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LIGAND BASED PHARMACOPHORE MODEL DEVELOPMENT FOR ANTI ANDROGEN RECEPTOR DRUGS FOR TREATING PROSTATE CANCER

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Key words:

Pharmacophore modeling, virtual screening, docking, androgen receptor, Ligand Scout, Zinc database.

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ABSTRACT: The computational modeling and high throughput screening techniques have been used to identify small molecules that specifically target functional surface sites of the androgen receptor in Prostate cancer. Pharmacophore modeling, Virtual screening, docking based analyses is used for development of new chemical entities. The purpose of the current work is to establish pharmacophore model for the FDA approved anti-androgen receptor drugs of prostate cancer by using the software Ligand Scout 3.1, The data sets for the anti-androgen compounds were downloaded in.sdf format from Pubchem database. The model consists of five hydrogen bond acceptors, and one hydrophobic moieties and one aromatic ring which are defined as essential feature for androgen receptor inhibitors. Then the derived pharmacophore model was compared with the Zinc database of available standard anticancer drugs, Virtual screening of ZINC chemical databases leads to identification of one hit, and this compound can be useful for the design of future targets and development of new drugs to cancer. The newly obtained compound is then docked with androgen receptor with the help of Autodock Vina 4.0.The result obtained from the present study suggests that the application of ligand based pharmacophore could assist in selection of potential leads for rational design of androgen receptor inhibitors in prostate cancer therapy.

INTRODUCTION: Prostate cancer is predicted to be the leading cause of cancer-related death in men over the next decade [1]. In its early stages and when localized to the prostate, this cancer can usually be cured by surgery or radiation therapy. However, for advanced, metastatic or recurrent disease, alternative systemic treatments are required. In this regard, the androgen receptor, a ligand-inducible transcription factor, is considered to be central for Prostate cancer development, growth and metastasis [2].

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The human androgen receptor, a member of the nuclear hormone receptor family, is a ligand-dependent transcription factor with known significant therapeutic relevance in prostate cancer[3].Similar to other nuclear receptors, the androgen receptor is organized into three distinct domains: An *N*-terminal domain, followed by a DNA binding and a *C*-terminal ligand binding domains [4].

All conventional androgen receptor -directed therapeutics, including the most potent new clinically approved anti-androgen, targets the hormone binding pocket of the receptor [5, 6]. The human androgen receptor is coded by a gene located on the chromosome at Xq11-12 and is composed of 919 amino acids. Accordingly, treatment of advanced prostate cancers usually involves some form of surgical or chemical

castration to lower the level of circulating androgens and, thereby, to prevent androgen receptor transcriptional activity [7]. In addition, to maximize androgen blockade, Prostate cancer patients are often treated with drugs called anti-androgens, which compete with naturally occurring androgens for the receptor's androgen-binding site. Unfortunately, most of these cancers eventually progress to a castration-resistant state, where they no longer respond to androgen deprivation or anti-androgen treatments.

In an attempt to overcome resistance to conventional anti-androgens, computational modeling and high throughput screening techniques have been used to identify small molecules that specifically target functional surface sites of the androgen receptor [4].

Computer Aided Drug Designing covers a broad range of applications spanning the drug discovery pipeline and helps to speed up and rationalize the drug design process while reducing costs [8, 9]. One approach to speed up drug discovery is to examine new uses for existing approved drugs, so-called 'drug repositioning' or 'drug repurposing' which has become increasingly popular in recent years. Analysis of the literature reveal many examples of US Food and Drug Administration–approved drugs(FDA) that are active against multiple targets (also termed promiscuity) can also be used to therapeutic advantage. Using the current *in silico* technologies and databases of the structure and biological activities of chemical compounds (drugs) and related data, as well as close integration with in vitro screening data, improved opportunities for drug repurposing will emerge for neglected or rare /orphan diseases [10].

Our goal was to retrieve a new drug for Prostate cancer from the available anti androgen FDA approved drugs through pharmacophore modeling, virtual screening and docking studies. In this study we performed the computational based methods to determine pharmacophore models. These models are essential functional groups of atoms in three dimensional position that interact with a receptor i.e. target molecule. A pharmacophore can be divided into two types, receptor based pharmacophore and ligand based pharmacophore (which function on lock and key mechanism). Ligand-based drug design can be performed in association with molecular docking, these methods can be combined to identify a number of new hit compounds with potent inhibitory activity and to understand the main interactions at the binding sites. The molecular docking and pharmacophore can produce reliable true positive and true negative results in the subsequent virtual screening procedure. The appropriate use of these methods in a drug discovery process should improve the ability to identify and optimize hits and confirm their potential to serve as scaffolds for producing new therapeutic agents [11].

We collected experimental data sets against prostate cancer. The dataset (FDA approved drugs) used in this present study which was cited by (Francesco *et al.*, 2014) [12] is used for the pharmacophore model generation. This data set is used to correlate the results of experimental and computational studies. The pharmacophore model was generated for the FDA approved drugs with help of the software Ligand Scout 3.1. pharmacophore modeling, virtual screening, docking based analyses are used for development of new chemical compounds. Hence the present study could be a new endeavour at the development of ligand based pharmacophore model which could assist in selection of potential leads for rational design of androgen receptor inhibitors in prostate cancer therapy.

