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IN-SILICO DESIGN OF FLUTAMIDE ANALOGUES AS ANDROGEN RECEPTOR ANTAGONIST AND MOLECULAR DOCKING STUDIES

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ABSTRACT: Androgenic hormones such as testosterone and dihydrotestosterone are essential for the progression of the prostate gland. Overexpression of androgenic receptors is responsible for the proliferation of prostate tumours and androgenic receptors are an essential target in prostate cancer therapy. Flutamide was the first Nonsteroidal androgen receptor antagonist used to treat prostate cancer, but it causes side effects such as hepatotoxicity. This study aims to develop less toxic compounds using a bioisosteric approach by replacing groups such as nitro, trifluoromethyl and aryl of Flutamide drug and to improve pharmacokinetic and toxicity prediction as well as docking studies of newly generated bioisosteres. The Lipinski rule of five was followed. In the docking study, docking scores were obtained in the range of -7.76 to -9.75 Kcal/mol. All ligands docked inside the binding pocket region share a shape that is complementary to the androgen receptor. Among the selected bioisosteres and flutamide, the common amino acid residue 746Val plays a key role in the activity and binding affinity. Based on their QED score, toxicity score, drug likeness, drug score, NR-AR score and binding scores with protein residue, compounds F3, F17, and F39 may be noble antiandrogen agents in the management of prostate cancer.

INTRODUCTION: Throughout the world, cancer is a major cause of mortality and a leading obstacle to extending life expectancy. Worldwide, approximately 10 million deaths from cancer were reported, compared to 19.3 million cases in 2020. According to estimated data, there are approximately 1.4 million new prostate cancer (PC) patients diagnosed each year and 0.38 million deaths [1].

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In men, prostate is a gland which is located in Pelvic region. For normal growth and development of prostate gland, androgenic hormones such as testosterone and dihydrotestosterone (metabolite of testosterone) are required [2-3]. Androgenic hormones bind with androgen receptors (AR) and mediate biological effects.

Before puberty, the secretion of androgens are less but in postpuberted male volume of androgens are increased up to ten times, result in continuous growth in prostate glands may lead to benign prostatic hyperplasia (BPH) [4-5]. Increased levels of androgens lead to cause proliferation of prostate tumours [6]. PC, precious puberty and hair loss are androgen dependent diseases in men, can be treated with antiandrogens.

Antiandrogen agents can be classified into two categories, a) androgen synthetic inhibitors (such as Abiraterone, Seviterone etc.); b) AR antagonist such as steroidal (Cyproterone, Allylestrenol *etc*.) and non-steroidal (Flutamide, Bicalutamide and Enzalutamide *etc*.) [7].

Flutamide is chemical propanamide derivative **Fig. 1A**, used in the treatment of PC and BPH [8]. It is an inactive molecule that is activated after going under first pass metabolism (using Cytochrome P450 1A2), resulting in the formation of 2-hydroxyflutamide **Fig. 1B** [9]. Flutamide shows some side effects like drug induced liver injury (DILI) which may lead to liver failure. FDA also reported a warning risk regarding liver nacrosis, jaundice and cholestasis [10-12].

Nitroreduction of Flutamide (formation of N-[4-amino-3-(trifluoromethyl) phenyl] isobutyramide) may cause hepatotoxicity [13]. At high doses, flutamide causes some difficulties such as prostatitis, hematuria, hematochezia, anaemia, low libido and elevated methemoglobin in the blood [14].

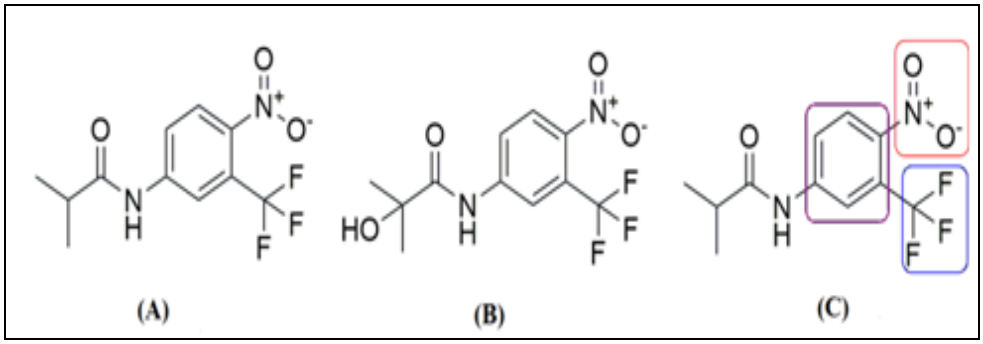


FIG. 1: STRUCTURE OF FLUTAMIDE, 2-HYDROXY FLUTAMIDE AND BIOISOSTERIC MODIFICATION OF GROUPS (NITRO, TRIFLUOROMETHYL AND ARYL) IN FLUTAMIDE

Bioisosters were compounds that have the same biological activities and are used for modification of potency, efficacy, bioactivitites, pharmacokinetics and toxicological properties [15-16]. They can be classified as classical and non-classical bioisosteres.

Classical bioisosters are atoms or molecules having the same valence electrons but share different numbers of atoms. Non-classical bioisosters differ in valance electron but similarity in some important parameters such as liophilicity, pKa, chemical reactivity *etc* [17-18]. For the design of novel and potent molecules chemists or scientists can use rational drug design approaches, among them molecular docking which is used to predict the ligand-protein interaction in three-dimentional mode. Also, docking gives the information about the binding score of the ligand-protein complex may help in lead optimisation [19-20].

The aim of the investigation is to develop a less toxic compound than flutamide through a bioisosteric approach, ADMET properties prediction, drug likeness (DL), drug score (DS) and moleculer docking studies. In Flutamide, three groups such as nitro, trifluromethyl and aryl are modified using the bioisosteric approach is shown in **Fig. 1C**.

MATERIALS AND METHODS:

Designing of Flutamide Bioisosteres: Flutamide is a pure androgen antagonist used to treat PC. However, in the course of medication, patients were suffering from hepatotoxicity, which led to liver damage. Therefore, it is necessary to modify the flutamide structure in order to reduce toxicity like hepatotoxicity. Various bioisosteres of groups such as nitro, trifluoromethyl, and aryl in Flutamide were generated using the MolOpt online tool. MolOpt, online software used for *in-silico* design of bioisosteres that uses deep generative models, data mining, and similarity comparisons as bioisosteric transformation rules. A useful feature of MolOpt is that it can navigate historical bioisosteric group space and identify new bioisosteric transformation ideas. The purpose of MolOpt is to assist the medicinal chemist in finding what to make next [21]. Types of newly generated analogues of nitro, trifluoromethyl and aryl groups in flutamide are shown in **Fig. 2A, 2B** and **2C**, respectively. The structures of newly generated analogues are shown in **Table 1**.

