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# Prediction of ADME and Toxicity of Anti-Fungal drugs by InSilico methods

Dr.Mohan raj P[1*], Dr.Perumal P[1*], Amudhavalli.K[1], Rajeshwari M K[2], Sarojini S[2], Kamaraj T[2], Nishanth P[2], Ravi Kumar G[2].

*Professor[1*], Assistant Professor[1], B.Pharm IV year[2].*
*Department of Pharmaceutical Chemistry.*
*JKK Munirajah Institute of Health Sciences College of Pharmacy, T.N.Palayam, Erode(D.T) -638506, Tamilnadu.*

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**ABSTRACT**

The research paper is about the Computer Aided Drug Design is a modern computational technique used in the drug discovery process to identify and develop a potential lead. The recent introduction of a new generation of anti-fungal drugs promises to alter significantly therapy for both systematic and superficial mycoses. The article present in depth view of the Azoles (Ketoconazole, Fluconazole, Clotrimazole), Polyenes (nystatin), Heterocyclic benzofuran (Griseofulvin). At the conclusion of the learning activity, discuss the selected approaches for the prediction of ADME/TOX properties of the drugs by In silico methods.

**KEYWORDS:** Anti-fungal, CADD, ADME/ TOX prediction, Target prediction.

## I. INTRODUCTION [1-5]

Computer aided drug design is a computer technology that design the product. Main efforts to increasing efficacy of development of drugs are directed to stage of discovery and optimization of leads. In silico method can help in identifying grid targets via bio informative tools. They are also used to analyse the target structure for possible binding sites, generate candidate molecule, dock these molecules with target according to binding affinities of structure-based drug design and ligand based drug design.Toxicity is the measure of any undesirable or unwanted effect of chemicals. Specific types of these adverse effects are called toxicity end points, such as carcinogenicity, mutagenicity, cytotoxicity, and can be quantitative (e.g., LD 50; toxicity test aimed to identify harmful effects caused by substances on human, animals, or the environment through single dose or multiple dose.

ADME properties of adsorption, distribution, metabolism, excretion. Animal models have been used for a long time for toxicity testing. However, in-vitro toxicity tests become plausible due to the advance in high throughput screening. In silico toxicology is one type of toxicity assessment that uses computational resources to organize,analyse, models, stimulate, visualize, or predict toxicity of chemicals.It is intertwined with in silico pharmacology which is information from computational tool to analyse beneficial or adverse effects of drugs for therapeutic purposes.Computational methods aim to complement in vitro or in vivo toxicity test to potentially minimize the need for animal testing, reduce the cost and time of toxicity tests and improve toxicity prediction and safety assessment.Marvin sketch features an extensive set to enable the fast and accurate drawing of chemical compounds, reactions, Markush structures and query molecules (Fig 1-3).

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**Fig.1: ADMET Prediction**

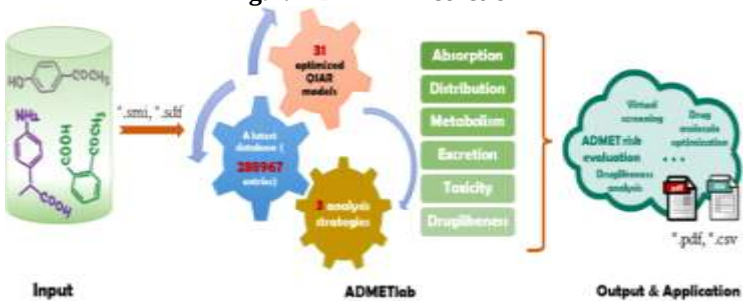



**Fig.2: CHEMDRAW**

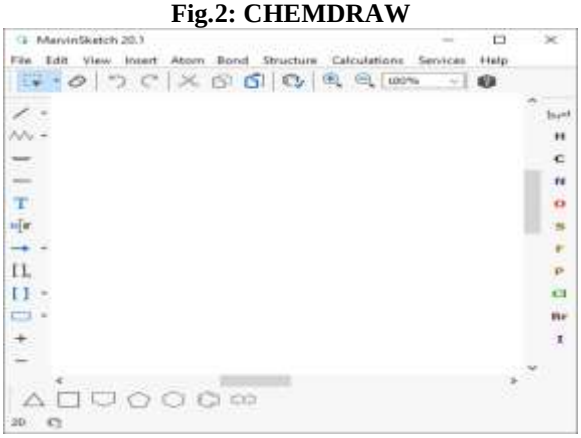
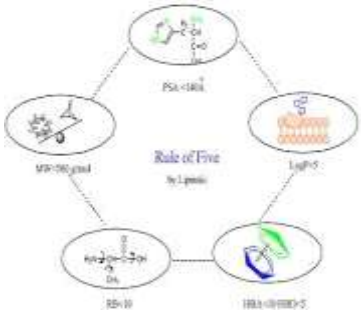



**Fig.3: LIPINSKI'S RULE**




## II. METERIALS AND METHODS[6,7]

### I).ADME Prediction

Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process, at a stage when considered compounds are numerous but access to the physical samples is limited. Swiss ADME web tool that gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness, among which in-house proficient methods such as the BOILED-Egg, iLOGP and Bioavailability Radar.