MATERIALS AND METHODS:

Pharmacophore modeling:

The pharmacophore model was generated for the FDA approved drugs for treating prostate cancer with help of the software Ligand Scout 3.1. The three dimensional structures of 6 anti-androgen receptors were downloaded in.sdf format from Pubchem database (www.ncbi.nlm.nih. gov/ pubchem). The training set consists of 6 compounds and was selected to generate the ligand based pharmacophore model. Ligand based pharmacophore model generation was performed with Ligand Scout using default settings. The pharmacophore for each group of compounds and MS-275 has been generated. Feature-based pharmacophores are then generated by determining interactions between ligand and target atoms.

Virtual Screening:

Pharmacophore based database searching is considered as a type of ligand-based virtual screening. The database used for Pharmacophore based database searching is ZINC which was downloaded from (http://zinc.docking.org). The derived pharmacophore model was compared with the Zinc database of available standard anti-cancer drugs. ZINCPharmer is an online interface for searching the compounds of ZINC database. Best aligned anti-androgen receptors pharmacophore model was used as a 3-D query for searching potent compounds from ZINC chemical database having approximately 2 × 108 compounds. Database screening was performed using ligand pharmacophore mapping protocol. Compounds which fitted minimum (n-2; n is total feature of present pharmacophore) pharmacophore features were considered as hits [13]. Virtual screening of ZINC chemical databases leads to identification of one hit, and this compound can be useful for the design of future targets and development of new drugs to cancer.

Molecular Docking:

Model validation has been performed through molecular docking studies which have been performed through Autodock 4.0 is an open-source program which is steadfast and authentic to perform docking simulations [14].

The structure of the androgen receptor was taken from PDB (4K7A-pdb id). The PDB structure which was chosen for the present study has good resolution of 2.00 when compared to other structures and its binding site is also analyzed under the property ligand chemical component and view can view its interactions site through Ligand explorer.

Compound which was reterived from ZINC database (ZINC06142274) have been docked into the binding pocket of androgen receptor with PDB id 4K7A obtained from Protein Data Bank. The optimized co-ordinates of inhibitors were saved in .pdbqt format with babel-2.2.3 to carry docking analysis. All inhibitors in this study were docked into binding site of ZINC06142274 using AutoDock 4.0 with standard protocol. The Lamarckian Genetic Algorithm (LGA) was applied to deal with protein-inhibitors interactions. Polar hydrogen atoms were added geometrically. Kollman united atom charges were assigned to protein and PDBQT file was created. The 3-D affinity grid fields with grid map of 60 × 80 × 60 points were created using the auxiliary program AutoGrid [15, 16] For evaluating binding energy in the docking step, Columbic electrostatic potential, vander waals interaction represented as a Lennard-Jones12-6 dispersion/repulsion 12-10 term and hydrogen bonding represented as a directional 12-10 term were taken into account [17]. The resultant structure files were analyzed using PyMOL visualization programs. PyMOL (molecular visualization software system) plug-in that visualize the protein structure along with the source protein and it is an offline visualization tool [18].

RESULTS AND DISCUSSION:

Ligand docking studies have widely been used for ligand based drug designing for cancer. In the present work, Pharmacophore is identified for the selected standard compounds in order to verify the result of the selected 6 anti-androgen compounds. Same technique followed for identification and generation of pharmacophore was reported before in different research work [19, 20, 21]. There are two different types of pharmacophore methods that can be used for discovery of most novel leads compounds: one is ligand based pharmacophore and other is structure-based pharmacophore [22].

Here we used ligand-based pharmacophore generation, which depends completely on the reported activity value (IC50) of anti-androgen prostate cancer compounds taken from literature studies cited by Francesco *et al*., 2014[12]. The identification of feature, responsible for enhancing binding to the ligand of interest has always attracted. The most important process in pharmacophore model generation is the selection of compounds for datasets. Therefore a set of 6 anti-androgen compounds were selected from literature described in order to find out the spatial arrangement of chemical features that attains drug activity towards the selected ligand. Major goal of modern drug design is identification and development of new ligands with high affinity of binding towards a given protein receptor through pharmacophore analysis [22].

Pharmacophore analysis is considered as a fundamental part of drug design [23]. The data sets for the 6 antiandrogen compounds were downloaded in.sdf format from Pubchem database were shown in **Fig.1.**