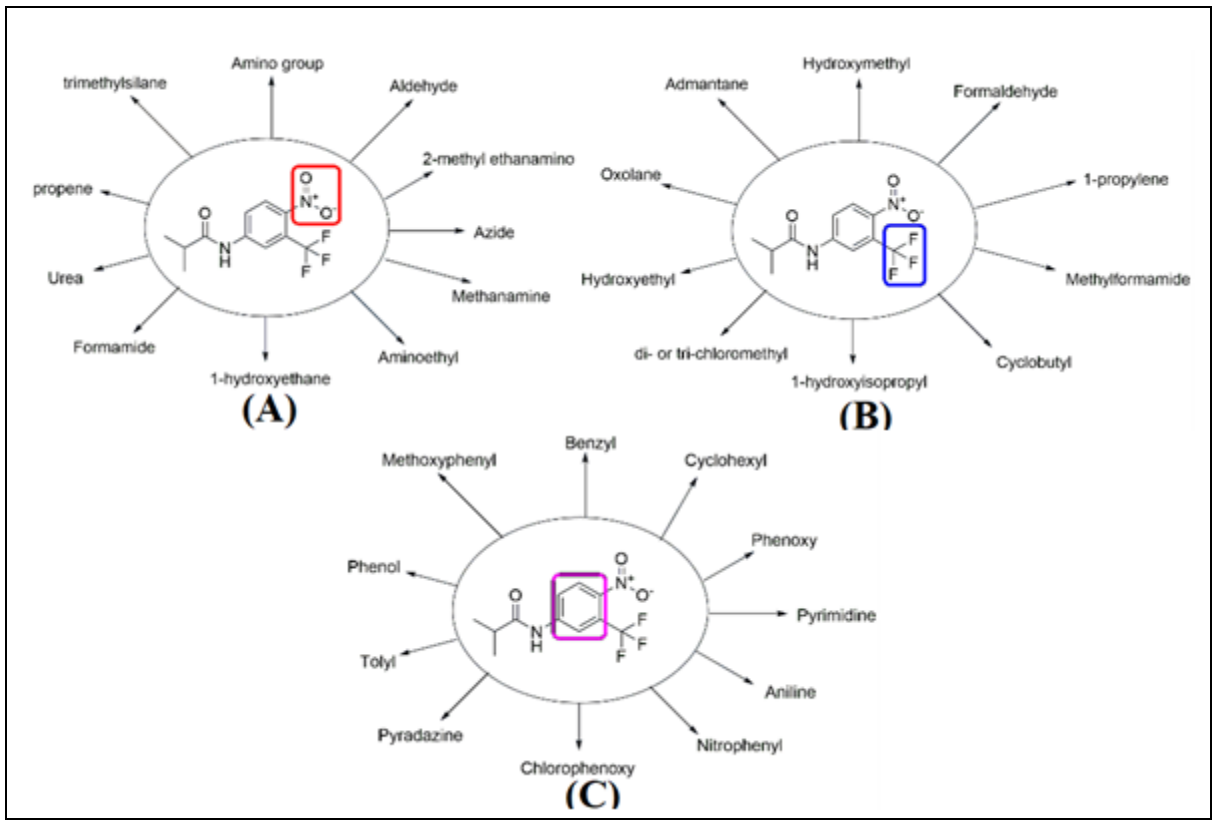


FIG. 2: TYPE OF BIOISOSTERES OF NITRO GROUP, TRIFLUOROMETHYL GROUP, ARYL GROUP IN FLUTAMIDE

Pharmacokinetic and Toxicity (ADMET) Properties Prediction: Absorption, distribution, metabolism and excretion and toxicological (ADMET) properties of newly generated analogues of flutamide were calculated using ADMET lab 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 novel ligands that mimic mammalian ADMET properties tool [22-25].

Drug Likeness and Drug Score Prediction: OSIRIS property explorer (PEO) was employed for DS and DL calculations. PEO includes the processing of all information related to compound synthesis, biological testing, and preclinical development. PEO Online platform with six quantitative and four qualitative regression models with comprehensive prediction of toxicity risk, DL and DS [26].

DL and DS properties determine whether a drug has the physicochemical and biological properties required to be successful and safe for use [27].

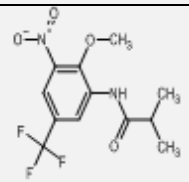
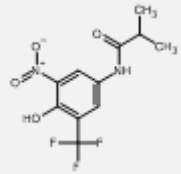
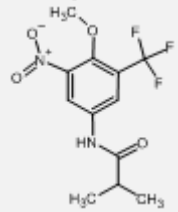
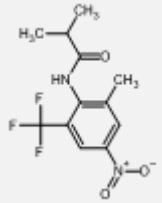
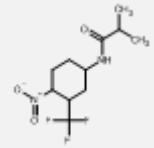
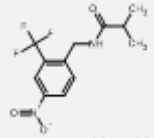
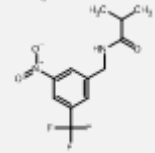
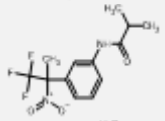
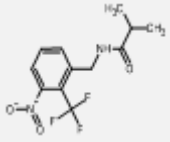
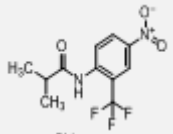
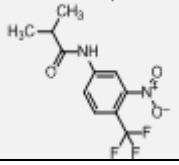
Molecular Docking Study: Molecular docking is used in understanding molecular biology, determining interactions between targets (macromolecules such as DNA, RNA and Proteins) and small molecules (ligands). Docking softwares is used to understand the recognition of binding affinity, binding score *etc* [28-29]. A molecular docking study of analogues was done using the crystal structure of the androgen receptor (PDB ID: 2AM9) and this study involved a number of steps like preparation of the ligand structure preparation of the protein structures and protein-ligand docking using Argus Lab 4.0 software[30-32].

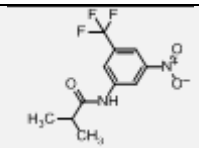
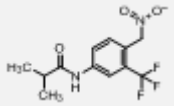
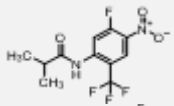
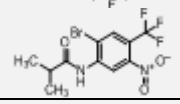
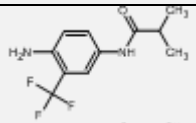
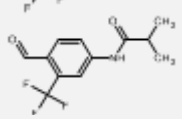
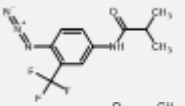
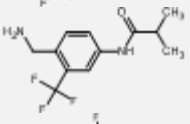
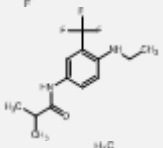
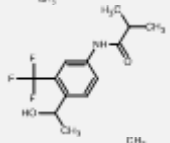
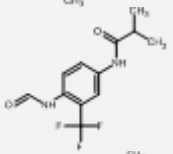
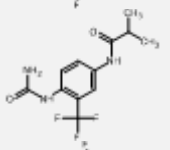
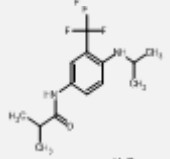
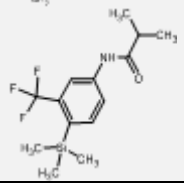
RESULTS AND DISCUSSION:

