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RATIONAL DESIGN OF PYRIMIDINE DERIVATIVES AS ANTICANCER AGENT

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ABSTRACT

Pyrimidine is a six membered aromatic heterocyclic compound containing two nitrogen atom at position 1 & 3. Pyrimidine derivative has been used in drugs for various diseases. in this ,we use insilico drug design techniques to determine pharmacokinetics properties and binding affinity of 2 amino[1,3] thiazolo [4,5-d] pyrimidine5,7 [4h,6h]-dione and 4,6dimethy l-2 phenyl [1,3] oxozolo [4,5-d] pyrimidine-5,6 [4h,6h]-dione. The molecular structure were drawn using chemsketch, followed by prediction of pharmacokinetics properties by swiss ADME. The binding affinity was by using the docking software PyRx. Among this the compound 4, 6-dimethyl 2-phenyl [1,3] oxazolo [4,5-d] pyrimidine -5,7 [4h,6h]-dione has better anti-cancer activity based on binding affinity.

KEYWORDS: Pyrimidine derivatives, Molecular docking, Swiss ADME, Anticancer activity.

INTRODUCTION

When a disease or medical condition lacks effective therapeutic means, a drug discovery program is initiated. Initial stage of research institution which mainli focus on understanding the disease mechanism and finding whether the inhibition or activation of a specific proteins or biological pathway will produce the therapeutic effect. During this stage we can use in silico drug design techniques. It is followed by clinical and preclinical studies and various approval procedures which all may span over 15 to 20 years.[1]

IN SILICO DRUG DESIGN

In silico drug design refers to the using computational tools to predict pharmacokinetic properties, biological activity, target prediction, and binding affinity etc. It can be mainly divided into two: structure-based and ligand-based approaches.[4]

Structure-based drug design is used when the 3D structure of the receptor is known, usually derived from X-ray crystallography or NMR.

Ligand-based drug design is used when the receptor structure is not known, but the active compounds are known. Structure-based drug design involves molecular docking, molecular dynamics simulations, and de novo drug design. Ligand-based drug design involves pharmacophore modeling, QSAR studies, and chemical similatory screening.[5]

Pyrimidine is a six-membered aromatic heterocyclic compound containing two nitrogen atoms at positions 1 and 3. Its derivatives have pharmacological activities such as antimicrobial, antiviral, anticonvulsant, anticancer, anti-inflammatory, and antioxidant activities.[6]

PLAN OF WORK

>**Over view**

To design new pyrimidine derivatives that may possess pharmacological activity.

>**Selection Criteria**

Based on known pharmacological activity and chemical data, pyrimidine derivatives are selected. Molecular structures of pyrimidine derivatives are obtained from PubChem.

>**Preparation of Molecular Structure**

The selected pyrimidine derivatives are drawn using ChemSketch.

>**Prediction of Properties**

By using software like Swiss ADME and Swiss TargetPrediction, various pharmacokinetic properties and target molecules can be predicted.

>**Molecular Docking**

Using docking software like PyRx, the ligand and the target protein can be docked and binding affinity can be found out.

>**Analysis of Docking Results**

By evaluating docking scores, the pyrimidine derivatives can be ranked.[3]

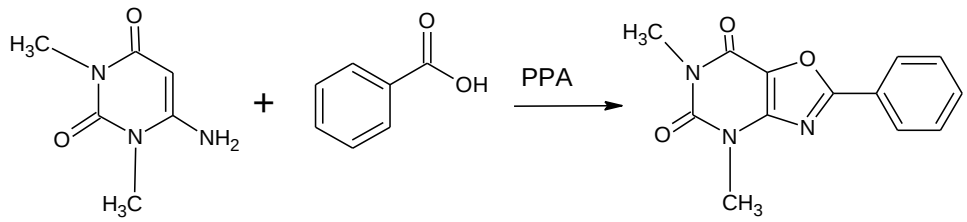
INSILICO STUDIES

In silico studies are carried out using various software to predict pharmacokinetic properties, biological properties, and binding energy etc. It helps to reduce the cost and time for drug discovery to a great extent.The in silico tools used are:[4]