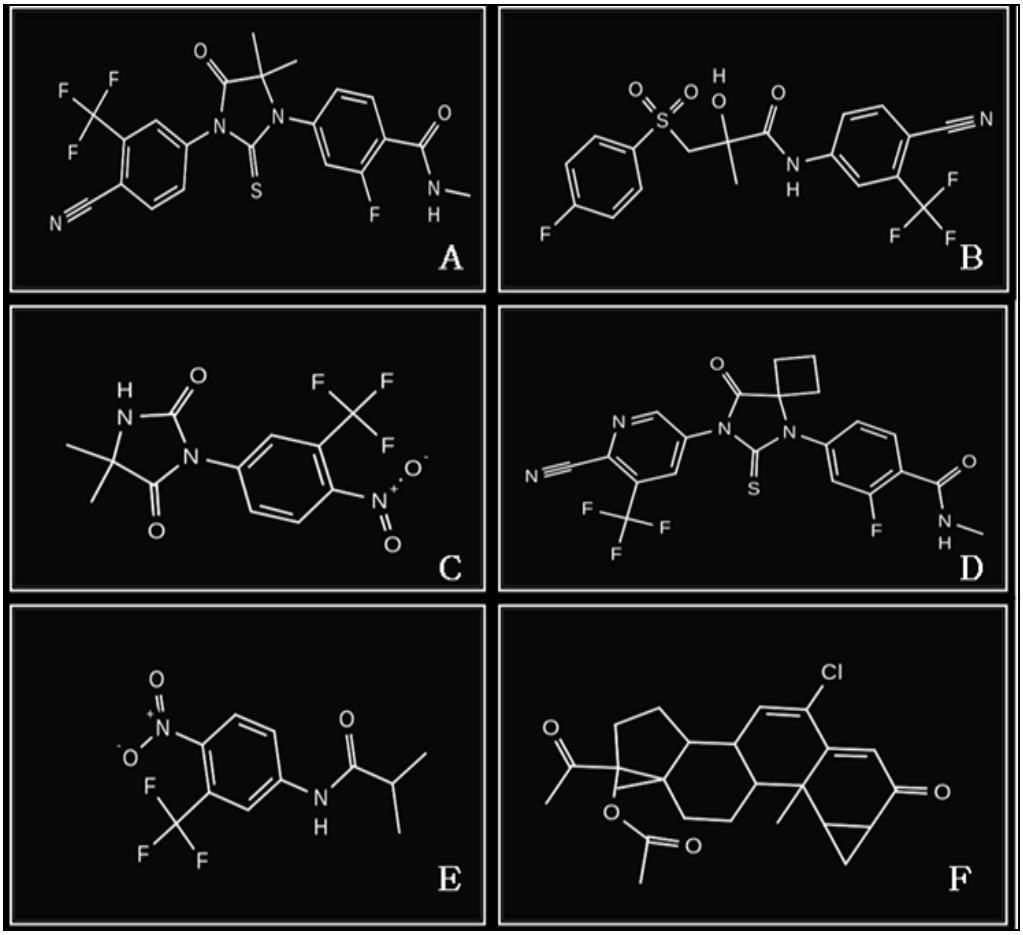

FIG.1: THE TWO DIMENSIONAL STRUCTURES OF SELECTED FDA APPROVED DRUGS FOR PROSTATE CANCER A) ENZALUTAMIDE B) BICALUTAMIDE C) NILUTAMIDE D)ARN 509 E) FLUTAMIDE F)CYPROTERONE ACETATE.

Ligand Scout software generate the pharmacophore models for the selected data's of 6 anti-androgen compounds which shows three main features as hydrogen bond acceptors, hydrophobic region and aromatic rings. The pharmacophore generated for the chosen group of compounds showed consistency in the above features. The modeled pharmacophores of each group and subgroups are shown in **Fig. 2, 3, 4, 5, 6** and **7**.