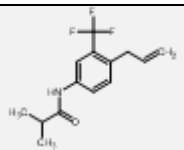
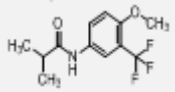
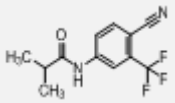
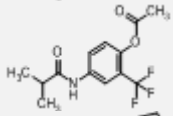
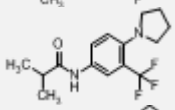
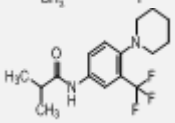
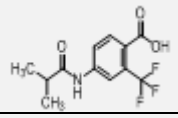
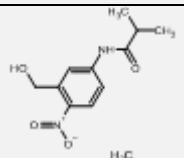
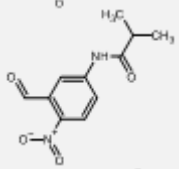
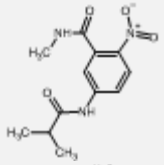
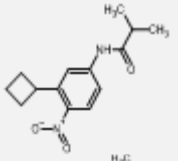
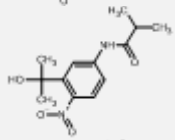
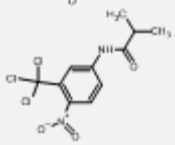
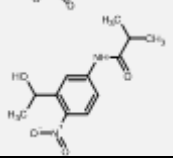
Bioisosteres of Trifluoromethyl, Nitro and Aryl Groups in Flutamide: As a drug discovery technique, bioisosteric replacement is widely used to improve potency and selectivity, address pharmacokinetic problems and remove unwanted side effects such as toxicity.

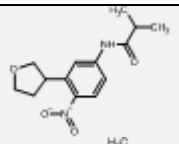
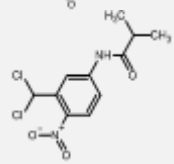
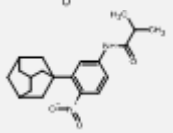
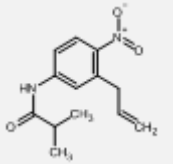
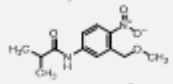
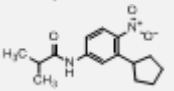
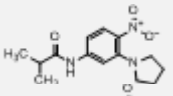
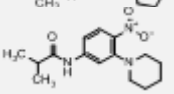
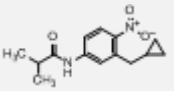
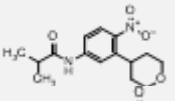
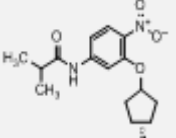
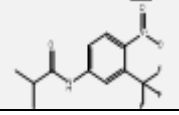
MolOpt was used to generate eighty-six, ninety-two and seventy-seven bioisosteres of trifluoromethyl, nitro and aryl groups, in flutamide, respectively. Among these, fifty analogues **Table 1** were chosen for further evaluation based on their QED value, DILI score, NR-AR score, DL and DS.

TABLE 1: STRUCTURE AND MOLECULAR PROPERTIES OF THE ANALOGUES

S. no.	Entry no.	Structure	MW	nHA	nHD	TPSA	nRot	LogS	LogP
Aryl Group Bioisosteres									
1	F1		306.08	6	1	81.47	6	-4.499	3.114
2	F2		292.07	6	2	92.47	5	-3.76	3.104
3	F3		306.08	6	1	81.47	6	-3.656	3.121
4	F4		290.09	5	1	72.24	5	-3.598	2.866
5	F5		282.12	5	1	72.24	5	-2.563	2.019
6	F6		290.09	5	1	72.24	6	-2.967	2.849
7	F7		290.09	5	1	72.24	6	-3.546	2.886
8	F8		304.1	5	1	72.24	6	-5.093	3.228
9	F9		290.09	5	1	72.24	6	-2.665	2.829
10	F10		276.07	5	1	72.24	5	-3.879	2.941
11	F11		276.07	5	1	72.24	5	-3.882	3.23

12	F12		276.07	5	1	72.24	5	-4.661	3.323
13	F13		290.09	5	1	72.24	6	-3.417	3.044
14	F14		294.06	5	1	72.24	5	-4.243	3.041
15	F15		353.98	5	1	72.24	5	-5.264	3.529
		Nitro Group Bioisosteres							
16	F16		246.1	3	3	55.12	4	-3.253	2.677
17	F17		259.08	3	1	46.17	5	-3.267	2.928
18	F18		272.09	5	1	77.86	5	-5.569	3.706
19	F19		260.11	3	3	55.12	5	-1.478	2.504
20	F20		274.13	3	2	41.13	6	-4.084	3.479
21	F21		275.11	3	2	49.33	5	-2.254	2.818
22	F22		274.09	4	2	58.2	6	-3.165	2.558
23	F23		289.1	5	4	84.22	6	-3.147	2.207
24	F24		288.14	3	2	41.13	6	-4.904	3.852
25	F25		303.13	2	1	29.1	5	-5.98	4.56

26	F26		271.12	2	1	29.1	6	-4.889	4.105
27	F27		261.1	3	1	38.33	5	-3.663	3.146
28	F28		256.08	3	1	52.89	4	-4.125	3.044
29	F29		289.09	4	1	55.4	6	-3.144	2.819
30	F30		300.14	3	1	32.34	5	-5.124	4.001
31	F31		314.16	3	1	32.34	5	-5.558	4.386
32	F32		275.08	4	2	66.4	5	-2.859	2.958
Trifluoromethyl Group Bioisosteres									
33	F33		238.1	6	2	92.47	5	-2.53	1.804
34	F34		236.08	6	1	89.31	5	-3.098	2.058
35	F35		265.11	7	2	101.34	6	-2.944	1.456
36	F36		262.13	5	1	72.24	5	-5.529	3.616
37	F37		266.13	6	2	92.47	5	-2.693	2.408
38	F38		323.98	5	1	72.24	5	-4.892	3.764
39	F39		252.11	6	2	92.47	5	-2.307	1.927

40	F40		278.13	6	1	81.47	5	-3.769	2.549
41	F41		290.02	5	1	72.24	5	-4.282	3.172
42	F42		342.19	5	1	72.24	5	-6.466	5.128
43	F43		248.12	5	1	72.24	6	-4.379	3.216
44	F44		252.11	6	1	81.47	6	-2.901	2.159
45	F45		276.15	5	1	72.24	5	-5.973	4.056
46	F46		291.16	6	1	75.48	5	-5.14	3.366
47	F47		291.16	6	1	75.48	5	-5.509	3.8
48	F48		262.13	5	1	72.24	6	-5.314	3.626
49	F49		292.14	6	1	81.47	5	-4.48	2.905
50	F50		292.14	6	1	81.47	6	-5.32	3.634
Std.	Flutamide		276.07	5	1	72.24	5	-3.842	3.243

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

Screening of Molecular Properties: The molecular properties of the newer analogue were calculated using the ADMETlab2.0 online tool and the results are shown in **Table 2**. Lipinski's rule of five promotes the bioavailability of the drug candidates. Lipinski's rule of five also predicts the absorption or permeation of the drug candidates [33]. The result indicates that all analogues met the acceptance criteria with flutamide as the standard.