CHEMSKETCH

ChemSketch is a chemical structure drawing software developed by ACD/Labs. The software helps in generating IUPAC names, basic physicochemical properties such as molecular weight and formula. It also helps to convert to 3D structures.[7]

SYNTHESIS 1

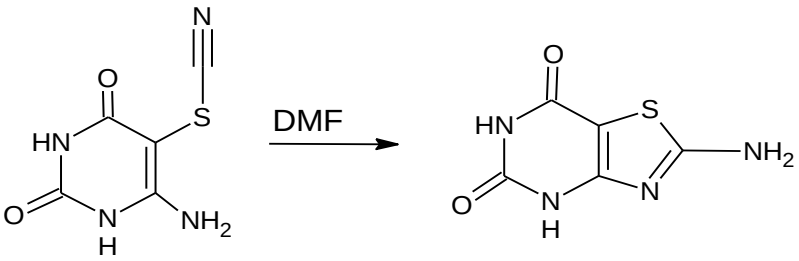


6-amino-1,3-dimethyl pyrimidine-2,4(1*H*,3*H*) -dione

benzoic acid

4,6-dimethyl-2-phenyl[1,3]oxazolo[4,5-*d*]pyrimidine -5,7(4*H*,6*H*)-dione

SYNTHESIS 2



6-amino-2,4-dioxo-1,2,3,4-tetrahydro pyrimidin-5-yl thiocyanate

2-amino[1,3]thiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione

Figure 1: Synthesis of pyrimidine derivatives.[8]

SWISS ADME

It is a web tool used to predict pharmacokinetic properties. Using this software, properties like lipophilicity, water solubility, number of hydrogen donors/acceptors, and TPSA (Topological Polar Surface Area) can be predicted.

The software also helps in predicting whether the drug can be used as a CNS drug, oral drug, or topical drug based on various parameters predicted.[9]

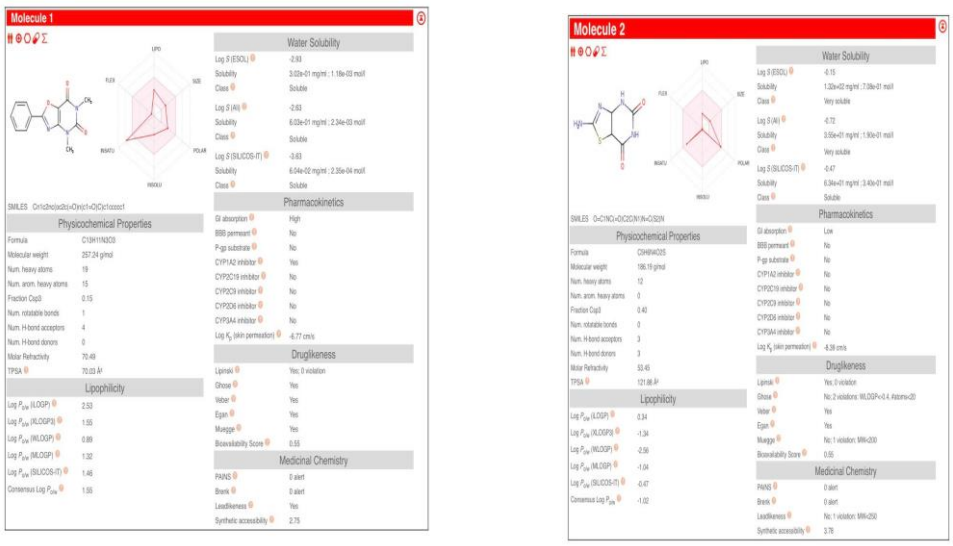


Figure 2: ADME Swiss.