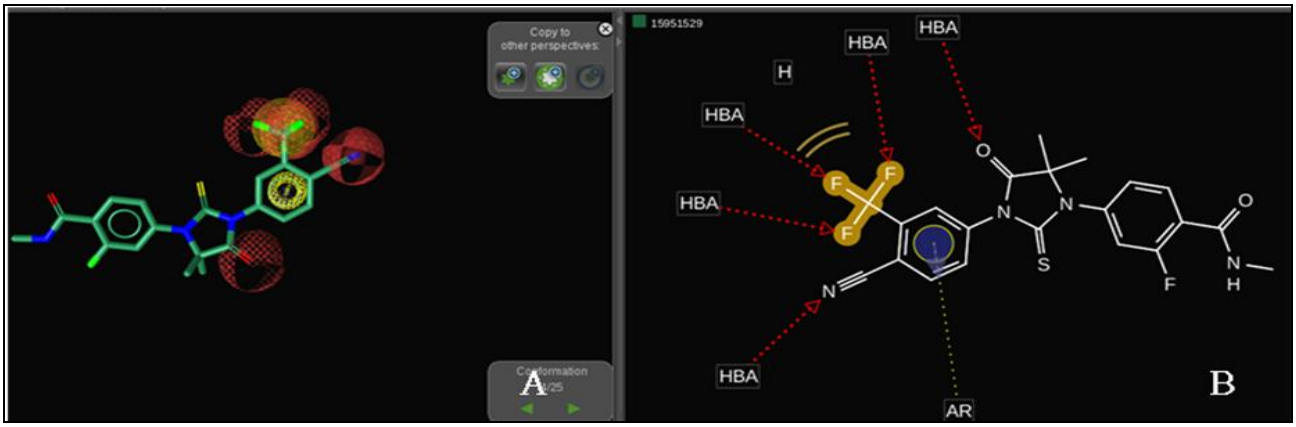

FIG.2: PHARMACOPHORE MODEL OF THE COMPOUND ENZALUTAMIDE.(A) 3D REPRESENTATION (B) 2D REPRESENTATION

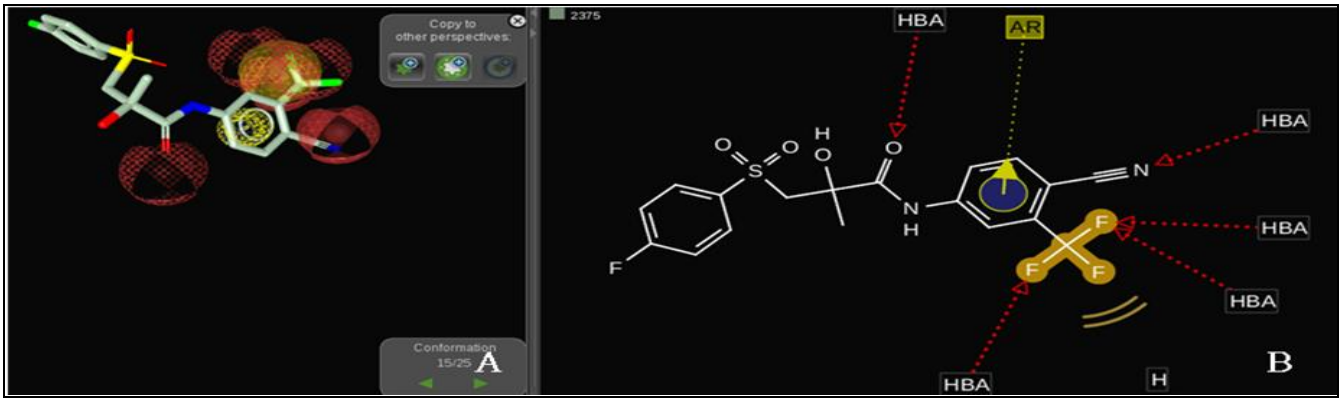

FIG.3: PHARMACOPHORE MODEL OF THE COMPOUND BICALUTAMIDE. (A) 3D REPRESENTATION (B) 2D REPRESENTATION

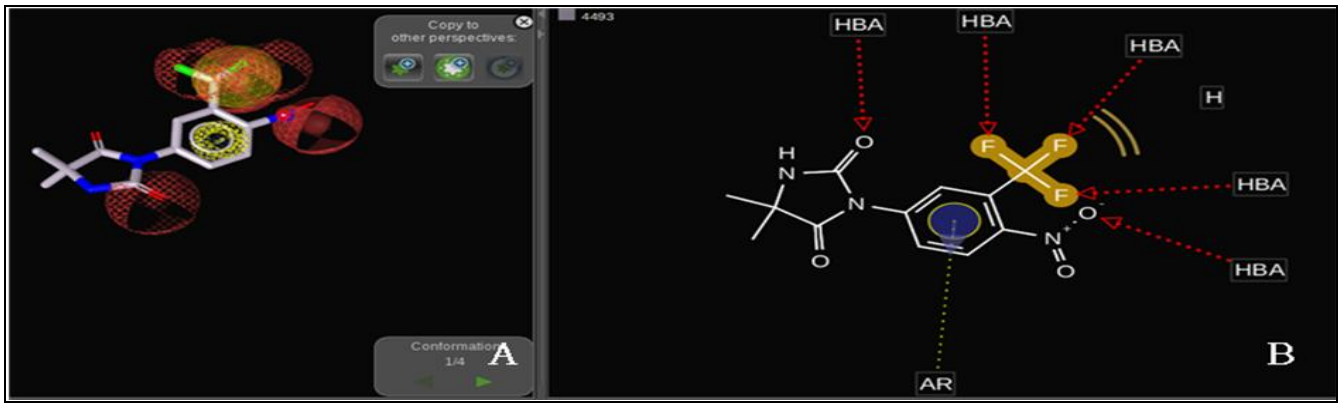

FIG. 4: PHARMACOPHORE MODEL OF THE COMPOUND NILUTAMIDE. (A) 3D REPRESENTATION (B) 2D REPRESENTATION

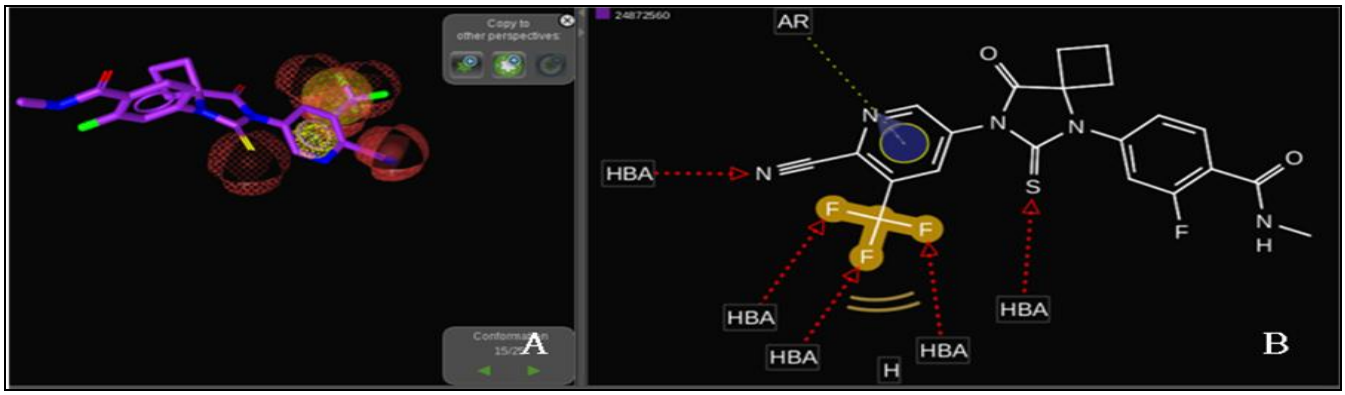

FIG.5: PHARMACOPHORE MODEL OF THE COMPOUND ARN 509. (A) 3D REPRESENTATION (B) 2D REPRESENTATION

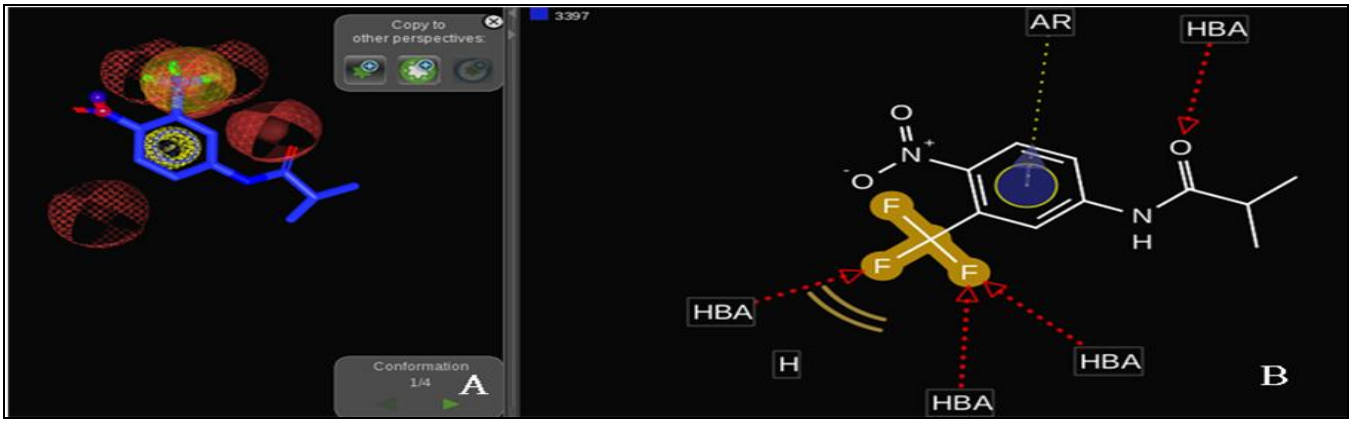

