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Original Research Article

In silico study of 5-alpha-reductase (5-AR) active site prediction and interaction with supernatural compound II

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A R T I C L E I N F O

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A B S T R A C T

Hair loss is the biggest problem of human being. It is also known as alopecia or baldness. It refers to a loss of hair. DHT has many roles. Apart from hair production, it is linked to benign prostatic hyperplasia. DHT is a sex steroid, which is produced in the gonads. It is an androgen (male hormone). In men, the enzyme 5-alpha-reductase (5-AR) converts testosterone into DHT in the testes and the prostate. For this study, we have built the 3D structure of 5-alpha-reductase (5-AR) for active site prediction. Super Natural compound II is a database of natural products. Natural products are small compounds synthesized by living organisms. The chemical diversity of these molecules is tremendous and offers inspiration for innovations in medicine, nutrition, agrochemical research and life sciences. Most of the currently used cosmetics and drugs are natural products. In this study we are going to find out the interaction of 5-alpha-reductase (5-AR) to inhibit the production of DHT.

K E Y W O R D S

DHT | Hyperplasia | Alopecia | Baldness

C I T A T I O N

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Introduction

Hair loss is the most common in men. Hairs at the temples and on the crown slowly become very thin and eventually disappear and it is also called alopecia or baldness. DHT seems to be essential for prostate development external genitalia and male body hair growth or male-pattern baldness. Testosterone converts to DHT with the help of 5α-reductase (pronounced 5-alpha-reductase) and an enzyme that is found in the oil glands of a hair follicle (Cilotti, *et al*., 2001). The main role of DHT was discovered after the description of 5-alpha-reductase2 deficiency in a group of males from the Dominican Republic Imperato *et al*., 1974). 5α-reductases, also known as 3-oxo-5α-steroid 4-dehydrogenases, are enzymes involved in steroid metabolism. They show their participation in 3 metabolic pathways: bile acid biosynthesis, androgen and estrogen metabolism. There are three isoenzymes of 5α-reductase, SRD5A1, SRD5A2, and SRD5A3, it varies with different age (Yamana *et al*., 2010; Killian *et al*., 2003). We are working on the protein-ligand interaction studies and active site prediction of the protein. We have selected protein domain from uniprot database (uniprot id- P31213) and then we have construct the 3D structure of protein by using online Phyre 2 server. For this study we also selected ligand domain super natural compound, has a drug like properties. At last the potent lead molecules with good docking score were screened for their ADMET properties.

Material And Methodology

Target Protein Preparations: Target protein sequences were download from uniprot database, UniProtKB - P31213 (S5A2_HUMAN) (Uniprot Database). and build the 3D structure of protein by using phyre2 online server. This protein 3D structure was checked and fixed for any missing residues, loops, bond length in ―macromolecule‖ module of SPDBV [v4.1.0] (Guex *et al.,* 1997). Then the structure was optimized and minimized. In the crystal structure of protein -5-alpha-reductase domain of chain A was taken as active site was chosen for grid generation as there was already a crystal inhibitor. Grid was made using - define site‖ module of Molegro virtual docker.

Ligand Collections and selection: All of the natural ligands were collected from supernatural V II database. These super natural compounds are of natural origin. These targets were selected from the metabolic pathway steroid hormone biosynthesis (Supernatural database). All the compound selected from supernatural V II database were checked on the basis of Lipinski's rule. This rule is helpful to identify the molecules. Whether it can be used as a drug like or not. It means that it can predict the success probability rate of a molecule. The molecules should have the following properties according to rules. MW --0 to 500 , Xlogp--0 to 5, HBD--0 to 5, HBA--0 to 10 .On the basis of above parameter we have selected 5 ligands for this study and found perfect for Potent and ADMET study.

Docking and Interaction Studies: Molecular docking study was done with super natural compounds and protein from Genetic optimization for ligand docking Molegro Virtual Docker (MVD 4.0.2) (Thomsen *et al.,* 2006). We find interactions from MVD in terms of good scoring function and search

space. We find active sites from MVD and cross checked with Active site prediction (5-Active site prediction).