### II). Toxicity Prediction

The prediction results for the acute toxicity and toxicity targets are generated instantly. The result page will show the predicted median lethal dose ($LD_{50}$) in mg/kg weight, toxicity class, and prediction accuracy as well as average similarity alongwith three most similar toxic compounds from the dataset with the known rodent oral toxicity value. A novelty of the ProTox-II webserver is that the prediction scheme is classified into different levels of toxicity such oral toxicity, organ toxicity (hepatotoxicity), toxicological endpoints (such as mutagenicity, carcinogenecity, cytotoxicity and immunotoxicity) and toxicity targets thereby providing insights into the possible molecular mechanism behind such toxic response.

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## III. RESULT

### I). ADMEStudies

TheADMEStudiesproventhatNystatincouldnotcross theBBB(Bloodbrainbarrier)(Table.1)andproveditas an inhibitorofcytochromeP450CYP3A4substrate. Itis notfollowed the lipinskisruleoffive.

**Table.1:ADMEPrediction**

| | NYSTATIN | GRESIOFULVIN | KETOCONAZOLE | FLUCONAZOLE | CLOTRIMAZOLE |
|---|---|---|---|---|---|
| TPSA | 319.61A2 | 71.06A2 | 69.06A2 | 81.65A | 17.82A |
| LOGPo/w (iLOGP) | 4.30 | 2.95 | 3.96 | 0.41 | 3.07 |
| LOGPo/w (XLOGP3) | -0.20 | 2.18 | 4.34 | 0.35 | 5.41 |
| LOGPo/w (WLOGP) | 0.94 | 2.81 | 3.34 | 1.47 | 5.38 |
| LOGPo/w(MLOGP) | -1.67 | 0.71 | 2.47 | 1.47 | 4.38 |
| LOG Po/w(SILICOS-IT) | -4.26 | 3.39 | 3.69 | 0.71 | 4.98 |
| LOGS(ESOL) | -5.26 | -3.39 | -5.69 | -2.17 | -5.80 |
| LOGS(Ali) | -6.06 | -3.31 | -5.51 | -1.63 | -5.54 |
| LOG S(SILICOS)-IT | 2.54 | -4.71 | -7.20 | -3.54 | -8.59 |
| GIABSORPTION | LOW | HIGH | HIGH | HIGH | HIGH |
| BBBPERMEANT | NO | YES | YES | NO | YES |
| P-GPSUBSTRATE | YES | NO | NO | NO | YES |
| CYP1A2INHIBITOR | NO | YES | NO | NO | YES |
| CYP2CI9INHIBITOR | NO | NO | YES | YES | YES |
| CYP2C9INHIBITOR | NO | YES | YES | NO | YES |
| CYP2D6INHIBITOR | NO | NO | YES | NO | YES |

### II). Toxicitystudies

Thetoxicity studiesrevealed that thedrug hastoxicity of immunotoxicity with active0.99 probabilityof lethaldose100 mg/kg (Table 2-7).

**Table.2: Hepatotoxicity Prediction Table**

| S.NO | DRUG | TARGET | $LD_{50}$ | PREDICTED ACCCURACY | PREDICTION | PROBABLITY |
|---|---|---|---|---|---|---|
| 1. | Nystatin | | 100mg/kg | 72.9% | Inactive | 0.97 |
| 2. | Clotrimazole | | 708mg/kg | 100% | Inactive | 0.67 |
| 3. | Fluconazole | | 1271mg/kg | 100% | Active | 0.84 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| **4.** | Ketoconazole | Hepatot oxicity | 166mg/kg | 100% | Active | 0.76 |
| **5.** | Griseofulvin | | 10000mg/kg | 100% | Active | 0.77 |

**Table.3: Carcinogenicity Prediction Table**

| S.NO | DRUG | TARGET | $LD_{50}$ | PREDICTED ACCCURACY | PREDICTION | PROBABLITY |
|---|---|---|---|---|---|---|
| **1.** | Nystatin | Carcinogenicity | 100mg/kg | 72.9% | Inactive | 0.73 |
| **2.** | Clotrimazole | | 708mg/kg | 100% | Inactive | 0.53 |
| **3.** | Fluconazole | | 1271mg/kg | 100% | Inactive | 0.62 |
| **4.** | Ketoconazole | | 166mg/kg | 100% | Inactive | 0.51 |
| **5.** | Griseofulvin | | 10000mg/kg | 100% | Active | 0.76 |