TABLE 2: MEDICINAL PROPERTIES OF THE ANALOGUES

Entry no.	QED	Synth	Fsp3	MCE-18	Lipinski	Pfizer	GSK	GT
Aryl Group Bioisosteres								
F1	0.684	2.276	0.417	13	Accepted	Accepted	Accepted	Accepted
F2	0.509	2.318	0.364	13	Accepted	Accepted	Accepted	Accepted

F3	0.684	2.324	0.417	13	Accepted	Accepted	Accepted	Accepted
F4	0.683	2.308	0.417	13	Accepted	Accepted	Accepted	Accepted
F5	0.636	3.858	0.909	31	Accepted	Accepted	Accepted	Accepted
F6	0.684	2.162	0.417	12	Accepted	Accepted	Accepted	Accepted
F7	0.684	2.191	0.417	12	Accepted	Accepted	Accepted	Accepted
F8	0.685	3.075	0.462	28	Accepted	Rejected	Accepted	Accepted
F9	0.684	2.407	0.417	12	Accepted	Accepted	Accepted	Accepted
F10	0.68	2.038	0.364	12	Accepted	Accepted	Accepted	Accepted
F11	0.68	2.127	0.364	12	Accepted	Rejected	Accepted	Accepted
F12	0.68	2.123	0.364	12	Accepted	Rejected	Accepted	Accepted
F13	0.684	2.438	0.417	12	Accepted	Rejected	Accepted	Accepted
F14	0.528	2.305	0.364	13	Accepted	Rejected	Accepted	Accepted
F15	0.659	2.4	0.364	13	Accepted	Rejected	Accepted	Accepted
Nitro Group Bioisosteres								
F16	0.788	2.001	0.364	11	Accepted	Accepted	Accepted	Accepted
F17	0.848	2.179	0.333	11	Accepted	Accepted	Accepted	Accepted
F18	0.498	2.587	0.364	11	Accepted	Accepted	Accepted	Accepted
F19	0.878	2.066	0.417	11	Accepted	Accepted	Accepted	Accepted
F20	0.878	2.029	0.462	11	Accepted	Rejected	Accepted	Accepted
F21	0.888	2.581	0.462	24	Accepted	Accepted	Accepted	Accepted
F22	0.829	2.231	0.333	11	Accepted	Accepted	Accepted	Accepted
F23	0.799	2.042	0.333	12	Accepted	Accepted	Accepted	Accepted
F24	0.875	2.094	0.5	12	Accepted	Rejected	Accepted	Accepted
F25	0.844	2.511	0.5	14	Accepted	Rejected	Rejected	Accepted
F26	0.823	2.219	0.357	11	Accepted	Rejected	Rejected	Accepted
F27	0.906	1.851	0.417	11	Accepted	Rejected	Accepted	Accepted
F28	0.883	2.064	0.333	11	Accepted	Rejected	Accepted	Accepted
F29	0.686	2.031	0.385	12	Accepted	Accepted	Accepted	Accepted
F30	0.918	2.01	0.533	35	Accepted	Rejected	Rejected	Accepted
F31	0.902	2.021	0.562	12	Accepted	Rejected	Rejected	Accepted
F32	0.891	1.958	0.333	36	Accepted	Accepted	Accepted	Accepted
Trifluoromethyl Group Bioisosteres								
F33	0.616	2.039	0.364	9	Accepted	Accepted	Accepted	Accepted
F34	0.492	2.133	0.273	9	Accepted	Accepted	Accepted	Accepted
F35	0.637	1.958	0.333	10	Accepted	Accepted	Accepted	Accepted
F36	0.667	2.091	0.5	31	Accepted	Rejected	Accepted	Accepted
F37	0.646	2.234	0.462	12	Accepted	Accepted	Accepted	Accepted
F38	0.518	2.394	0.364	12	Accepted	Rejected	Accepted	Accepted
F39	0.634	2.587	0.417	20	Accepted	Accepted	Accepted	Accepted
F40	0.678	2.77	0.5	44	Accepted	Accepted	Accepted	Accepted
F41	0.522	2.405	0.364	10	Accepted	Rejected	Accepted	Accepted
F42	0.639	3.626	0.65	62	Accepted	Rejected	Rejected	Accepted
F43	0.494	2.212	0.308	9	Accepted	Rejected	Accepted	Accepted
F44	0.644	2.033	0.417	9	Accepted	Accepted	Accepted	Accepted
F45	0.67	2.103	0.533	32	Accepted	Rejected	Rejected	Accepted
F46	0.678	1.991	0.5	31	Accepted	Accepted	Accepted	Accepted
F47	0.683	2	0.533	32	Accepted	Accepted	Accepted	Accepted
F48	0.654	2.133	0.5	30	Accepted	Rejected	Accepted	Accepted
F49	0.683	2.281	0.533	32	Accepted	Accepted	Accepted	Accepted
F50	0.665	2.103	0.533	32	Accepted	Accepted	Accepted	Accepted
Flutamide	0.68	2.07	0.364	12	Accepted	Rejected	Accepted	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.

Screening of Medicinal Properties: The medicinal property of analogues are shown in **Table 2**. QED indicates drug-like properties. The QED value of all analogues has shown > 0.67 with some exceptions such as F2, F5, F14, F15, F18, F33-39, F41-F44, F48 and F50, whereas flutamide has 0.68 which indicates analogues may have drug like properties. All analogues will be easy to synthesise as per synthetic accessibility prediction criteria (< 6). Newer analogues of flutamide were

found to be acceptable to Lipinski and the Golden Triangle (GT), indicating good bioavailability. Analogues F3, F17, and F39 have been found to meet Lipinski, Pfizer, GSK, and GT rules, whereas the Pfizer rule for flutamide is rejected.

Screening of Pharmacokinetic (ADME) Properties: Pharmacokinetic properties such as absorption (caco-2, MDCK, HIA), distribution (BBB, PPB, VDss), metabolism (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), excretion (CL and $T_{1/2}$) have been calculated using the ADMET lab2.0 online tool and results are tabulated in **Table 3** and **4**. Intestinal absorption of analogues was found to be good (absorption score based on the caco-2 score and HIA score). The caco-2 score of analogues was found to be greater than -5.15 which indicates the proper *in-vivo* drug permeability of analogues.