Total 142 natural ligands were collected from super natural database of metabolic pathway steroid hormone biosynthesis which act as potent natural drugs for the targets of 5α-reductase.

ADME Analysis and Best Ligand Proposal

ADMET stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. If a ligand follows ADMET properties then its likeness to become a drug molecule increases. Pharmacokinetics and Pharmacodynamic come under ADMET studies. We have used OSIRIS PROPERTY EXPLORER to check whether they are obeying all the ADMET properties or not. On the basis of non-bonded and bonded interactions, ADMET properties and scoring functions, we can propose these ligands as potent inhibitors of 5α-reductases. OSIRIS PROPERTY EXPLORER (Osiris property explorer) was used to know the mutagenicity, carcinogenicity, reproductively and toxicity. Red color indicates its unfavorability to consume as a drug while green color indicates its favorability to consume as druglike.

Result and Discussion

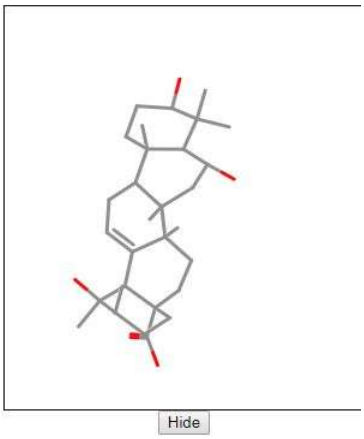
Total 142 natural ligands were collected from super natural database of metabolic pathway steroid hormone biosynthesis which act as potent natural drugs for the targets of 5α-reductase.

SN000030621 SN00030620 SN00030622 SN00037142 SN00037141 SN00037140 SN00037139 SN00040142 SN00040143 SN00040144 SN00020131 SN00020132 SN00020133 SN00020134 SN00037197 SN00037198 SN00037199 SN00038959 SN00006862 SN00033203 SN00033204 SN00033205 SN00033206 SN00033622 SN0005723 SN00005993 SN00007282 SN00011482 SN00007283 SN00019801 SN00007284 SN00017923 SN00011595 SN00033469 SN00033470 SN00033471 SN00033472 SN00011381 SN00011596 SN00005742 SN0005743 SN00006582 SN00006583 SN00006584 SN00006585 SN00005680 SN00006019 SN00006568 SN00018454 SN00006219 SN00006841 SN00013570 SN00003341 SN00011564 SN00011565 SN00011566 SN00011567 SN00006567 SN00006220 SN00030607 SN00030659 SN00003588 SN00003586 SN00006463 SN00006464 SN00003585 SN00003586 SN00006464 SN00003587 SN00003492 SN00007313 SN00007314 SN00011399 SN00013672 SN00011400 SN00030645 SN00030644 SN00011401 SN00011402 SN00063895 SN00067380 SN00067144 SN00072119 SN00072120 SN00072137 SN00072138 SN00072139 SN00072140 SN00072151 SN00064491 SN00064492 SN00064493 SN00064494 SN00064495 SN00064498 SN00064501 SN00064502 SN00072171 SN00072173 SN00072174 SN00072211 SN00072213 SN00072214 SN00072215 SN00064692 SN00064693 SN00064694 SN00064695 SN00067273 SN00067274 SN00067275 SN00067279 SN00067280 SN00067281 SN00067357 SN00067381 SN00067382 SN000067407 SN00067408 SN00067409 SN00072284 SN00072285 SN00048883 SN00048884 SN00064908 SN00064909 SN00064910 SN00064911 SN00072300 SN00072301 SN00091121 SN00072302 SN00091121 SN00072302 SN00072382 SN00072384 SN00048991 SN00067985 SN00067986 SN00067987 SN00071849 SN00072146