FIG.6: PHARMACOPHORE MODEL OF THE COMPOUND FLUTAMIDE. (A) 3D REPRESENTATION (B) 2D REPRESENTATION

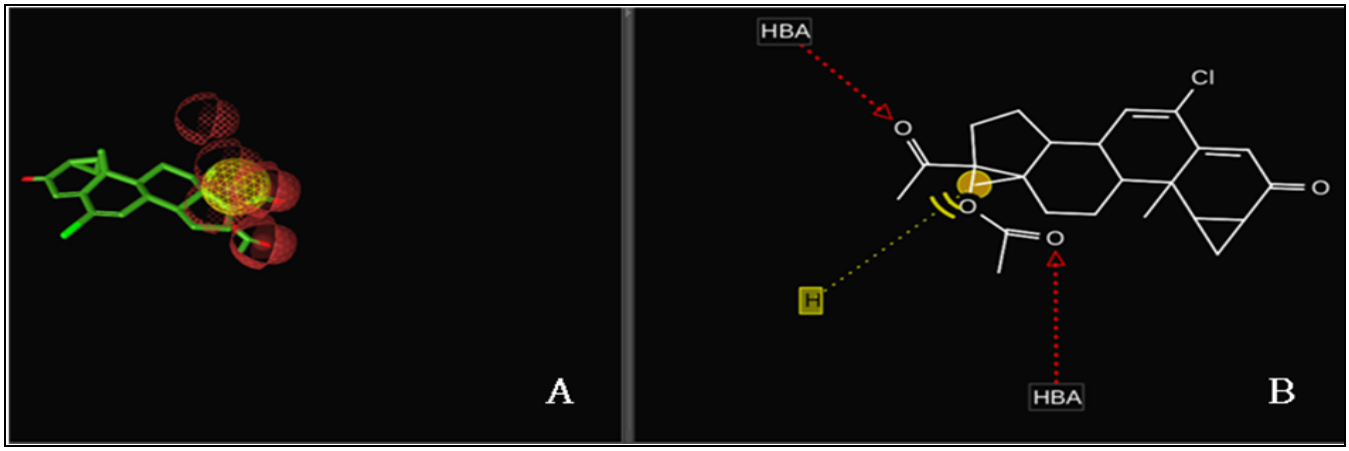

FIG.7: PHARMACOPHORE MODEL OF THE COMPOUND CYPROTERONE ACETATE. (A) 3D REPRESENTATION (B) 2D REPRESENTATION

The merged pharmacophore of 6 anti-androgen compounds are shown in **Fig 8** and **9.** These figures show the 3D and 2D views of the pharmacophores. The features identified in red color are the HBAs and the aromatic rings are shown in blue color and hydrophobic in yellow color in both views. All the ligands showed consistency in these three features. On the whole, the pharmacophoric features for each compound are shown in **Table 1.**

