.0 and saved in .Pdb format. Ligands were dropped into ADV and saved in. PDBQT format. In continuation, protein was dropped into ADV for grid box formation, keeping the ligand at the center.

8. **Docking using AutoDock Vina:** From grid output file, the configuration file "conf.txt" was prepared, and a command prompt was used for molecular docking by a giving command. A command was given to the PC to run as administrator and give the suitable path of the folder where you placed your prepared files in multiple ways. After the completion of the process, it generates an output file with a docking score or binding affinity *(Kcal/mol*). Similarly, all the designed molecules were studied as were their binding affinities. The results revealed that the designed analogues and ENZ did not show any hydrogen bonds in the aryl group with amino acid residues of protein. It was also observed that ENZ and E6 has pi-alkyl interactions of Pro868 between aryl group and protein (2OZT) is being shown in Figure 2 and 3. Ligand E6 were showing same amino acid interaction with Pro868 same as ENZ. As a result, E6 could be effective in the management of PC.

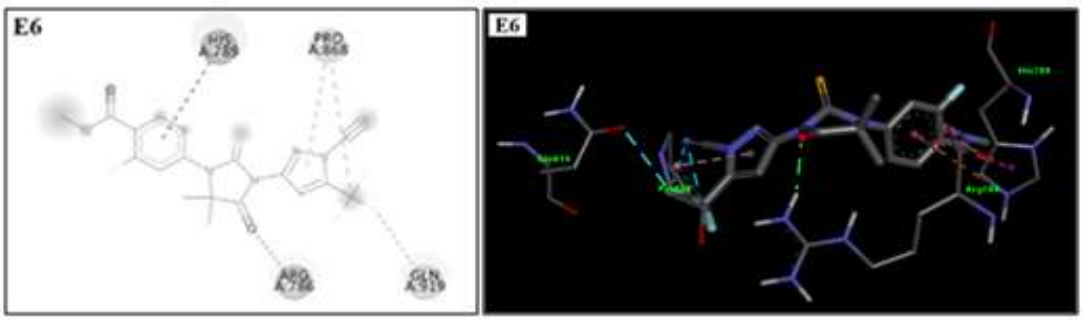


Figure 2: 2D and 3D interaction of E6.

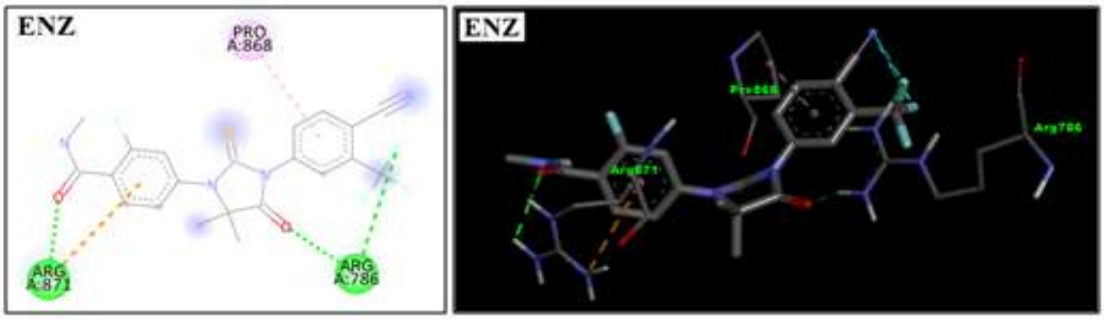


Figure 3: 2D and 3D interaction of enzalutamide.

IV. CONCLUSION

The treatment for PC that involves the use of ENZ is an antiandrogen drug. Patients treated with ENZ experience cardiovascular toxicity. *In- silico* drug design is one method that may be used for the development of androgen receptor antagonists. In the development of more effective analogues of ENZ, a bioisosteric approach was used as the method of choice. The bioisosteric approach was used for the structural modification of ENZ using MolOpt in order to develop newer analogues that were less toxic than ENZ. For the calculation of the ADMET characteristics of newer ENZ analogues, ADMETlab 2.0 was used. ADV was used for docking studies and it was observed that no-hydrogen bonds formed between ligands and protein. DL and DS were also computed for all newly designed analogues of ENZ. Based on predictions of ADMET properties, DL, DS and docking study, ligands E6 and E20 may be used for further screening as androgen antagonists in the treatment of PC therapy.

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VI. CONFLICT OF INTEREST

The authors affirm that they have no known financial conflicts of interest.

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