Proposed ligands structure with Basic descriptors

SN00040142

Name	(1R,2R,4aS,6aS,6bR,8S,8aR,10S,12aR,12bS,14bS)-1,8,10-trihydroxy-1,2,6a,6b,9,9,12a-heptamethyl-2,3,4,5,6,7,8,8a,10,11,12,12b,13,14b-tetradecahydropicene-4a-carboxylate
Molecular weight	487.342
Formula	$C_{30}H_{47}O_5$
desolv polar	-54.63
desolv apolar	7.08
H-bond donors	3
H-bond acceptors	5
TPSA	101
Charge	-1
NRB	1
logp	3.8405
Ring count	5
Atom count	82
Bond count	39
SMILES	C[C@@H]1CC[C@@]2(CC[C@@]3(C(=CC[C@@H]4[



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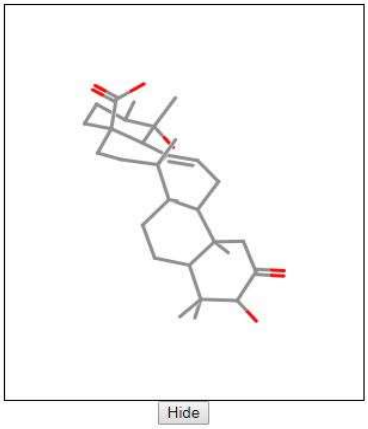
SN00030622

Name	(1S,2R,4aR,6aS,6bS,8aR,10R,12aR,12bS,14bS)-1,10-dihydroxy-1,2,6a,6b,9,9,12a-heptamethyl-11-oxo-3,4,5,6,7,8,8a,10,12,12b,13,14b-dodecahydro-2H-picene-4a-carboxylate
Molecular weight	485.327
Formula	$C_{30}H_{45}O_5$
desolv polar	-42.21
desolv apolar	9.55
H-bond donors	2
H-bond acceptors	5
TPSA	98
Charge	-1
NRB	1
logp	4.0487
Ring count	5
Atom count	80
Bond count	39
SMILES	C[C@@H]1CC[C@]2(CC[C@@]3(C(=CC[C@@H]4[C@



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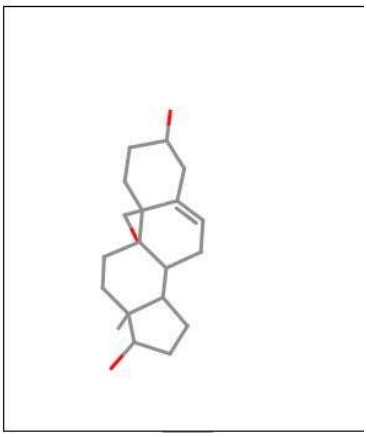
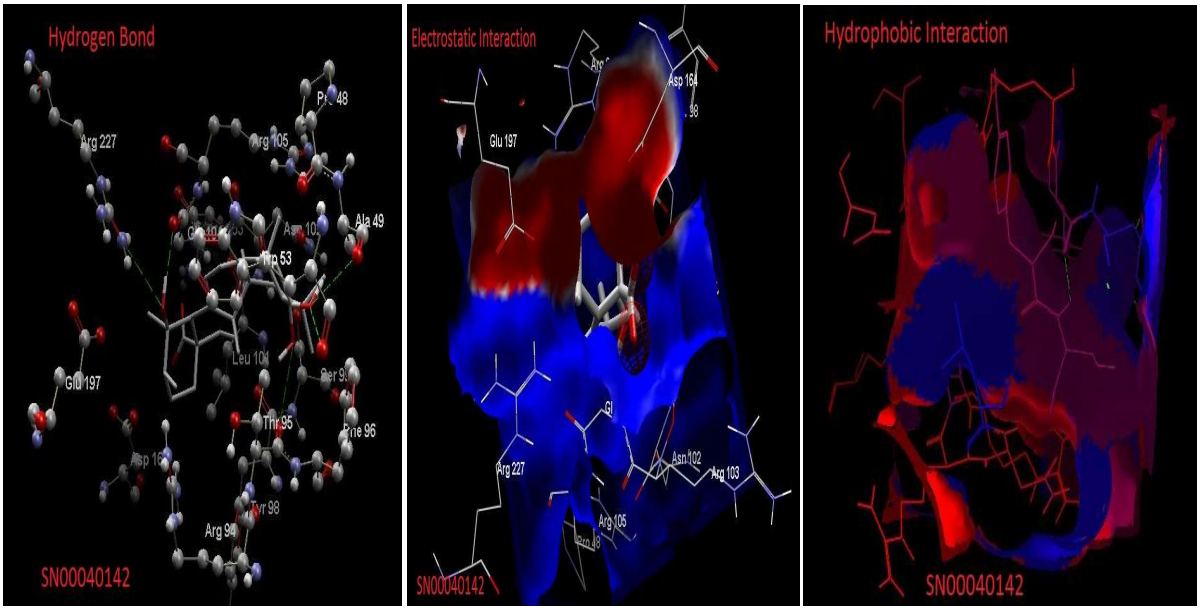
SN00072138