HIA scores were also found in the range between 0 to 0.3 which indicates oral bioavailability of molecules. The MDCK score of analogues was found to be excellent, indicating high passive permeability. These analogues have moderate to poor BBB permeability, ranging from 0.353 to 0.919. Most of the newer analogues have a predicted plasma protein binding (PPB) score under 90%, which indicates that the high plasma protein binding causes a decrease in the free plasma fraction, which decreases distribution volume and lengthens the half-life of elimination. The volume of distribution (VDs) of all analogues has a good predicted score that is between 0.04-20. From the predicted scores of absorptions and distribution, analogues F3, F6, F17, F19, F37 and F39 and others also have good to moderate permeability effects.

TABLE 3: ABSORPTION AND DISTRIBUTION PROFILE OF THE ANALOGUES

Entry no.	Caco-2	MDCK	HIA	BBB	PPB (%)	VDss	Fu (%)
Aryl Group Bioisosteres							
F1	-4.414	Ex	0.007	0.499	96.99	1.033	3.06
F2	-4.437	Ex	0.004	0.574	98.06	1.004	2.48
F3	-4.448	Ex	0.007	0.485	96.93	1.074	3.22
F4	-4.348	Ex	0.005	0.353	97.17	1.089	3.90
F5	-4.582	Ex	0.005	0.525	77.83	0.833	23.89
F6	-4.458	Ex	0.004	0.723	93.18	0.699	7.30
F7	-4.444	Ex	0.004	0.515	95.16	0.773	6.14
F8	-4.362	Ex	0.005	0.494	95.52	0.984	8.00
F9	-4.383	Ex	0.004	0.794	93.84	0.666	5.75
F10	-4.333	Ex	0.004	0.474	94.61	0.87	5.52
F11	-4.344	Ex	0.004	0.533	95.92	0.835	4.49
F12	-4.435	Ex	0.004	0.316	97.15	1.062	4.37
F13	-4.479	Ex	0.004	0.896	94.02	0.835	7.44
F14	-4.336	Ex	0.005	0.261	96.80	1.042	3.67
F15	-4.332	Ex	0.023	0.582	97.88	0.982	2.39
Nitro Group Bioisosteres							
F16	-4.526	Ex	0.004	0.687	85.00	1.196	15.61
F17	-4.507	Ex	0.004	0.966	90.11	1.527	10.32
F18	-5.062	Ex	0.007	0.518	97.60	5.137	3.32
F19	-4.787	Ex	0.004	0.481	62.00	2.318	35.81
F20	-4.58	Ex	0.005	0.446	95.62	3.014	4.20
F21	-4.408	Ex	0.004	0.86	87.90	0.89	14.97
F22	-4.435	Ex	0.004	0.896	88.02	1.574	10.29
F23	-5.088	Ex	0.004	0.93	88.87	1.129	11.70
F24	-4.561	Ex	0.006	0.419	96.68	3.462	3.52
F25	-4.391	Ex	0.007	0.791	93.80	3.936	6.30
F26	-4.372	Ex	0.003	0.826	97.11	1.34	2.27
F27	-4.495	Ex	0.004	0.746	94.55	3.195	5.36
F28	-4.464	Ex	0.005	0.966	92.18	0.911	6.07
F29	-4.61	Ex	0.008	0.99	89.13	0.969	24.02
F30	-4.566	Ex	0.003	0.775	95.74	2.16	2.77
F31	-4.576	Ex	0.003	0.747	96.38	2.233	2.18
F32	-4.566	Ex	0.004	0.425	91.98	1.165	10.09
Trifluoromethyl Group Bioisosteres							

F33	-4.406	Ex	0.005	0.88	73.78	0.843	28.74
F34	-4.399	Ex	0.006	0.919	84.50	1.057	14.68
F35	-4.909	Ex	0.005	0.875	80.52	0.936	23.62
F36	-4.472	Ex	0.003	0.739	96.58	0.806	2.94
F37	-4.326	Ex	0.01	0.731	80.12	0.909	23.43
F38	-5.52	Ex	0.004	0.872	98.18	1.28	1.59
F39	-4.404	Ex	0.005	0.781	76.36	0.83	26.13
F40	-4.485	Ex	0.003	0.642	92.80	0.851	7.98
F41	-4.79	Ex	0.004	0.811	96.53	1.263	3.62
F42	-4.683	Ex	0.004	0.69	96.28	1.015	1.15
F43	-4.249	Ex	0.004	0.557	96.00	0.986	2.68
F44	-4.333	Ex	0.004	0.881	74.80	0.927	23.54
F45	-4.489	Ex	0.003	0.699	97.30	0.842	2.09
F46	-4.42	Ex	0.004	0.824	94.79	0.924	4.86
F47	-4.441	Ex	0.004	0.806	95.96	0.915	3.98
F48	-4.466	Ex	0.003	0.735	95.56	0.664	2.70
F49	-4.471	Ex	0.002	0.598	93.96	0.756	6.25
F50	-4.375	Ex	0.003	0.779	96.90	0.728	2.63
Flutamide	-4.346	Ex	0.004	0.58	95.62	0.832	4.59

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.

Cytochrome P450 (CYT P450) is involved in the digestion of drugs, lipids, steroidal components, and carcinogens. Analogues may be substrate or inhibitors. If they are substrates for the enzyme CYT P450 result in the metabolism takes place with molecules, on the other hand, if they inhibit the enzyme, it will be inactive in metabolism. Analogue F3 was an inhibitor while analogues F17 and F34 were substrates for all five isozymes. Approximately 50% of analogues have an excellent clearance score, indicating a low risk of toxicity. Among them analogue F3 and F29 have excellent clearance scores ($\geq$ 5) and analogue F17 has a moderate clearance score ($\leq$ 5). $T_{1/2}$ of analogues F3 and F39 were found under the range (0 to 0.3) which indicates excellent clearance from the body.