**Table.4: Immunogenicity Prediction Table**

| S.NO | DRUG | TARGET | $LD_{50}$ | PREDICTED ACCCURACY | PREDICTION | PROBABLITY |
|---|---|---|---|---|---|---|
| **1.** | Nystatin | Immunotoxicity | 100mg/kg | 72.9% | Active | 0.99 |
| **2.** | Clotrimazole | | 708mg/kg | 100% | Inactive | 0.99 |
| **3.** | Fluconazole | | 1271mg/kg | 100% | Inactive | 0.83 |
| **4.** | Ketoconazole | | 166mg/kg | 100% | Active | 0.98 |
| **5.** | Griseofulvin | | 10000mg/kg | 100% | Active | 0.85 |

**Table.5: Mutagenicity Prediction Table**

| S.NO | DRUG | TARGET | $LD_{50}$ | PREDICTED ACCCURACY | PREDICTION | PROBABLITY |
|---|---|---|---|---|---|---|
| **1.** | Nystatin | Mutagenicity | 100mg/kg | 72.9% | Inactive | 0.89 |
| **2.** | Clotrimazole | | 708mg/kg | 100% | Inactive | 0.65 |
| **3.** | Fluconazole | | 1271mg/kg | 100% | Inactive | 0.52 |
| **4.** | Ketoconazole | | 166mg/kg | 100% | Inactive | 0.69 |
| **5.** | Griseofulvin | | 10000mg/kg | 100% | Inactive | 0.87 |

**Table.6: Cytotoxicity Prediction Table**

| S.NO | DRUG | TARGET | $LD_{50}$ | PREDICTED ACCCURACY | PREDICTION | PROBABLITY |
|---|---|---|---|---|---|---|
| **1.** | Nystatin | Cytotoxicity | 100mg/kg | 72.9% | Inactive | 0.83 |
| **2.** | Clotrimazole | | 708mg/kg | 100% | Inactive | 0.87 |
| **3.** | Fluconazole | | 1271mg/kg | 100% | Inactive | 0.76 |
| **4.** | Ketoconazole | | 166mg/kg | 100% | Inactive | 0.69 |
| **5.** | Griseofulvin | | 10000mg/kg | 100% | Inactive | 0.58 |

**Table.7: Toxicity Prediction Table**

| S.NO | TARGET | DRUG | $LD_{50}$ | PREDICTION | PROBABLITY |
|---|---|---|---|---|---|
| **1.** | Hepatotoxicity | NYSTATIN | 100mg/kg | Inactive | 0.97 |
| **2.** | Carcinogenicity | | | Inactive | 0.73 |
| **3.** | Immunotoxicity | | | Active | 0.99 |
| **4.** | Mutagenecity | | | Inactive | 0.89 |
| **5.** | Cytotoxicity | | | Inactive | 0.83 |

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Toxicity prediction of the compounds Nystatin, Griseofulvin, Ketoconazole Fluconazole, Clotrimazolewere predicted by using PRO TOX II. The toxicity was compared by LD50 values. The lowest compared valueindicates the highest toxicity compound. The highest toxicity of the compared compound is NYSTATIN. In theprediction nystatin with toxicity of immunotoxicity with active toxicity of probability 0.99. The target predictionwhichofnystatin with thekinaseenzymewiththe46.7 percentage.

**Figure4:TargetPredictionChart**

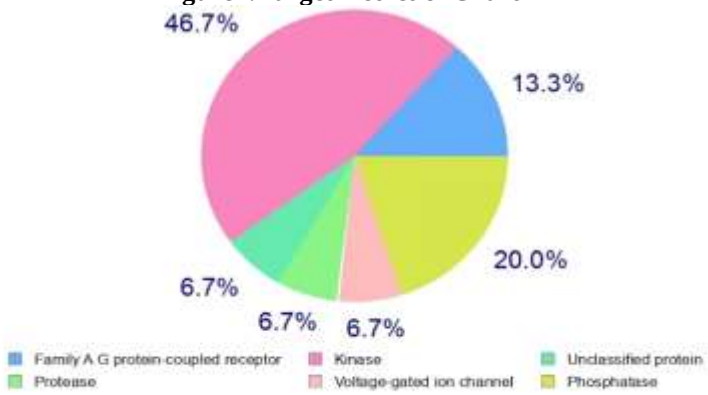


**Table8:TargetPredictionTable**

| TARGET | Commonname | UniprotID | ChEMBLID | TargetClass | Probability* |
|---|---|---|---|---|---|
| Alpha-1aadrenergic receptor (byhomology) | ADRA1A | P35348 | CHEMBL229 | Family A Gprotein coupledreceptor | 0.0642387798076 |
| Vascularendothelial growthfactorreceptor2 | KDR | P35968 | CHEMBL279 | Kinase | 0.0642387798076 |
| Proteinkinase Cdelta | PRKCD | Q05655 | CHEMBL2996 | Kinase | 0.0642387798076 |
| Proteinkinase Calpha | PRKCA | P17252 | CHEMBL299 | Kinase | 0.0642387798076 |
| Motilinreceptor | MLNR | O43193 | CHEMBL2203 | Family A Gprotein coupledreceptor | 0.0642387798076 |