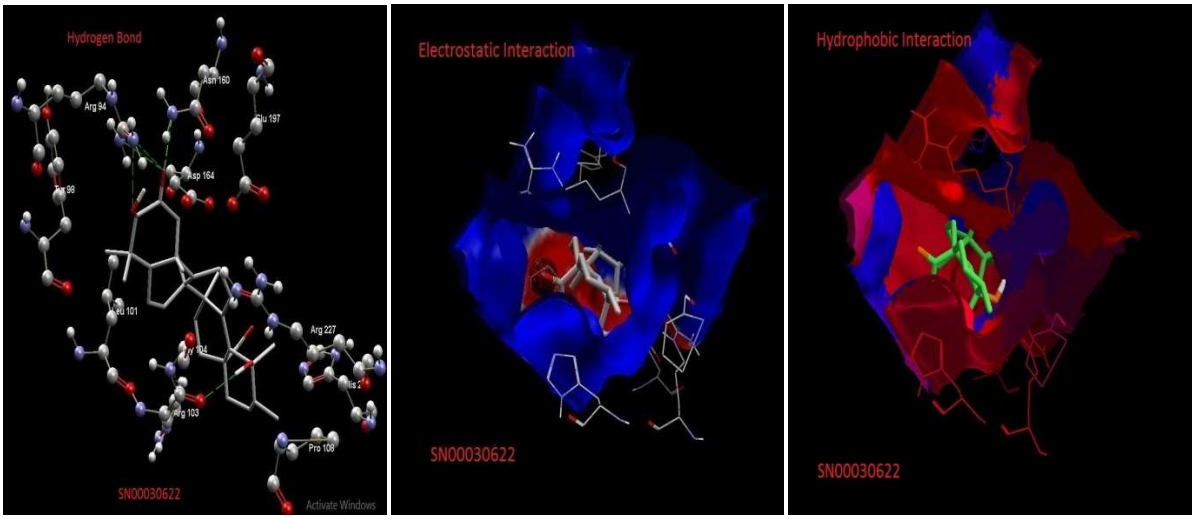
Name	androst-5-ene-3β,17β,19-triol
Molecular weight	306.219
Formula	$C_{19}H_{30}O_3$
desolv polar	-4.93
desolv apolar	-5.14
H-bond donors	3
H-bond acceptors	3
TPSA	61
Charge	0
NRB	1
logp	2.6434
Ring count	4
Atom count	52
Bond count	25
SMILES	C[C@]12CC[C@H]3[C@H]([C@@H]1CC[C@@H]2O)C