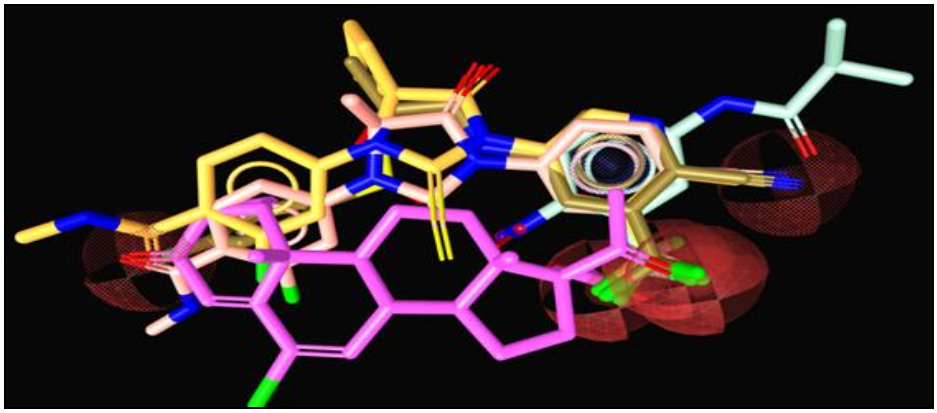

FIG. 8: MERGED PHARMACOPHORE OF THE COMPOUNDS ENZALUTAMIDE, BICALUTAMIDE, FLUTAMIDE, NILUTAMIDE, ARN 509, CYPROTERONE ACETATE WITH FEATURES HBA (RED SPHERES), HYDROPHOHIC REGION (YELLOW SPHERE), AROMATIC RING (BLUE SPHERE).

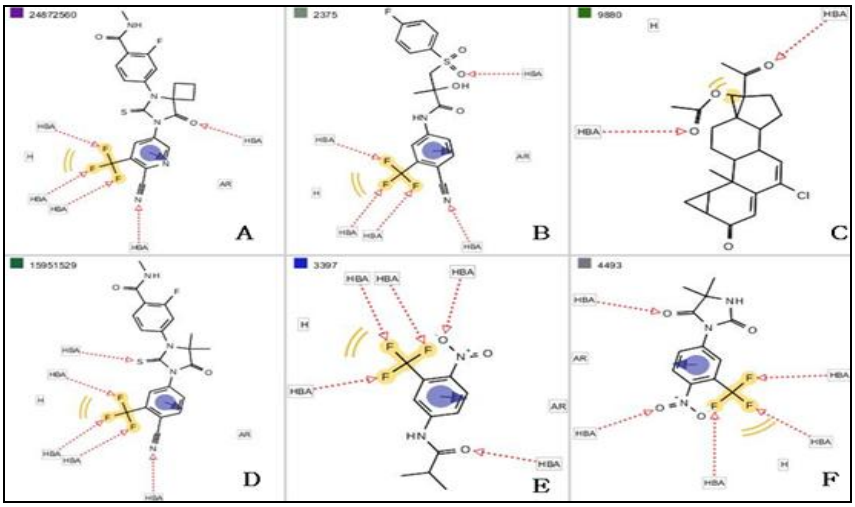

FIG. 9: THE 2D REPRESENTATION OF THE MODELED PHARMACOPHORE A) ENZALUTAMIDE B) BICALUTAMIDE C) CYPROTERONE ACETATE D) NILUTAMIDE E) FLUTAMIDE F) ARN 509

The generated pharmacophores of all the compounds were then matched and a unique pharmacophore was identified after a detailed analysis. Similar features were identified after analyzing the pharmacophores of all compounds generated by Ligand scout. The similar features of all the compounds were then superimposed and merged into a single pharmacophore. Superimposed ligands are shown in **(Fig. 9).**

TABLE 1: PHARMACOPHORIC FEATURES OF THE COMPOUND

S.No	Compound Name	IC50 values	HBA	Hydrophobic region	Aromatic Ring
1.	Enzalutamide	36 nM	5	1	1
2.	Bicalutamide	160nM	5	1	1
3.	Nilutamide	9nM	5	1	1
4.	ARN 509	16nM	5	1	1
5.	Flutamide	154nM	4	1	1
6.	Cryprotene acetate	7.1nM	2	1	0

Best fitting pharmacophore model was used as a 3-D structural query for retrieving potential compound from ZINC chemical databases, which consists of 22,72,3,923 compounds. Zinc Pharmer gives a library of explicit compound conformations, that match a 3D pharmacophore model [13] a result, a total of one compound which showed good mapping with pharmacophore (relative pharmacophore fit score>0.95), are selected and subsequently subjected to molecular docking analysis [11] and the properties of the reterived compound(ZINC06142274)are shown in Supplementary **Table 2.**

TABLE 2: THE PROPERTIES OF THE COMPOUND (ZINC06142274)

Zinc Pharmer ID	ZINC06142274
Name of the compound	6-[[9-[3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2yl]-6-oxo-1H-purin-8yl]sulfanyl]2H-1,2,4-t
Smiles notation	c1[nH]c(=0)c2c(n1)n(c(n2)Sc3c(=O)[nH]c(nn3)[O-])[C@@H]([C@@H]([C]))
pH Range	7
XlogP	-1.77
Apolar Disolvation (Kcal/mol)	-8.87
polar Disolvation (Kcal/mol)	-71.44
HBond Donars	5
HBond Acceptors	14
Net caharge	-1
Molecular Weight(g/mol)	410.348
Rotatable Bonds	4

The predicted hits are further evaluated by molecular docking analysis for the compound (ZINC06142274) with the androgen receptor (4K7A). Androgen levels within the prostate may only be reduced by approximately 80% and for this reason anti-androgens are often also administered to reach "total androgen blockade". Anti-androgens are ligands that can bind to the androgen receptor and hold it in an inactive state and found that the Anti-androgens were recruited to the promoter region of the Prostate specific antigen gene following treatment with the anti-androgen Bicalutamide [24].