TABLE 4: METABOLISM AND EXCRETION PROFILE OF THE ANALOGUES

Entry no.	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	CL	$T_{1/2}$
Aryl Group Bioisosteres							
F1	-	-	-	+	-	4.349	0.3
F2	-	-	+	-	+	4.579	0.495
F3	-	-	-	-	-	6.774	0.283
F4	+	+	-	+	+	3.408	0.419
F5	+	+	-	+	+	6.446	0.4
F6	-	-	+	+	-	5.882	0.297
F7	-	+	-	+	-	5.217	0.454
F8	+	+	+	+	+	4.821	0.345
F9	-	-	+	+	-	6.586	0.642
F10	+	+	+	+	+	3.795	0.308
F11	+	+	+	+	+	4.608	0.224
F12	+	+	-	-	-	4.096	0.259
F13	-	-	-	+	+	6.624	0.246
F14	+	-	+	+	+	3.016	0.232
F15	+	-	+	+	+	1.226	0.207
Nitro Group Bioisosteres							
F16	+	+	-	+	+	7.88	0.192
F17	-	+	+	+	+	2.634	0.252
F18	+	+	+	+	+	0.783	0.321
F19	-	+	+	+	+	8.645	0.547
F20	+	+	+	+	+	7.332	0.295
F21	+	+	+	+	+	4.611	0.37
F22	+	+	+	+	+	4.077	0.366
F23	+	+	+	+	+	5.808	0.216

F24	+	+	-	+	+	5.312	0.17
F25	+	+	-	+	+	2.284	0.198
F26	+	-	+	+	-	7.543	0.169
F27	+	+	+	+	+	9.662	0.322
F28	+	+	-	+	+	8.524	0.297
F29	-	+	+	-	-	2.998	0.411
F30	+	+	-	+	+	5.648	0.095
F31	+	+	-	+	-	5.31	0.076
F32	+	+	-	+	+	1.355	0.691
Trifluoromethyl Group Bioisosteres							
F33	+	+	+	+	+	6.474	0.882
F34	-	+	+	+	+	2.213	0.58
F35	-	-	+	+	+	8.056	0.696
F36	+	-	+	+	+	1.385	0.234
F37	+	+	+	+	+	4.194	0.689
F38	+	+	+	+	+	3.464	0.316
F39	+	+	+	+	+	4.76	0.762
F40	+	+	+	+	+	4.775	0.429
F41	+	+	+	+	+	3.047	0.485
F42	+	-	+	+	-	1.74	0.07
F43	+	-	+	+	-	5.556	0.604
F44	+	+	+	+	+	5.252	0.615
F45	+	-	+	+	-	1.436	0.2
F46	+	-	-	+	-	4.765	0.364
F47	+	-	-	-	-	4.396	0.299
F48	+	-	+	+	-	3.098	0.272
F49	+	+	+	-	+	5.391	0.341
F50	+	-	+	-	-	3.617	0.24
Flutamide	+	-	+	+	+	4.681	0.237

(-); indicates inhibitor, (+); indicates substrate of human cytochrome P450 (five isozymes-1A2, 3A4, 2C9, 2C19 and 2D6), CL; the clearance of a drug, $T_{1/2}$; the half-life of a drug.

Screening of Toxicity Profile: Toxicity parameters of newer analogues such as Drug Induced Liver Injury (DILI), mutagenicity (Ames), androgen receptor-a nuclear hormone receptor (NR-AR) were calculated using ADMET lab 2.0 online tool and their results are shown in **Table 5**. The DILI scores for analogues F6, F17, F19, F25, F34, F35, F37 and F42 are moderate (0.3 to 0.7). However, analogues F7, F37 and F41 are safe, while flutamide has high liver toxicity (0.858). Studies have shown that analogues such as F17, F34, F38, F41 do not cause human hepatotoxicity (H-HT) as compared to Flutamide (0.578). The mutagenicity of analogues such as F1, F2, F3, F5, F7, F8, F17, F19, F20, F21, F23, F24, F25, F26 and F42 was predicted to be safer than flutamide (0.498), indicating that the analogues could not cause mutagenesis. The rat oral acute toxicity (ROA) method is used to determine acute toxicity in rats and mice, which is an important safety profile for drug candidates. Based on the outcome of ROA, analogues are as safe as flutamide, except for F19. The carcinogenicity of chemicals is 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 carcinogenicity scores, analogues such as F17, F19, F20, F21, F22, F23, F24, F25, F33, F34, F35, F38, F39, F41 and F42 were found to have a safe predictive value. NR-AR plays a vital role in AR-dependent PC, as well as other androgen-related diseases. In more than 75% of cases, analogues bind to the NR-AR, inhibiting the activity of the Androgen receptor. In general, analogues F1-F4, F6, F7, F9, F23, F36, F38 and F39 were found to have more than 0.8 scores.

TABLE 5: TOXICITY PROFILE OF THE ANALOGUES

Entry no.	H-HT	DILI	Ames	ROA	Carc.	NR-AR	NR-AR-LBD
Aryl Group Bioisosteres							
F1	0.724	0.572	0.196	0.159	0.74	0.847	0.095
F2	0.552	0.671	0.177	0.271	0.737	0.807	0.178
F3	0.708	0.58	0.205	0.199	0.741	0.85	0.103

F4	0.736	0.654	0.488	0.238	0.844	0.849	0.017
F5	0.919	0.622	0.008	0.041	0.882	0.089	0.002
F6	0.485	0.43	0.458	0.115	0.725	0.845	0.009
F7	0.485	0.185	0.29	0.108	0.588	0.826	0.011
F8	0.338	0.675	0.013	0.06	0.751	0.011	0.003
F9	0.379	0.609	0.457	0.128	0.52	0.816	0.007
F10	0.662	0.87	0.624	0.123	0.793	0.861	0.032
F11	0.626	0.874	0.616	0.063	0.788	0.862	0.027
F12	0.62	0.729	0.498	0.058	0.753	0.844	0.048
F13	0.527	0.714	0.216	0.069	0.682	0.803	0.007
F14	0.749	0.889	0.5	0.158	0.731	0.874	0.075
F15	0.405	0.934	0.305	0.118	0.683	0.878	0.12
Nitro Group Bioisosteres							
F16	0.596	0.696	0.524	0.234	0.357	0.749	0.006
F17	0.258	0.347	0.204	0.084	0.183	0.732	0.006
F18	0.454	0.691	0.993	0.079	0.965	0.001	0.013
F19	0.481	0.384	0.039	0.868	0.231	0.795	0.004
F20	0.82	0.456	0.129	0.243	0.123	0.619	0.003
F21	0.654	0.533	0.116	0.156	0.117	0.762	0.003
F22	0.416	0.688	0.391	0.127	0.111	0.742	0.006
F23	0.352	0.95	0.284	0.105	0.147	0.847	0.003
F24	0.65	0.488	0.04	0.153	0.153	0.191	0.002
F25	0.33	0.399	0.012	0.01	0.111	0.61	0.002
F26	0.426	0.522	0.063	0.113	0.553	0.572	0.004
F27	0.263	0.839	0.023	0.139	0.285	0.786	0.004
F28	0.913	0.896	0.105	0.17	0.391	0.836	0.037
F29	0.049	0.733	0.042	0.138	0.304	0.789	0.007
F30	0.848	0.78	0.121	0.535	0.329	0.745	0.005
F31	0.84	0.815	0.114	0.512	0.293	0.722	0.005
F32	0.218	0.973	0.017	0.339	0.082	0.852	0.004
Trifluoromethyl Group Bioisosteres							
F33	0.575	0.419	0.832	0.046	0.262	0.635	0.021
F34	0.156	0.39	0.964	0.024	0.109	0.36	0.205
F35	0.58	0.4	0.918	0.054	0.079	0.035	0.005
F36	0.48	0.839	0.884	0.329	0.534	0.828	0.008
F37	0.598	0.395	0.629	0.037	0.378	0.709	0.005
F38	0.109	0.5	0.978	0.018	0.147	0.815	0.016
F39	0.589	0.225	0.698	0.045	0.136	0.8	0.013
F40	0.585	0.535	0.944	0.17	0.428	0.756	0.016
F41	0.066	0.247	0.96	0.029	0.112	0.659	0.019
F42	0.338	0.374	0.143	0.317	0.55	0.382	0.006
F43	0.316	0.455	0.93	0.049	0.214	0.719	0.017
F44	0.659	0.778	0.913	0.045	0.268	0.744	0.035
F45	0.441	0.853	0.885	0.392	0.599	0.838	0.006
F46	0.461	0.921	0.97	0.168	0.369	0.825	0.017
F47	0.41	0.925	0.969	0.166	0.389	0.842	0.013
F48	0.495	0.827	0.931	0.078	0.489	0.812	0.005
F49	0.489	0.694	0.912	0.669	0.531	0.733	0.008
F50	0.506	0.846	0.937	0.123	0.665	0.868	0.017
Flutamide	0.578	0.858	0.498	0.067	0.786	0.862	0.018