DOCKING SOFTWARE PYRX

It is free software which can be used to dock a ligand and its target protein and predict its binding affinity.The protein is downloaded from the Protein Data Bank (PDB) and the ligand is downloaded from PubChem. Both are uploaded in PyRx software and docking is carried out.[11]

Table 1: Target name.

SL. NO.	Target	PDB ID
1	Vascular endothelial growth factor receptor 2	4SAD
2	Glycogen synthase kinase (GSK-3)	1Q5K

RESULTS AND DISCUSSION

In silico studies are carried out using ChemSketch, SwissADME, and PyRx softwares. Results are shown in tables.[13]

Table 2: Pharmacokinetic Properties as Per Lipinski rule (Swiss ADME).

Compound	Log P	MW	No of H-bond accepters	No of H-bond donors	No of rotatable bond	Violations
Molecule 1	1.55	257.24 g/mol	4	0	1	0
Molecule 2	-1.02	186.19 g/mol	3	3	0	0

Table 3: Prediction of Pharmacokinetic Properties by Swiss ADME.

Compound	Log P	Log S	GI absorption	BBB penetration	Log Kp(cm/s)	Bioavailability
Molecule 1	1.55	-2.93	High	No	-8.39	0.55
Molecule 2	-1.02	-0.15	Low	No	-6.77	0.55

MOLECULAR DOCKING

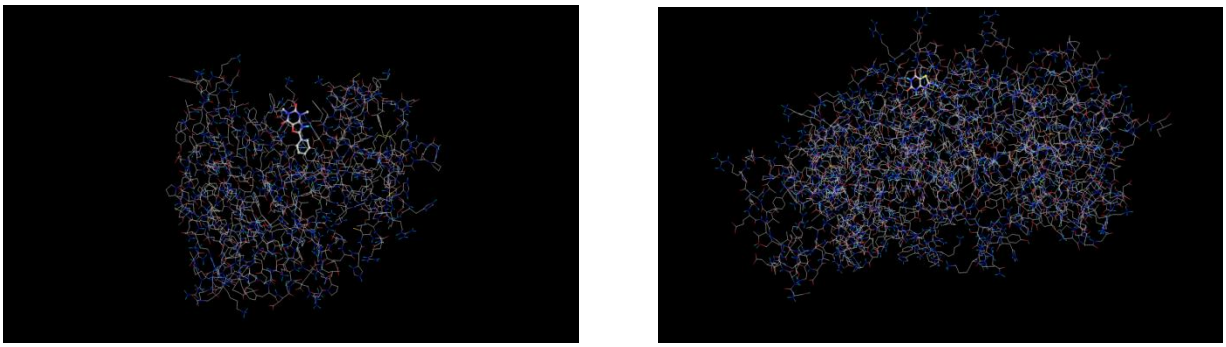


Figure 3: Docking image result.

MOLECULE 1

Molecular docking of 4,6-dimethyl-2-phenyl[1,3]oxazolo[4,5-d]pyrimidine-5,7(4H,6H) dione and Vascular Endothelial Growth Factor Receptor 2.

MOLECULE 2

Molecular docking of 2-amino[1,3]thiazolo[4,5-d]pyrimidine-5,7(4H,6H) dione and glycogen synthase kinase (GSK-3).

Table 4: Docking Result.

Molecules	Protein	Binding affinity
Molecule 1	Vascular endothelial growth factor receptor 2	-8.2
Molecule 2	Glycogen synthase kinase (GSK-3)	-5.9

CONCLUSION

The study titled "Rational design of pyrimidine derivatives as anticancer agents user in silico techniques" is to analyze the potential of pyrimidine derivatives as anticancer agents. The study mainly focuses on predicting ADME properties, drug-likeness, and binding affinity. Using Swiss Target Prediction, their probable targets were predicted. Among them, targets related to cancer are selected and the molecules are docked using them. Binding affinity shows the strength of binding with these proteins.

These studies show that pyrimidine derivatives have a good potential to be developed as future drugs. These studies also show the importance of carrying out future studies on pyrimidine derivatives to develop various anticancer agents.

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