From the analyses of these literature studies the PDB structure of the androgen receptor(4K7A) was downloaded from PDB database which was shown in **Fig. 10 (A)** and the interactions is shown in **Fig.10(B)** and Binding site analysis along with the receptor in **Fig. 10**(C)asMet895A, Met745A, Phe 764A.

Pharmacophore modeling, virtual screening, docking simulation and pharmacokinetics based analyses are used for development of new chemical entities. Amresh *et al*., 2013[11] who worked in "Receptor Chemoprint Derived Pharmacophore Model for Development of CAIX Inhibitors" in his work he explains Carbonic anhydrase IX (CAIX) is an attractive target for anti-cancer therapy because it is selectively overexpressed in tumor cells. In this regard the docking was performed for the compound (ZINC06142274) into androgen

receptor(4K7A) cavity and its binding interactions are shown in **Fig.11.**

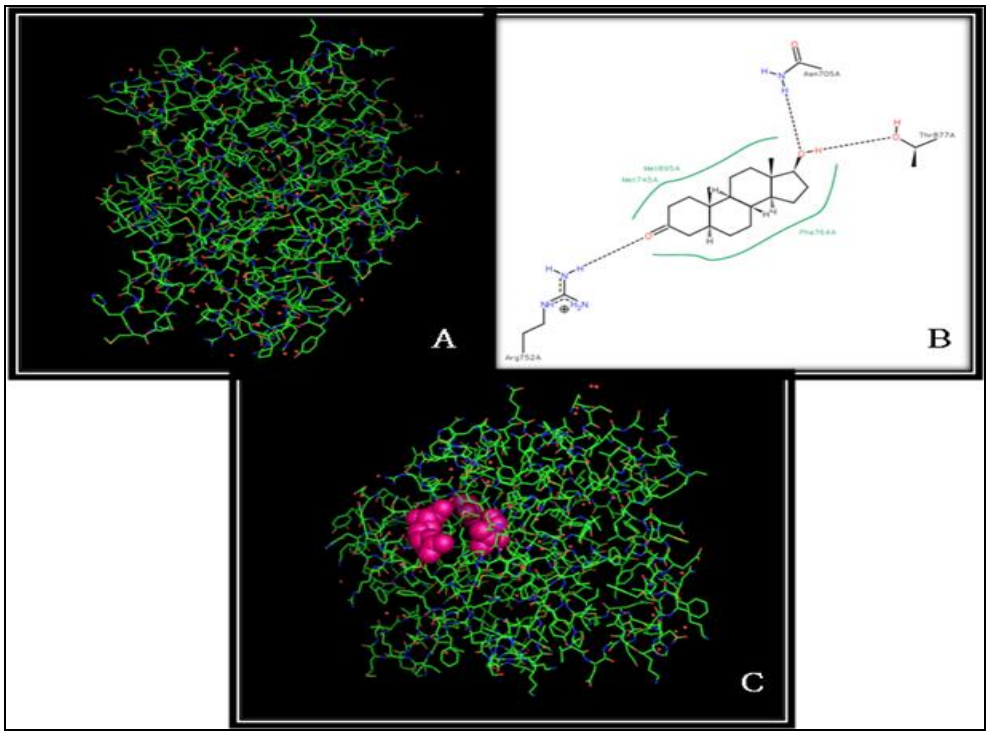

FIG. 10: THE PDB STRUCTURE OF THE ANDROGEN RECEPTOR(4K7A) IN FIGURE 10 (A) AND THE INTERACTIONS IS SHOWN IN FIGURE 10(B) AND BINDING SITE ANALYSIS ALONG WITH THE RECEPTOR IN FIGURE 10(C).