H-HT; the 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 bind with LBD of androgen receptor, Carc.; carcinogenicity.

Screening of DL and DS: Parameters like mutagenicity, tumorigenicity, irritant, reproductive, DL, and DS have been calculated using PEO. The results of DL and DS are shown in **Table 6**. Around 75% of analogues showed good DL scores and all newer analogues showed higher DS than flutamide. The DL score was -6.59 for analogue F19 followed by ligand F24 with a DL score of -6.14. The maximum DS was found 0.44 for analogue F2 and F5 followed by ligands F6, F7, F9 and F10 with the DL score of 0.43.

TABLE 6: DRUG LIKENESS AND DRUG SCORE OF ANALOGUES

Entry no.	Toxicity Risk				DL	DS
	M	T	I	R		
Aryl Group Bioisosteres						
F1	G	G	G	G	-10.19	0.42
F2	G	G	G	G	-11.50	0.44
F3	G	G	G	G	-10.66	0.42
F4	G	G	G	G	-11.23	0.40
F5	G	G	G	G	-10.84	0.44
F6	G	G	G	G	-12.02	0.43
F7	G	G	G	G	-21.78	0.43
F8	G	G	G	G	-11.16	0.41
F9	G	G	G	G	-12.89	0.43
F10	G	G	G	G	-12.4	0.43
F11	R	O	G	O	-14.93	0.16
F12	G	G	G	G	-22.34	0.43
F13	R	O	G	O	-11.53	0.14
F14	G	G	G	G	-12.76	0.41
F15	G	G	G	G	-14.55	0.36
Nitro Group Bioisosteres						
F16	R	O	G	O	-9.74	0.17
F17	R	O	G	O	-8.65	0.16
F18	R	O	G	O	-8.45	0.15
F19	R	O	G	O	-6.59	0.17
F20	R	O	G	O	-7.01	0.16
F21	R	O	G	O	-8.69	0.17
F22	R	O	G	O	-7.32	0.16
F23	R	O	G	O	-6.8	0.16
F24	R	O	G	O	-6.14	0.15
F25	R	O	R	O	-52.49	0.08
F26	R	O	G	O	-9.24	0.14
F27	R	O	G	O	-5.93	0.17
F28	R	O	G	O	-10.78	0.16
F29	R	O	G	O	-5.94	0.16
F30	R	O	G	O	-5.59	0.15
F31	R	O	G	O	-7.1	0.14
F32	R	O	G	O	-8.92	0.17
Trifluoromethyl Group Bioisosteres						
F33	R	O	G	O	-6.86	0.18
F34	R	O	G	O	-9.02	0.17
F35	R	O	G	O	-5.32	0.18
F36	R	O	G	O	-7.22	0.15
F37	R	O	G	O	-7.81	0.17
F38	R	O	R	R	-6.87	0.05
F39	R	O	G	O	-8.02	0.18
F40	R	O	G	O	-8.03	0.17
F41	R	R	R	R	-6.6	0.05
F42	R	O	G	O	-6.4	0.11
F43	R	O	G	O	-9.6	0.16
F44	R	O	G	O	-6.88	0.18
F45	R	O	G	O	-8.94	0.15
F46	R	O	G	O	-4.31	0.17
F47	R	O	G	O	-5.82	0.16
F48	R	O	G	O	-5.87	0.16
F49	R	O	G	O	-9.87	0.16
F50	R	O	G	O	-11.67	0.15
Flutamide	R	O	G	O	-12.9	0.16

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.

Molecular Docking Study of Flutamide Analogues: The structures of all ligands **(Table 1)** were drawn in 2D, converted into 3D, and saved as .mol/PDB file. In order to optimise the ligands for docking, they were first optimised. All the ligands we reanalysed for their interaction with proteins through docking scores. A molecular docking score identifies ligands that interact with orientation, as seen with the androgen receptor. A 3D and 2D interaction between ligands and androgen receptors is shown in **Fig. 3** and **4**, respectively. The ligands showed good docking poses. **Table 7** displays the log values of the ligands as well as the protein-ligand interaction scores (total score values) found during docking (the docked postures obtained through visualisation). Docking poses were identified for the ligands with the target protein. Docking poses must demonstrate how the ligand fits into the binding region of the protein.

