Drug Designing and Docking studies on PCOS and Hypothyroidism using advanced Cheminformatics tools and database

D.Parimala nandhini¹, D.Leelavathi¹ and Balaji.M²

¹P.G & Research Department of Zoology, Ethiraj College for Women, Chennai-600 008, Tamilnadu, India.
²Managing Director, Akshaya Computational Medicine Pvt, Ltd., Chennai-5, Tamilnadu, India.

Abstract
PCOs and hypothyroidism have many symptoms in common, such as “anovulation” i.e. menstruation without releasing an oocyte (egg cell). Some propose this is the cause of PCOs if anovulation is long term with its related low progesterone. Other symptoms the two conditions share are: insulin resistance, blood sugar problems leading to diabetes, high cholesterol levels, heavy periods, weight gain (obesity), hair loss and ovarian cyst. These two disorders are clinically associated. The aim of our research is to deliver the potential gene which is involved in both hypothyroidism and PCOs. In our drug designing study we use advanced cheminformatics software and tools for designing a combination of novel drug candidates which would act as a potential inhibitor for the SHBG target protein. We also analyzed the complete pharmacokinetic studies of the novel drug candidate. Hence, in future this drug would act as a potential therapeutic agent for patients affected by PCOs along with hypothyroidism.

Keywords: Anovulation, PCOs and hypothyroidism

INTRODUCTION
Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of male hormones (androgens), in particular testosterone, by either one or a combination of the following: the release of excessive luteinizing hormone (LH) by the anterior pituitary gland. Through high levels of insulin in the blood (hyperinsulinaemia) in women whose ovaries are sensitive to this stimulus. The syndrome acquired its most widely used name due to the common sign on ultrasound examination of multiple (poly) ovarian cysts. These “cysts” are actually immature follicles not cysts. The follicles have developed from primordial follicles, but the development has stopped (“arrested”) at an early antral stage due to the disturbed ovarian function [1-3]. In the United States hyperthyroidism affects about 1.2% of the population [4]. About half of these cases have obvious symptoms while the other half do not. It occurs between two and ten times more often in women. The disease is more common in those over the age of 60 years [5].

Drug selections and Designing

In this project we choose a potential existing molecule for PCOS and Hypothyroidism which was retrieved from NCBI–Pubchem compound chemical database in order to perform molecular drug docking studies. The selected ligands were combined with help of Molinspiration Cheminformatics software and the calculations of drug properties are validated using Chemaxon software.

Ligand 3D structure prediction and validation

After design and validation, the 2D de novo drug was converted into 3D using Online Smiles Translator for drug docking protocols.

QSAR prediction

The complete QSAR procedure was done using VEGA software in order to analyze to what extent the designed drugs obey the drug likeliness properties and biological activity.

To whom correspondence should be addressed:
D.Parimala
Email: parimalanandhini.d@gmail.com
The Absorption, Distribution, metabolism, Excretion and Toxicity prediction was done using (PkScM) in order to analyze the complete pharmacokinetic properties of the designed de novo drug.

**Molecular Drug Docking**

Molecular drug docking studies were performed using an automated molecular drug docking server called patch dock. The results obtained from drug docking studies, we analyse the binding affinities and ligand protein interactions.

**RESULTS AND DISCUSSION**

The target protein sequence of SHBG (Sex hormone binding globulin) shows the total number of 344 amino acids which is present in chromosome number 17. We used a protein modelling server; Swiss-Model workspace which integrates programs and databases required for Protein structure modelling in a web-based workspace. Using PUBCHEM chemical database [6], we selected the drugs in order to perform drug designing studies. The selected drug for PCOS (Polycystic Ovary Syndrome) is Estradiol (CID No: 5757) and for Hypothyroidism is Amphetamine (CID No: 5826). The selected drugs were combined with Cheminformatics software called molinspiration [7]. The results of the mol inspiration software show a log p value of 4.09 and a molecular weight of 405.58 g/mol. Thus the designed drug obeyed the drug likeliness properties.

The 2D structure validation of the designed chemical structure was done using CHEMAXON [8] software. The result clearly shows that the designed De Novo drug obeys the drug properties and Bioactivity protocols Figure (8). After validation, the 2D structure was converted into 3D using Online Smiles Translator [9] server for further drug docking studies. The 3D structure was viewed using discovery studio software. QSAR (Quantitative Structure Activity Relationship) [10] studies were done using VEGA software tool. A complete QSAR properties study of the designed drug was done and the results explain the scores of the drug properties is show in Table 1. The results clearly elucidate that the designed de novo drug has no toxic effect, is a Non-mutagen and a Non-carcinogen.