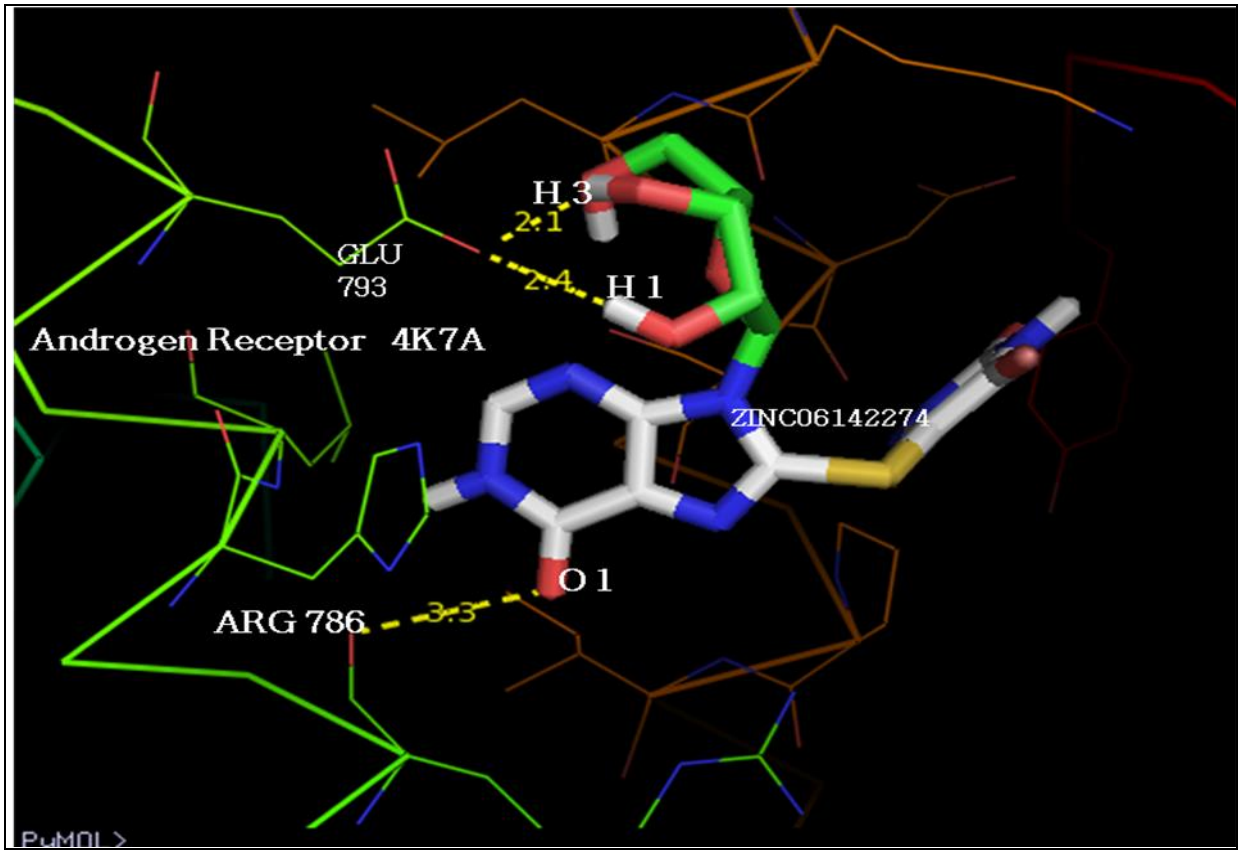

FIG.11: ACTIVELY DOCKED CONFORMATION THE COMPOUND (ZINC06142274) INTO ANDROGEN RECEPTOR(4K7A) CAVITY. THE YELLOW COLOUR DOTTED LINE REPRESENTS THE HYRDOGEN BOND INTERACTIONS BETWEEN THE COMPOUND (ZINC06142274) WITH THE ANDROGEN RECEPTOR(4K7A), AND ITS BINDING AFFINITY IS 10KCAL/MOL IS DEPICTED IN FIGURE 11.

TABLE 3: RESULTS OF PROTEIN-LIGAND INTERACTIONS

Protein	Ligand	Binding energy
Androgen Receptor(4K7A)	ZINC06142274	-6.3 kcal/mol

According to Irwin,(2002) [25] molecular docking continues to hold great promise in the field of computer based drug designing which screens small molecules by orienting and scoring them in the binding site of the protein with high binding affinity is by evaluating the accuracy of docking by its lowest binding energy. When a drug binds to a target in molecular modeling and molecular design software's, the lower the energy value the higher affinity of the drug. The important binding interactions which include hydrogen are shown in **Fig.11** as yellow line. The figure shows the interactions at particular distances. The binding interactions of the compound(ZINC06142274) with the androgen receptor(4K7A) include 3 hydrogen bonds.

The hydrogen bonds include H of the ligand with the O1 of ARG786 at distances of 3.3, with the H1 of GLU793 at 2.4and 2.1 with the H3 of GLU793. When a drug binds to a target in molecular modeling and molecular design software's, the lower the energy value the higher affinity of the drug [9]. Hence low energy is observed for the ligand ZINC06142274 as -6.3 Kcal/mol as shown in Table 3.Hence it proved that this compound may have the effect on androgen receptor(4K7A) against Prostate Cancer.

CONCLUSION: The computational modeling and high throughput screening techniques have been used to identify small molecules that specifically target functional surface sites of the androgen receptor in Prostate cancer. Ligand based Pharmacophore modeling, virtual screening, docking based analyses are used for development of new chemical entities. Thus the current study reveals the pharmacophore model for the FDA approved anti-androgen receptor drugs of prostate cancer by using the software Ligand Scout 3.1, the Pharmacophore model consists of five hydrogen bond acceptors, and one hydrophobic moieties and one aromatic ring which are defined as essential feature for Androgen receptor inhibitors. Then the derived pharmacophore model was compared with the Zinc database of available standard anti-cancer drugs, Virtual screening of ZINC chemical databases leads to identification of one hit, and this compound can be useful for the design of future targets and development of new drugs to cancer. The newly obtained compound is then docked with androgen receptor with the help Autodock Vina., having pharmacophore fit score ≥ 0.95. These hits were subsequently subjected to molecular docking analysis.

These results suggest that the application of ligand based pharmacophore could assist in selection of potential leads for rational design of Androgen receptor inhibitors in prostate cancer therapy. This model has broadened the vision for the generation of more specific drugs for human cancers and it opens the way to produce and identify more effective drugs. The results obtained in this study could be recommended for further studies for the identification of structurally diverse anticancer cancer compounds with the desired biological activity by purchasing the compound (ZINC06142274) and testing it through further *in vitro* and *in vivo*.

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