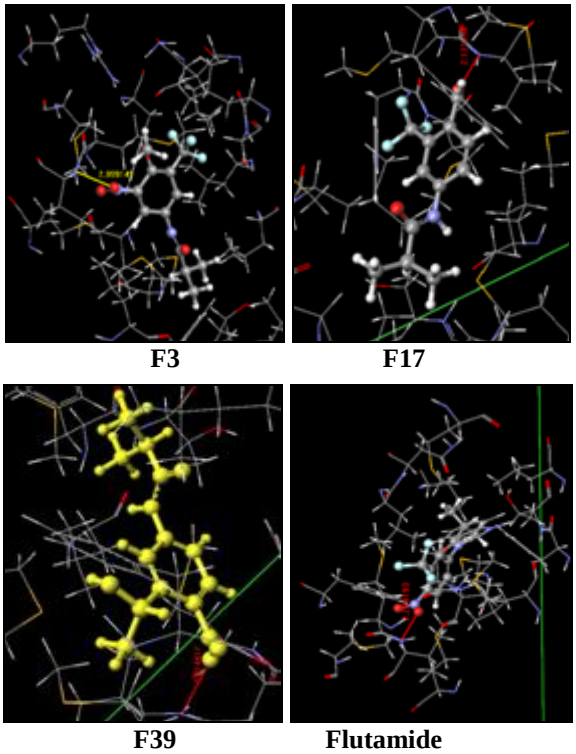


FIG. 3: 3D DOCKING POSES OF COMPOUND F3, F17, F39 AND FLUTAMIDE

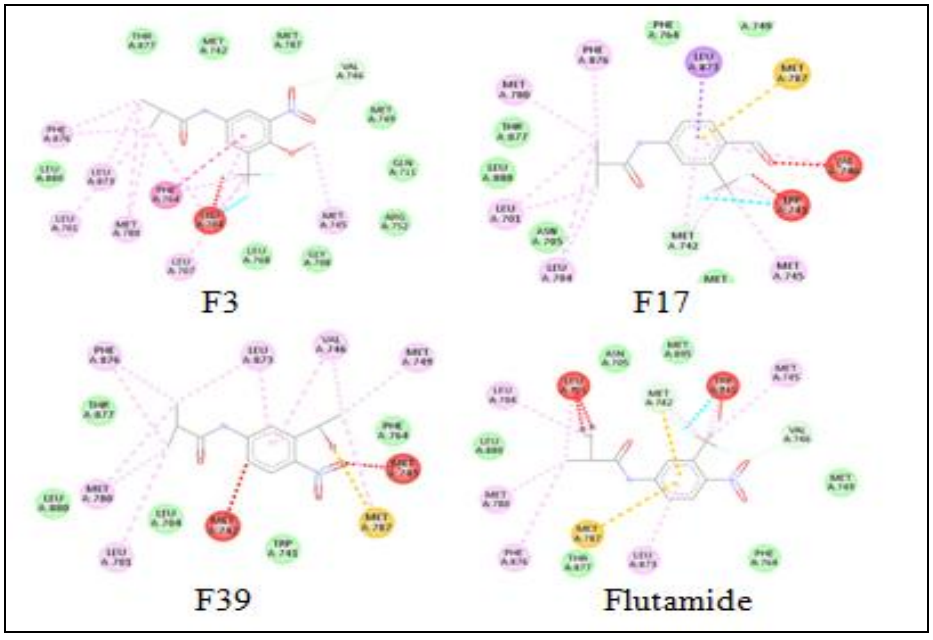


FIG. 4: 2D DOCKING POSES OF COMPOUND F3, F17, F39 AND FLUTAMIDE

Based on the docked conformations of the androgen receptor complex, intermolecular docking simulations were conducted and energy values calculated. Most of the ligands had good binding scores with *2AM9*. The interaction was measured by the binding energy of the best ligand pose measured in *kcal/mol*. The binding poses and their energy are listed in **Table 7**. The obtained docking scores are between -7.76 to -9.75Å. All the ligands docked within the binding pocket region suggest their shape complements with the androgen receptor. The 3-dimentional presentation of the docking pose of ligand molecules like F3, F17, F39, and Flutamide with androgen receptors is shown in **Fig. 3**. Compared to flutamide as a standard, most compounds have very good docking scores. Ligands like F3, F17, F19, and F37 showed higher docking scores and multiple docking poses. In ligand F1, multiple interactions were observed, including 845ARG, 858GLN, and 845ARG at distances of 2.99Å, 2.55Å, and 2.98Å, respectively. Ligand F6 had multiple interactions with amino acid residues such as 752ARG at different distances of 2.83Å, 2.32Å, and 2.99Å. There was no interaction between Ligand F7 and any amino acid residue. Ligand F9 shows the interaction with the 746VAL residue of amino acid at a distance of 2.74Å. Ligand F19 interacted with 746PHE and 752ARG residue of amino acid at distance 2.99Å and 2.83Å, respectively. In addition, Ligand F37 has interacted with various amino acid residues such as 752ARG, 708GLY, and 704LEU at a distance of 2.25Å, 2.52Å, and 2.89Å, respectively. Furthermore, ligands F3, F17, and F39 were found to show interaction with the same amino acid residue 746VAL at a distance of 2.99Å, 2.13Å and 2.31Å, respectively, as shown in **Table 7**. These compounds might be powerful androgen receptor inhibitors, based on the results. In this study, it has been observed that some compounds show common amino acid residue (746VAL) interactions with ligands which have a significant role in binding and biological activity. 746Val protein amino acid residue and flutamide interacted with carbon-hydrogen residue which is also shown in the literature [34]. 746VAL might account for this anti-tumour activity. An important outcome of this study may result in the design of novel androgen receptor antagonists along with docking analysis.

TABLE 7: DOCKING SCORE OF THE ANALOGUES

Entry no.	Docking score (*Kcal/mol*)	Amino acids interaction
Aryl Group Bioisosteres		
F1	-7.76024	1500N-854ARG,2.99A, 1543N-858GLN,2.55A, 1500N-854ARG,2.93A, 1543N-858GLN,2.49A, 1497N-854ARG,2.33A
F3	-7.88016	1180N-746VAL,2.99A
F4	-9.55183	1826S-784CYS,2.53A
F6	-8.74	1284N-752ARG, 2.83A, 1284N-752ARG, 2.32A, 1283N-752ARG, 2.99A
F7	-	No Hydrogen Bonds
F9	-9.052	1284N-752ARG, 2.74A
Nitro Group Bioisosteres		
F17	-8.75	1180N-746VAL, 2.131A
F19	-9.48	1482O-764PHE, 2.99A, 1284N-752ARG, 2.83A
F21	-9.71	1166O-745MET, 2.900A
Trifluoromethyl Group Bioisosteres		
F37	-9.01	1284N-752ARG, 2.25A, 559N-708GLY, 2.52A, 495O-704LEU, 2.89A
F38	-9.75	1812N-783GLN,2.99A, 3494N-883LYS, 2.59A
F39	-8.81937	1180N-746VAL,2.31A
F40	-7.90854	1740N-779ARG,2.56A, 1740N-779ARG,2.99A
Flutamide	-8.26474	1180N-746 VAL,2.25A

CONCLUSION: Flutamide is one of the antiandrogen drugs used in the treatment of PC. Hepatotoxicity is a major side effect, which is why drugs are pulled from the market. Flutamide was structurally modified by using a bioisosteric approach to get less toxic compounds than flutamide. The *in-silico* design of drugs is a promising method for developing antiandrogen drugs. In the design of newer analogues of flutamide, a bioisosteric approach was used. As part of the investigation, ADMET lab 2.0 and PEO were used to calculate ADMET properties, DL and DS. For the docking study, Argus Lab 4.0.1 was used to confirm the best docking score by

interaction between ligand and protein. A docking study of F3, F7, F17, F19, F37, and F39 ligands demonstrated that these ligands had better binding characteristics with the androgen receptor model in comparison to the other ligands. The docking study reflects that the ligands interact with the androgen receptor, which is evident by the docking scores. Ligands F3, F17, F39 and flutamide had similar interactions (746Val amino acid residue). The common amino acid residue 746Val plays a crucial role in the activity and binding affinity of the selected compounds. The data obtained from ADMET properties prediction, DL, DS, and docking studies of ligands, compounds F3, F17, and F39 could be promising drugs in the management of PC.

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