**Pharmacokinetics properties**

The ADMET) properties were found out using (pkCSM) server in order to find out the complete Pharmacokinetics profile of the designed de novo drug. Drug development has a high attrition rate, with poor pharmacokinetic and safety properties a significant hurdle. Computational approaches may help minimize these risks [11]. Douglas and Pires et al., (2015) represents a novel approach (pkCSM) which uses graph-based signatures to develop predictive models of central ADMET properties for drug development. pkCSM is better than current methods. Thus we choose the pkCSM server for designing the de novo drug. Fig 1. explains the molecular scores and values of the compound. Thus our results obey the control values of Pharmacokinetics properties. Thus the designed candidates are eligible for drug docking studies Fig 2. In Molecular drug docking studies, Patch Dock server [12] was used. The modelled target protein (SHBG) and the designed drug candidates were docked (Figure-18). Duhovny et al., in the year 2002 employed this technique. For given two molecules i.e. receptor and ligand, they are divided into patches according to the surface nature. These patches correspond to patterns that visually distinguish between puzzle pieces. Once the patches are identified, they can be superimposed using shape matching algorithms. The best Protein-ligand interaction was found to be in the new drug (Estradiol+Amphetamine with the value of -451.40) with SHBG gene receptor when compared to the Estradiol with SHBG value is -344.80 and SHBG with Amphetamine value is -195.12. Fig 3. shows the statistical analysis of docking scores represented by means of various graphs. (Fig 4) It clearly explains the high binding affinities of the de novo drug when compared to the existing drugs.

<table>
<thead>
<tr>
<th>Model</th>
<th>Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinogenicity model (CAESAR) (version 2.1.6)</td>
<td>Prediction is NON-Carcinogen</td>
</tr>
<tr>
<td>Mutagenicity model (CAESAR) (version 2.1.10)</td>
<td>Prediction is NON-Mutagen</td>
</tr>
<tr>
<td>Mutagenicity SarPy model (version 1.0.5-BETA)</td>
<td>Prediction is NON-Mutagen</td>
</tr>
<tr>
<td>Skin Sensitisation model (CAESAR) (version 2.1.3)</td>
<td>Prediction is NON-Sensitizer</td>
</tr>
</tbody>
</table>
QSAR PREDICTION OF DE NOVO DRUG \((1S,10R,11S,14S,15R)-15-(3\text{-}AMINO\text{-}4\text{-}PHENYL\text{BUTYL})\)TETRACYCLO \([8.7.0.0^2,^7.0^{11},^{15}]\) HEPTADEC-2,4,6-TRIENE-5,14-DIOL

Table 2. Patch Dock Results for the Drugs Amphetamin, Estradiol And De Novo

<table>
<thead>
<tr>
<th>Drugs</th>
<th>De Novo ((1S,10R,11S,14S,15R)-15-(3\text{-}amino\text{-}4\text{-}phenylbutyl)) tetracyclo ([8.7.0.0^2,^7.0^{11},^{15}]) heptadeca-2, 4, 6-triene-5, 14-diol</th>
<th>Estradiol</th>
<th>Amphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHBG</td>
<td>-451.40</td>
<td>-344.80</td>
<td>-195.12</td>
</tr>
</tbody>
</table>

Fig 1. Admet studies of amphetamine with estradiol (PKCSM software)

Fig 2. Cheminformatics Studies Of De Novo Three-Dimensional Structure (Discovery Studio Software)

Fig 3. molecular docking studies of de novo Three Dimensional structure (Discovery Studio)

Pose view protein ligand binding sites prediction : ligand green stick model and protein wire frame
CONCLUSION
In this Insilco research project, SHBG gene analysis was carried out. Here we focus on both PCOS and Hypothyroidism which are mostly correlated. Hence we choose the drug Amphetamine and Estradiol. (1S,10R,11S,14S,15R)-1-aminoo4phenylbutyl) tetracyclo [8.7.0.0^3,7.0^11,15] heptadeca-2,4,6-triene-5,14-diol which are combined and delivered as a de novo drug which is introduced to SHBG receptor. The designed de novo Drug is a non mutagen and non carcinogen and it has no toxic effect. Our drug docking results shows that the de novo drug has a high binding affinity to SHBG receptor. Hence we conclude that this drug can be used for treating both PCOS and hypothyroidism. In future our work could be extended in the field of Clinical Pharmacology studies where it could be found out whether our drug is an Antagonist or Agonist. Our drug could be used to cure any level of hormonal imbalance in SHBG protein. Hence our de novo drug would definitely act as a potential therapeutic agent for hormonal imbalance disorders such as PCOS and hypothyroidism.

AKNOWLEDGEMENT
None

CONFLICT OF INTERESET
No conflict of interest.

REFERENCES
4. Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, Laurberg P, McDougall IR, Montori VM, Rivkees SA, Ross DS, Sosa JA, Stan MN. Hyperthyroidism and other causes of


8. www.chemicalize.org


10. www.vega-qsar.eu/