SN00040142



SN00030622



SN00072138

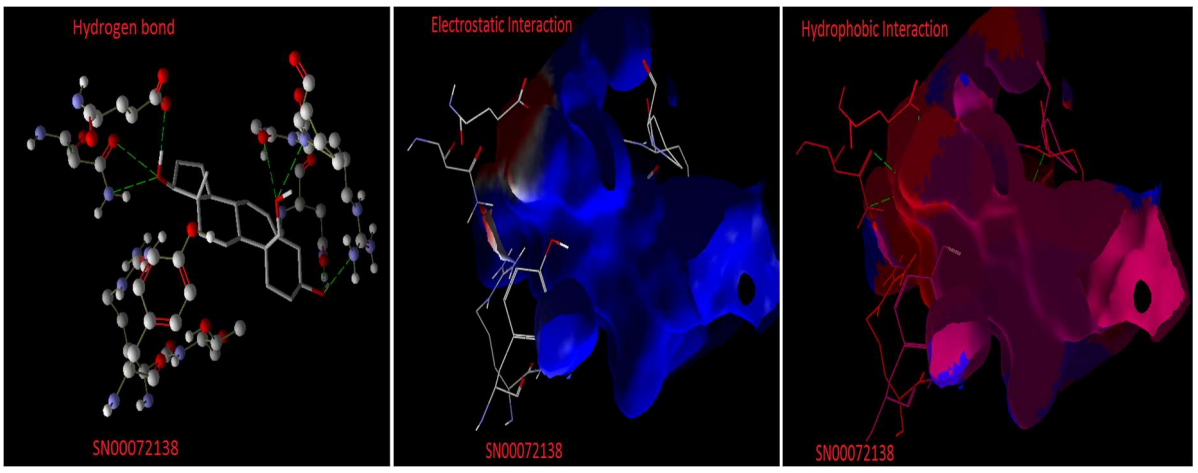


Fig. 1: Electrostatic, Hydrophobic and H bond interaction of 3 best ligands with target proteins

Compound ID	Compound Name
SN00040142	(1R,2R,4aS,6aS,6bR,8S,8aR,10S,12aR,12bS,14bS)-1,8,10-trihydroxy-1,2,6a,6b,9,9,12a-heptamethyl-2,3,4,5,6,7,8,8a,10,11,12,12b,13,14b-tetradecahydropicene-4a-carboxylate
SN00030622	(1S,2R,4aR,6aS,6bS,8aR,10R,12aR,12bS,14bS)-1,10-dihydroxy-1,2,6a,6b,9,9,12a-heptamethyl-11-oxo-3,4,5,6,7,8,8a,10,12,12b,13,14b-dodecahydro-2H-picene-4a-carboxylate
SN00072138	androst-5-ene-3β,17β,19-triol

Table 1: Best 3 compounds as inhibitor to 5α-reductase protein - 1

Ligand	H-bond	Moldock score (Energy)	RMSD
SN00040142	5	-133.047	0.06
SN00030622	5	-132.3	0.21
SN00072138	7	-114.3	0.04

Table 2: Molecular docking Results

5α-reductase protein sequence was downloaded from uniprot database with ID P31213 (S5A2_HUMAN) and construct the 3D structure of 5α-reductase using phyre2 online server. Find the key active site residues from MVD and cross checked with active site prediction. (Volume of cavity = 657). To propose ligands to inhibit 5α-reductase protein, we have selected 3 ligands compound, which follow the lipinski's rule of five. After ligands validation we performed Molecular docking studies of 5α-reductase protein with these proposed three ligands. Molecular Docking Score are given in Table 2.

Conclusion

Drug Discovery process is a very useful and important in drug designing. As per interaction studies of these natural compounds with 5α-reductase protein, only three ligands were found to be most energetically stable on the basis of molecular docking score and also found promising in protein-ligand interactions. Out of these three screened ligands, SN000072138 (androst-5-ene-3β,17β,19-triol) is quite promising at all ADMET properties except LogP. So we may conclude that SN00007210 ligand can work as of 5α-reductase inhibitor and thus could be useful for controlling the hair loss.

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Osiris property explorer: http://www.organic-chemistry.org/prog/peo/