## IV. DISCUSSION[8 -11]

Pharmacokineticsisthestudyofadrug'sabsorption,distribution,metabolismandexcretionovertime .Topredictpharmaceuticalpartitioningbetweentheblodandthebrain,thelogBBvalueis employed.Compoundsthatarelipophilicaredispersed through the blood-brain barrier (BBB). Highlipophilic substances flow through the BBB due todiffusion,whereaslowlipophilicmoleculespassthroughduetospecificcarriers.Inordertobesuccessful,CNStherapeuticdrugsmustbeabletopenetrate the BBB. Compounds with a log BB valuemore than 0.3 have ahigh absorption to the CNS,those with a log BB value between 0.3 and 1.0 have amediumabsorptiontotheCNS,andthosewithalog BB valueless than -1.0have alow absorptiontotheCNS.Humanintestinalabsorption is the process by which drugs are absorbedfrom the gut into the bloodstream (HIA). Compoundswithabsorptionratesof0-20percentarepoorlyabsorbed, those with absorption rates of 20-70 percentaremoderatelyabsorbed,andthosewithabsorption ratesof70-100percentarewell-absorbed.Proteinbindinghasanimpactonadrug'seffectiveness. Drugs bind to albumin and other plasmaproteins. Medicines' half-lives are influenced by theirinteractionswithplasmaproteins.Amedication's plasmaproteinbindingshouldbeminimisedfordiffusionanddistributionacrossthebody.Drugprotein complexes are too large to pass through theplasmamembrane.The difference in pharmaceutical binding to plasmaproteins might be anything from 11 and 82 percent.The drug's

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efficacy is influenced by plasma proteinbindingoverathresholdof80-85percent.Theoctanol-waterpartitioncoefficient(logP)andmolecular weight are thought to have an impact on theexcretion process that eliminates the molecule fromthe human body. The log P scale is used to determinelipophilicity. In the membrane permeability equation,it isa critical variable. The greater the lipophilicity ofa chemical, the slower its metabolism and absorption.It's also more prone to bind to undesired hydrophobicmacromolecules,perhapscausingtoxicity.Thehydrophobicity of medication increases, making it lesssolubleinthestomachandmoresolubleinfatglobules.The Cytochrome P450 enzymesare incharge of drug metabolism in the liver. The enzymesCYP3A4,CYP2D6,CYP2C9,andCYP2C19 help withdrugmetabolism.Eachdrughasadifferentinteraction with CY450. Drugs can either inhibit orincrease the cytochrome P450 enzymes. Drugs may ormaynotinhibitorstimulateallkindsofCYP450enzymes. One CYP450 is adequate for metabolism ToxicityandPharmacodynamicStudies.

Anti- fungal agents are the agents used to treat fungal infections by the microbes. The compounds of Nystatin, Griseofulvin, Fluconazole, Ketoconazole, Clotrimazole. It works on the mechanism of inhibition of cell wall synthesis, depletion of ergosterols, inhibit DNA transcription, cell death by depolarization.

The toxicity is the study of the drug toxicity by which produce by the drug, it includes to the drug which are more toxic effects with they are compared with lethal dose. The low value of Lethal Dose 50 value indicates the high toxicity compound.In which we compared, Nystatin, Ketoconazole, Griseofulvin, Fluconazole, Clotrimazole that the nystatin is high toxicity compound compared by the Lethal Dose 50 value of 100 mg/kg, The nystatin which has Immunotoxicity with probability of 0.99% with active toxicity.The immunotoxicity caused by the nystatin is predicted by the target prediction chart given in the fig.4, the Family A G Protein coupled receptor with the 46.7%.

## V. CONCLUSION

In this study, we designed 5 derivatives of 5 drugs and evaluate their ADME and toxicity study of antifungal drugs through Insilico studies. The comparison study showed Nystatin has no effective pharmacokinetics,not cross the BBB decreased absorption, not obey the Lipinski's rule and has high toxicity of immunotoxicity.Accordingtothisstudy,Nystatindoesnotgivestothepersonwithlowimmuneresponseaccordingtotheinsilicoprediction.

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